WHO 2016: Important Revisions/Additions
Myeloid neoplasms and acute leukemia

- Mastocytosis is no longer considered a subgroup of the MPNs due to its unique clinical and pathologic features, ranging from indolent cutaneous disease to aggressive systemic disease, and is now a separate disease category in the classification.
- CSF3R mutation is strongly associated with chronic neutrophilic leukemia (CNL).

PB WBC >25 x 10^9/L
Segmented neutrophils plus band forms >80% of WBCs
- Criteria for CML, accelerated phase

CML, accelerated phase criteria
Any 1 or more of the following hematologic/cytogenetic criteria or response-to-TKI criteria:
• Persistent or increasing WBC (>10 x 10^9/L), unresponsive to therapy
• Persistent or increasing splenomegaly, unresponsive to therapy
• Persistent thrombocytosis (>1000 x 10^9/L), unresponsive to therapy
• Persistent thrombocytopenia (<100 x 10^9/L) unrelated to therapy
• 20% or more basophils in the PB
• 10%-19% blasts in the PB and/or BM
• Additional clonal chromosomal abnormalities in Ph+ cells at diagnosis that include “major route” abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2
• Any new clonal chromosomal abnormality in Ph+ cells that occurs during therapy “Provisional” response-to-TKI criteria
• Hematologic resistance to the first TKI (or failure to achieve a complete hematologic response to the first TKI) or
• Any hematological, cytogenetic, or molecular indications of resistance to 2 sequential TKIs or therapy
• Occurrence of 2 or more mutations in BCR-ABL1 during TKI therapy
- (A new subtype) Molecular genetic abnormalities in myeloid/lymphoid neoplasms associated with eosinophilia: PCM1-JAK2 Eosinophilia: t(8;9)(p22;p24.1) May respond to JAK2 inhibitors. Often presents with T-LBL or B-ALL, Bone marrow shows left-shifted erythroid predominance and lymphoid aggregates
- Refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T), used to be a provisional entity within the MDS/MPN unclassifiable group, now termed MDS/MPN with ring sideroblasts and thrombocytosis. Presence of a SF3B1 mutation or, in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features
- aCML is associated with SETBP1 and/or ETNK1 mutations in up to a third of cases
- Juvenile myelomonocytic leukemia (JMML): Approximately 90% of patients carry either somatic or germline mutations of PTPN11, KRAS, NRAS, CBL, or NF1. JMML also has association with monosomy 7 and hyperphosphorylation of STAT5
- MDS has changed to remove terms such as “refractory anemia” and “refractory cytopenia” and replaces them with “myelodysplastic syndrome” followed by the appropriate modifiers: single vs multilineage dysplasia, ring sideroblasts, excess blasts, or the del(5q) cytogenetic abnormality.
There are no changes to childhood MDS; refractory cytopenia of childhood remains as a provisional entity within this category.

- The presence of 1% blasts in the PB, with <5% BM blasts, defines as MDS, unclassifiable (MDS-U). However, because 1% blasts may not be reproducible as a single observation, this finding must now be demonstrated on at least 2 separate occasions in order to diagnose MDS-U according to this criterion.

- There is a major change in the diagnostic criteria for myeloid neoplasms with erythroid predominance (erythroid precursors >50% of all BM cells). In the updated classification, the denominator used for calculating blast percentage in all myeloid neoplasms is all nucleated BM cells, not just the “nonerythroid cells.” The subcategory of acute erythroid leukemia, erythroid/myeloid type (previously defined as a case with >50% BM erythroid precursors and >20% myeloblasts among nonerythroid cells) has been removed from the AML category. Pure erythroid leukemia remains as an AML, NOS subtype and is now the only type of acute erythroid leukemia (>80% immature erythroid precursors with >30% proerythroblasts).

- Based on recent data showing no adverse effect of 1 chromosomal abnormality in addition to the del(5q), the entity MDS with isolated del(5q) may be diagnosed if there is 1 additional cytogenetic abnormality besides the del(5q), unless that abnormality is monosomy 7 or del(7q). Evaluation for TP53 mutation is recommended in patients with MDS with isolated del(5q) to help identify an adverse prognostic subgroup in this generally favorable prognosis MDS entity.

