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Appendix 1

WHO-HAEM4R	WHO-HAEM5	ICC
Myeloproliferative neoplasms (MPNs)		
Chronic myeloid leukaemia (CML) • Biphasic or triphasic natural history: indolent chronic phase (CP) followed by a blast phase (BP) +/- an intervening accelerated phase (AP). Polycythaemia Vera (PV) • ^{51}Cr-labelled increased red blood cells mass (>25% above mean normal predicted value) formed part of the major criteria to determine the presence of a significant erythrocytosis. Chronic eosinophilic leukaemia (CEL), NOS • Time interval for eosinophilia not required to meet criteria. • Abnormal bone marrow morphology not in diagnostic criteria. • Either clonality OR an increase in blasts as an alternative to clonality should be met. MPN, Unclassifiable Criteria of Essential Thrombasthaenia, Primary Myelofibrosis and Chronic Neutrophilic Leukaemia are the same.	CML • AP is omitted. • Emphasis is placed on high-risk features associated with CP progression and resistance to tyrosine kinase inhibitors (TKI). • BP criteria is similar. • Cut-off for lymphoblasts and significance of low-level B-lymphoblasts remain unclear. PV • Determining increased red cell mass has become uncommon in routine clinical practice. This criterion has been removed. CEL • The qualifier NOS is omitted. • Time interval required to define sustained hypereosinophilia is 4 weeks. • Addition of bone marrow findings to diagnostic criteria: megakaryocyte or erythroid dysplasia. • Clonality is a required criterion and increased blasts as an alternative has been removed. MPN, Unclassifiable renamed MPN, NOS New: Juvenile Myelomonocytic Leukaemia (JMML) • *KMT2A* rearrangements should be excluded. • Monosomy 7 as cytogenetic criterion has been removed.	CML • AP remains: blasts 10-19%, basophilia ≥20% or additional cytogenetic abnormality. • BP: blasts ≥ 20% in PB or BM. • Presence of morphologically apparent lymphoblasts >5% warrants consideration of lymphoblastic crisis (BP). PV • Increased red cell mass is retained as one of the diagnostic thresholds for erythrocytosis. CEL, NOS • Qualifier NOS is retained. • Relative eosinophilia of 10% required in addition to absolute eosinophilia of ≥ 1.5 x 10^9/L. • Abnormal bone marrow findings is incorporated into diagnostic criteria as an alternative to increased PB or BM blasts. • Clonality is a required criterion. MPN, Unclassifiable renamed MPN, NOS

Mastocytosis		

• Major criteria and minor criteria.
• Minor criteria:
  ○ *KIT* point mutation at codon 816 (*KIT* D816V).
  ○ CD2 or CD25 expression in mast cells.
  ○ Serum tryptase level >20ng/ml.
 	
BM Mastocytosis included under indolent systemic mastocytosis.
	• Major criteria unchanged.
	• Minor criteria:
	  ○ Any *KIT* mutation causing ligand-independent activation.
	  ○ Addition of CD30 expression.
	  ○ Serum tryptase should be adjusted for patients with hereditary alpha-tryptasaemia.
	
	• BM Mastocytosis is recognised as a separate subtype of SM.
	  ○ Characterized by absence of skin lesions and B-findings and basal serum tryptase <125 ng/ml.
		• Major criteria modified – addition of the demonstration of trypase and *KIT* (CD117) immunoreactivity to ensure proper ID of mast cells.
		• Minor criteria:
		  ○ *KIT* mutations.
		  ○ Addition of CD30.
		
		• Clinicopathologic variant of SM termed BM Mastocytosis.
		• SM with associated haematologic neoplasm is changed to SM with an associated myeloid neoplasm.

Myelodysplastic Syndrome/Neoplasms (MDS)		

• Category called Myelodysplastic syndromes.
 	
• Subtyped according to:
  ○ Excess blasts
  ○ Isolated del(5q)
  ○ Ringed sideroblasts (RS)
  ○ Number of dysplastic lineages: multilineage dysplasia (MDS-MLD); single lineage dysplasia (MDS-SLD)
  ○ MDS unclassifiable
  ○ Refractory cytopenias of childhood
	• Renamed myelodysplastic neoplasms but abbreviation MDS is retained.
	
	New organisation:
	• **MDS with defining genetic abnormalities**
	• **MDS, morphologically defined**
	• **MDS of childhood**
	  ○ Renaming of refractory cytopenias of childhood.
	
	MDS with defining genetic abnormalities
	• MDS with low blasts and isolated 5q deletion (MDS-5q)
	• MDS with low blasts and *SF3B1* mutation (MDS-SF3B1)
	  ○ MDS with low blasts and RS is retained as an acceptable alternative in cases with WT *SF3B1* and ≥15% RS (that have mutations of other RNA splicing components).
		• Category called premalignant clonal cytopenias and MDS.
		• Retains term myelodysplastic syndrome.
		