- Targeted sequencing of a limited number of genes can detect mutations in 80% to 90% of MDS patients; the most commonly mutated genes in MDS are SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53, and EZH2. Importantly, acquired clonal mutations identical to those seen in MDS can occur in the hematopoietic cells of apparently healthy older individuals without MDS, so-called “clonal hematopoiesis of indeterminate potential” (CHIP). Although some patients with CHIP subsequently develop MDS, the natural history of this condition is not yet fully understood; thus, the presence of MDS-associated somatic mutations alone is not considered diagnostic of MDS in this classification, even in a patient with unexplained cytopenia.

- If an SF3B1 mutation is identified, a diagnosis of MDS-RS may be made if ring sideroblasts comprise as few as 5% of nucleated erythroid cells, whereas at least 15% ring sideroblasts are still required in cases lacking a demonstrable SF3B1 mutation. MDS-RS cases will be subdivided into cases with single lineage dysplasia (previously classified as refractory anemia with ring sideroblasts) and cases with multilineage dysplasia (previously classified as refractory cytopenia with multilineage dysplasia).

- A new provisional category of AML with BCR-ABL1 is added to recognize these rare de novo AML cases that may benefit from TKI therapy. Although the diagnostic distinction between de novo AML with BCR-ABL1 and blast transformation of CML may be difficult without adequate clinical information.

- The finding that the improved prognosis associated with AML with mutated CEBPA is associated with biallelic, but not single, mutations of the gene has resulted in a change in that disease definition to require biallelic mutations.

- NPM1 or biallelic CEBPA: these mutations now supersede the presence of multilineage dysplasia in the classification.

- A provisional category of AML with mutated RUNX1 has been added to the classification for cases of de novo AML with this mutation that are not associated with MDS-related cytogenetic
abnormalities. This new provisional disease category appears to represent a biologically distinct group with a possibly worse prognosis than other AML types.

-Both TAM and myeloid leukemia associated with Down syndrome are characterized by GATA1 mutations and mutations of the JAK-STAT pathway.
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Lymphoid neoplasms
CLL/SLL
• Cytopenias or disease-related symptoms are now insufficient to make a diagnosis of CLL with <5 x 10^9/L PB CLL cells.
• Large/confluent and/or highly proliferative proliferation centers are adverse prognostic indicators.
• Mutations of potential clinical relevance, such as TP53, NOTCH1, SF3B1, ATM, and BIRC3, have been recognized. However, the literature is inconsistent regarding the clinical implications of some of the mutations and combined risk profile, and it will not be recommended at this time.
- Proliferation centers (PC) can have cyclin D1 expression in up to about 30% of CLL/SLL, they express MYC protein, and, PCs which are large/confluent and/or have a high proliferative fraction are a significant and independent adverse prognostic indicator.

Monoclonal B-cell lymphocytosis
• Must distinguish low-count from high-count MBL.
• MBL precedes virtually all cases of (CLL/SLL). The updated WHO will retain the current criteria for MBL, but will emphasize that “low-count” MBL, defined as a PB CLL count of <0.5 x 10^9/L, must be distinguished from “high-count” MBL [0.5-5 x 10^9/L] because low count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and, until new evidence is provided, does not require routine follow-up outside of standard medical care. In contrast, high count MBL requires routine/yearly follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 of CLL.
- The best candidates for tissue-based MBL: lymph nodes with CLL/SLL in which proliferation centers were not observed and patients in whom adenopathy was <1.5 cm based on CT scans.

Hairy cell leukemia
- Almost all cases of hairy cell leukemia (HCL) have BRAF V600E mutations
- HCL without BRAF V600E mutations and half of HCL-variant (HCL-v): use IGHV4-34, have mutations in MAP2K1 which encodes MEK1 (which is downstream of BRAF)

Lymphoplasmacytic lymphoma (LPL)
• MYD88 L265P mutation in vast majority of cases (90%) impacting diagnostic criteria even though finding is not specific for LPL.
• IgM MGUS is more closely related to LPL and other B-cell lymphomas than to myeloma.
• CXCR4 mutations are found in about 30% of LPL.

Follicular lymphoma (FL)
• Mutational landscape better understood but clinical impact remains to be determined (no recommended mutations at this time).

In situ follicular neoplasia (ISFN)
• Have a low rate of progression, but are more often associated with prior or synchronous overt lymphomas, thus requiring additional clinical assessment. Flow cytometric studies demonstrate populations of B cells with a FL-type phenotype in about half of all lymph nodes with ISFN.