		New organisation:
		• **MDS with mutated *SF3B1***
		• **MDS with del5q**
		• **MDS, NOS**
		  ○ Without dysplasia (previously MDS-U which has been removed)
		  ○ With single lineage dysplasia
		  ○ With multilineage dysplasia
		• **MDS with excess blasts**
		• **MDS/AML**
		• **MDS with mutated *TP53***
		• **MDS/AML with mutated *TP53***
		• **Refractory cytopenias of childhood**

	• MDS with biallelic *TP53* inactivation (MDS-biTP53)
	  ○ Requires ≥2 *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or copy neutral loss of heterozygosity.
	  ○ MDS-biTP53 supersedes MDS-5q and MDS-SF3B1.
	
	MDS morphologically defined
	• Includes, MDS with low blasts (MDS-LB), MDS, hypoplastic (MDS-h), MDS with increased blasts (MDS-IB1/2) and MDS with fibrosis (MDS-f) as a subtype of MDS-IB.
	• Hypoplastic MDS is listed as a distinct MDS subtype (several features overlap with PNH and AA).
	• Terminology change to MDS-IB1/2 (increased blasts).
	• Blast cut-offs are retained from previous classification.
	• Retains 20% blast cut-off to define AML.
	  ○ A lower cut-off carries risk of overtreatment.
	  ○ MDS-IB2 may be regarded as AML-equivalent for therapeutic considerations and clinical trials.
	
	Childhood MDS
	• Includes Childhood MDS with low blasts and with increased blasts.
	• Childhood MDS with low blasts has two subtypes: hypocellular and NOS.
	• Childhood MDS with increased blasts: 5–19% BM, 2–19% PB.
		MDS subtypes without excess blasts
		• MDS with *SF3B1* mutation replaces MDS-RS:
		  ○ Neither dysplasia nor RS required for this diagnosis.
		  ○ MDS with RS and WT *SF3B1* share clinical features and outcomes with MDS-SLD/MLD so classified as MDS, NOS irrespective of number of RS.
		• MDS-U no longer included, but restructured:
		  ○ All previous MDS-defining cytogenetic abnormalities [aside from del(5q), -7/del(7q)] with cytopenias in the absence of dysplasia, are considered CCUS and not MDS-U.
		  ○ SLD with pancytopenia and 1% PB blasts is acceptable in any non-excess blast MDS subtype.
		
		MDS subtypes with excess blasts
		• Retains the term MDS-EB but only recognises one subtype – defined by PB ≥2% / BM ≥5% blasts.
		  ○ The presence of excess blasts supersedes any of the MDS subtypes, except for MDS with mutated *TP53.*
		• Introduce a separate category – MDS/AML: merging the previous MDS-EB2 with AML and adopting a cut-off of 10% blasts in PB or BM.

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)		

Chronic myeolomonocytic leukaemia (CMML)
• Prerequisite criteria: persistent peripheral blood monocytosis ≥1 x 10^9/L with monocytes accounting for ≥10% of the leukocytes.
• Presence/evidence of clonality is not a requirement for diagnostic criteria.
• Subtypes:
  ○ CMML type 0: <2% blasts in PB and <5% blasts in BM.
  ○ CMML type I: 2 - 4% blasts in PB or 5 - 9% blasts in BM and no Auer rods.
  ○ CMML type II: 5 - 19% blasts in PB, 10 - 19% blasts in BM OR Auer rods are present.
 	
Atypical CML
 	
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
 	
MDS/MPN unclassifiable
 	
Juvenile myelomonocytic leukaemia (JMML)
	CMML
	• Cut-off for absolute monocytosis lowered to 0.5 x 10^9/L.
	• Proven clonality AND documentation of dysplasia in at least one lineage are required if the monocytosis is ≥0.5 but <1 x 10^9/L.
	• Abnormal partitioning (increased classical monocytes >94%) of PB monocyte subsets are introduced as a new supporting criterion.
	• Subtypes:
	  ○ Myelodysplastic-CMML (MD-CMLL; WCC <13) and myeloproliferative-CMML (MP-CMML; WCC ≥13) subtypes of CMML is formally recognised.
	  ○ CMML-0 removed – provides no/limited prognostic significance.
	  ○ CMML-1 requires <5% blasts in PB and <10% in BM.
	
	MDS/MPN with neutrophilia
	• Entity renamed for clarity.
	• Diagnostic criteria remain largely unchanged.
	
	MDS/MPN with *SF3B1* mutation and thrombocytosis OR MDS/MPN-RS-T
	• Redefined if there is the presence of an *SF3B1* mutation.
	• Previous term is still acceptable for cases with WT *SF3B1* and ≥15% RS.
	
	MDS/MPN, NOS
	• Renamed from unclassifiable to NOS.
	