Pediatric-type FL
- Pediatric FL now known as pediatric-type FL because similar lymphomas may occur in young and rarely in older adults. It is a nodal disease characterized by large expansile highly proliferative follicles that often have prominent blastoid follicular center cells rather than classic centroblasts (or centrocytes). Some have reported a moderate number of cases as grade 1-2 of 3. BCL2 rearrangements must not be present, but there may be some BCL2 protein expression.
They also lack BCL6 and MYC rearrangements with ongoing investigations of their genetic/molecular landscape.

- Nearly all cases are localized and may not require treatment other than excision. Some studies have raised the possibility that pediatric-type FL might be a “benign clonal proliferation with low malignant potential. [how to differentiate from follicular hyperplasia?]

- The criteria for pediatric-type FL, however, must be strictly applied to avoid underdiagnosing conventional grade 3 FL, with particular caution required before making this diagnosis in an adult.

**Large B-cell lymphoma with IRF4 rearrangement**
- New provisional entity to distinguish from pediatric-type FL and other DLBCL.
- Localized disease, often involves cervical lymph nodes or Waldeyer ring. Occurs most commonly in children and young adults, most typically occurs in Waldeyer ring and/or cervical lymph nodes and are low stage. They may have a follicular, follicular and diffuse, or pure diffuse growth pattern resembling FL grade 3B or a DLBCL. Strong IRF4/MUM1 expression is seen usually with BCL6 and a high proliferative fraction. BCL2 and CD10 are also expressed in more than half of the cases with a minority CD5+. They are most often of germinal center type, particularly based on gene expression profiling (GEP) studies. Most cases have IG/IRF4 rearrangements sometimes together with BCL6 rearrangements but they uniformly lack BCL2 rearrangements. This lymphoma is considered to be more aggressive than other pediatric-type FL but patients, at least when treated, have done very well.[how to differentiate from FL, DLBCL?]

**Duodenal-type FL**
- Having features of a localized overt low-grade FL, is distinct from other GI tract FL, and has many features that overlap with ISFN as well as some features resembling an extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. Localized process with low risk for dissemination. These patients appear to have an excellent outcome, including some cases managed with a watch-and-wait strategy.

**Predominantly diffuse FL with 1p36 deletion**
- Accounts for some cases of diffuse FL, lacks BCL2 rearrangement; presents as localized mass, often inguinal.

**Mantle cell lymphoma (MCL)**
- Two MCL subtypes recognized: one largely with unmutated/minimally mutated IGHV and mostly SOX11+ and the other largely with mutated IGHV and mostly SOX11(-) (indolent leukemic nonnodal MCL with PB, bone marrow (BM), splenic involvement, may become more aggressive with secondary abnormalities, often involving TP53.
- Mutations of potential clinical importance, such as TP53, NOTCH 1/2, recognized in small proportion of cases.
- CCND2 rearrangements in approximately half of cyclin D1(-) MCL cases.

**In situ mantle cell neoplasia (ISMCN)**
- New name for in situ MCL, reflecting low clinical risk.
- Characterized by the presence of cyclin D1+ cells, most typically in the inner mantle zones of follicles, in lymphoid tissues that do not otherwise suggest the diagnosis of a MCL, and is often found incidentally, sometimes in association with other lymphomas.

**Diffuse large B-cell lymphoma, NOS**
- Distinction of GCB vs ABC/non-GC type is required with use of immunohistochemical algorithm acceptable (Hans’), may affect therapy.
Most of DLBCL with concomitant expression of MYC/BCL2 do not carry MYC/BCL2 chromosomal alterations and have been named “double-expressor lymphoma.” Most studies use a cutoff of 40% MYC-expressing cells to define these cases; the cutoff for BCL2 expression 50% is recommended. In several but not all studies, the double-expressor lymphomas have a worse outcome than other DLBCL, NOS but they are not as aggressive as the HGBL, with rearrangements of MYC and BCL2 and/or BCL6.

- Mutational landscape better understood but clinical impact remains to be determined.

**EBV+ DLBCL, NOS**
- This term replaces EBV+ DLBCL of the elderly because it may occur in younger patients.
- Does not include EBV+ B-cell lymphomas that can be given a more specific diagnosis.

**EBV+ mucocutaneous ulcer**
- Newly recognized entity associated with iatrogenic immunosuppression or age-related immunosenescence.

**Burkitt lymphoma**
- TCF3 or ID3 mutations in up to ~70% of cases.

**Burkitt-like lymphoma with 11q aberration**
- New provisional entity that closely resembles Burkitt lymphoma but lacks MYC rearrangement and has some other distinctive features.

**High-grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 translocations**
- The old “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL” (BCLU)"-> now designated HGBL, with MYC and BCL2 and/or BCL6 rearrangements (“double-/triple-hit” lymphomas)
- A consensus has not yet been reached to provide specific guidelines as to which LBCL should have fluorescence in situ hybridization studies. Some believe that all DLBCL should have genetic studies for the detection of MYC, BCL2, and BCL6 rearrangements, whereas others would limit them, for example, to cases with a GCB phenotype and/or high-grade morphology or to cases with >40% MYC+ cells.

**High-grade B-cell lymphoma, NOS**
- Includes blastoid-appearing large B-cell lymphomas and cases lacking MYC and BCL2 or BCL6 translocations that would formerly have been called BCLU.

**T-cell large granular lymphocyte leukemia**
- New subtypes recognized with clinicopathologic associations.
- STAT3 and STAT5B mutations in a subset, latter associated with more clinically aggressive disease.

**Systemic EBV+ T-cell lymphoma of childhood**
- Name changed from lymphoproliferative disorder to lymphoma due to its fulminant clinical course and desire to clearly distinguish it from chronic active EBV infection.
- Increased frequency in Asians, and in indigenous populations from Central and South America and Mexico.

- Has a fulminant clinical course usually associated with a hemophagocytic syndrome

**Hydroa vacciniforme-like lymphoproliferative disorder**
- Name changed from lymphoma to lymphoproliferative disorder due to its relationship with chronic active EBV infection and a spectrum in terms of its clinical course.
- Increased frequency in Asians, and in indigenous populations from Central and South America and Mexico.
-Chronic active EBV infection of T/NK type shows a broad range of clinical manifestations from indolent, localized forms like hydroa vacciniforme-like LPD and severe mosquito bite allergy to a more systemic form characterized by fever, hepatosplenomegaly, and lymphadenopathy with or without cutaneous manifestations

**Enteropathy-associated T-cell lymphoma (EATL)**
- Diagnosis only to be used for cases formerly known as type I EATL, typically associated with celiac disease, primarily a disease of individuals of northern European origin
- EATL generally has a polymorphic cellular composition and wide range in cytology
- Most EATL cases express TCR αβ

**Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)**
- Formerly type II EATL; segregated from type I EATL and given a new name due to its distinctive nature and lack of association with celiac disease.
- MEITL is monomorphic, and usually positive for CD8, CD56, and MATK
- Gains in chromosome 8q24 involving MYC are seen in a high proportion of cases.
- Many cases of MEITL are derived from γδ T cells

**Indolent T-cell lymphoproliferative disorder of the GI tract**
- New provisional entity with superficial monoclonal intestinal T-cell infiltrate, usually composed of CD8+ T cells, with an indolent clinical course, some cases show progression. Their optimal management is not yet determined.

**Lymphomatoid papulosis**
- New subtypes described with similar clinical behavior but atypical histologic/immunophenotypic features:
  - LyP with chromosome 6p25 rearrangement at IRF4/DUSP22 locus

**Primary cutaneous γδ T-cell lymphoma**
- Cutaneous γδ T-cell lymphoma are generally aggressive. Important to exclude other cutaneous T-cell lymphomas/lymphoproliferative disorders that may also be derived from γδ T cells such as mycosis fungoides or lymphomatoid papulosis.

**Primary cutaneous acral CD8+ T-cell lymphoma**
- New indolent provisional entity, originally described as originating in the ear.

**Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder**
- No longer to be diagnosed as an overt lymphoma due to limited clinical risk, localized disease, and similarity to clonal drug reactions.
- The cells have a TFH phenotype
- Remains a provisional entity.

**Peripheral T-cell lymphoma (PTCL), NOS**
- Subsets based on phenotype and molecular abnormalities being recognized that may have clinical implications but are mostly not a part of routine practice at this time.

**Nodal T-cell lymphomas with T-follicular helper (TFH) phenotype**
- An umbrella category created to highlight the spectrum of nodal lymphomas with a TFH phenotype including angioimmunoblastic T-cell lymphoma, follicular T-cell lymphoma, and other nodal PTCL with a TFH phenotype (specific diagnoses to be used due to clinicopathologic differences).
- T follicular helper (TFH) phenotype: the neoplastic cells should express at least 2 or 3 TFH-related antigens, including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5.
• Overlapping recurrent molecular/cytogenetic abnormalities recognized that potentially could impact therapy.

**ALK(-) anaplastic large-cell lymphoma**

• Now a definite entity that includes cytogenetic subsets that appear to have prognostic implications:
  - A subset with 6p25 rearrangements at IRF4/DUSP22 locus tends to be relatively monomorphoic, usually lack cytotoxic granules, and have been reported to have a superior prognosis,
  - A small subset with TP63 rearrangements are very aggressive

**Breast implant–associated anaplastic large cell lymphoma**

• New provisional entity distinguished from other ALK(-) ALCL; noninvasive disease associated with excellent outcome.
  - Presents as an accumulation of seroma fluid between the implant itself and the surrounding fibrous capsule. Both saline- and silicone-filled implants have been implicated, with a median interval from the time of the implant to the lymphoma of about 10 years. In most cases, the neoplastic cells are confined to the seroma fluid, without invasion of the capsule. In such cases, conservative management is recommended, with removal of the implant and capsule. If there is invasion through the capsule, there is risk of lymph node involvement and systemic spread, warranting systemic chemotherapy.

**Nodular lymphocyte–predominant Hodgkin lymphoma**

• Variant growth patterns, if present, should be noted in diagnostic report, due to their clinicopathologic associations.
  - Cases associated with synchronous or subsequent sites that are indistinguishable from T-cell histiocyte-rich large B-cell lymphoma (THRLBCL) without a nodular component (lacking any follicular dendritic cells) should be designated THRLBCL-like transformation of NLPHL.
  - Progression to a process with features of THRLBCL is associated with a more aggressive clinical course, and requires different management, such that the term NLPHL in this setting may not be sufficient

**Lymphocyte-rich classical Hodgkin lymphoma**

• Features recognized that are intermediate between NLPHL and other types of classical Hodgkin lymphoma.

**Erdheim-Chester disease**

• Should be distinguished from other members of the juvenile xanthogranuloma family; often associated with BRAF mutations.

**Other histiocytic/dendritic neoplasms**

• Clonal relationship to lymphoid neoplasms recognized in some cases.
  - Some of these neoplasms are associated with or preceded by FL, CLL, B- or T-lymphoblastic neoplasms, or PTCL. These cases carry the same TCR or IGHV rearrangements and chromosomal aberrations as the associated lymphoid neoplasms, suggesting a process of transdifferentiation.
  - The BRAF V600E mutation has been reported in the setting of Langerhans cell histiocytosis, histiocytic sarcoma, disseminated juvenile xanthogranuloma, Erdheim-Chester disease, and follicular dendritic cell sarcoma.
Tests currently available from Genoptix (June 2016)

- Bcr-abl1 mutations: abl1 kinase domain mutation (PCR)
- Bcr/abl1 translocation for AML: Bcr/abl1 by FISH or PCR
- CSF3R mutation: in Next-Gen Sequencing/MPN Molecular Profile (a total of 5 genes)
- SF3B1 mutation: in Next-Gen Sequencing/AML Molecular Profile (a total of 21 genes)
- SETBP1 mutation: in Next-Gen Sequencing/MPN Molecular Profile (a total of 5 genes)
- PTPN11, KRAS, NRAS, CBL mutations: in Next-Gen Sequencing/Myeloid Molecular Profile (a total of 40 genes)
- RUNX1 mutation: in Next-Gen Sequencing/AML Molecular Profile (a total of 21 genes)
- TP53 mutation: in Next-Gen Sequencing/AML Molecular Profile (a total of 21 genes)
- BRAF V600E: PCR
- MAP2K1 mutation: in Next-Gen Sequencing/NexCourse Complete (a total of 173 genes)
- CXCR4 mutation: in Next-Gen Sequencing/Lymphoid Molecular Profile (a total of 75 genes)
- TCF3, ID3 mutations: in Next-Gen Sequencing/Lymphoid Molecular Profile (a total of 75 genes)
- STAT3, STAT5B mutations: in Next-Gen Sequencing/Lymphoid Molecular Profile (a total of 75 genes)

- PCM1-JAK2: FISH not available--> look for t(8;9) by Cytogenetics
- MYD88 mutation: PCR