	JMML no longer an MDS/MPN - categorised under MPNs
		CMML
		• Cut-off lowered to 0.5.
		• In the absence of clonality: monocytes ≥1 x 10^9/L and >10% of WCC AND increased blasts OR morphologic dysplasia OR an abnormal immunophenotype consistent with CMML (possibly similar to abnormal partitioning).
		• CMML-MP and CMML-MD.
		• Subtypes:
		  ○ CMML-0 removed.
		
		Atypical CML (aCML)
		• Retained WHO-HAEM4R term of atypical CML but the notion of "BCR::ABL1-negative" is dropped from the aCML name.
		• aCML is NOT characterized by eosinophilia and should be <10% of WBC, otherwise chronic eosinophilic leukaemia should be considered.
		• Requires a cytopenia for diagnosis.
		
		MDS/MPN with *SF3B1* mutation and thrombocytosis OR MDS/MPN-RS-T, NOS
		• Same terminology changeif *SF3B1* mutation present.
		• But if WT *SF3B1*, then inclusion of NOS: MDS/MPN with RS and thrombocytosis, NOS.
		
		MDS/MPN, NOS
		• Renamed from unclassifiable to NOS.
		
		JMML no longer an MDS/MPN - categorised under paediatric and/or germline mutation associated disorders

		MDS/MPN with isolated isochromosome (17q) • Addition of this new provisional entity. Unclear if this is a distinct entity or falls within spectrum of aCML.
Acute Myeloid Leukaemia (AML)		

• Nomenclature: Subtypes of AMLs with balanced translocations/inversions are described using cytogenetics and gene fusion.
• Gene fusions are separated by a -
• Subcategories are:
  ○ **AML with recurrent genetic abnormalities**
  ○ **AML with myelodysplasia-related changes**
  ○ **Therapy-related myeloid neoplasms**
  ○ **AML, NOS**
  ○ **Myeloid Sarcoma**
  ○ **Myeloid proliferations associated with Down syndrome**
 	
AML with myelodysplasia-related changes
• Blasts >20% expressing myeloid immunophenotype.
• Cytogenetic abnormalities (specified balanced translocations and unbalanced abnormalities)
  ○ Gene mutations were not considered diagnostic evidence.
• Arising de novo with multilineage dysplasia or following a known history of MDS or MDS/MPN.
	• Nomenclature: Subtypes of AMLs with balanced translocations/inversions are described using gene fusion only.
	• Gene fusions are separated by a ::
	• Subcategories are:
	  ○ **AML with defining genetic abnormalities**
	  - Removal of ≥ 20% blast requirement, except for AML with *BCR::ABL1* fusion and AML with *CEBPA* mutation, where ≥ 20% blasts are required.
	  - AML, myelodysplasia-related is a subtype of this category.
	  ○ **AML, defined by differentiation**
	  ○ **Myeloid Sarcoma**
	• Secondary myeloid neoplasms (e.g. therapy-related, Down Syndrome associated) are moved to their own category.
	
	Modified subtypes:
	• AML with MECOM rearrangement – this broadens the the AML with inv(3)(q21.3q26.2) t(3;3)(q21.3;q26.2)/*GATA2, MECOM* of WHO-HAEM4R to include any rearrangements of *MECOM*.
	• AML with *CEBPA* mutation
	  ○ Both biCEBPA & smbZIP-CEBPA.
	• AML, myelodysplasia-related (MR)
	  ○ Removal of morphology driven diagnosis.
	  ○ The presence of ≥1 cytogenetic or molecular abnormalities and/or history of
		• Nomenclature: Subtypes of AMLs with balanced translocations/inversions are described using cytogenetics and gene fusion.
		• Gene fusions are separated by a ::
		• **Not subcategorised** – all subtypes just listed.
		• Reduction of the blast requirement to ≥ 10% for AML, except for AML with t(9;22)(q34.1;q11.2)/*BCR::ABL1* and AML, NOS where ≥ 20% blasts are required.
		
		Modified subtypes:
		• AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2; MECOM*(EVI1) is retained, but there is inclusion of other MECOM rearrangements (see new subtypes).
		• AML with in-frame bZIP *CEBPA* mutations.
		• AML with myelodysplasia-related (MR) gene mutations (>20% blasts)
		  ○ Defined by same mutations as WHO-HAEM5 with the addition of *RUNX1* mutations (now encompassing the WHO-HAEM4R provisional entity of AML with mutated *RUNX1*).
		  ○ If 10-19% blasts then MDS/AML with MR gene mutations.
		• AML with MR cytogenetic abnormalities (>20% blasts)
		  ○ Defined by same cytogenetic abnormalities with the addition of +8.
		  ○ If 10-19% blasts then MDS/AML with MR cytogenetic abnormalities.

	MDS or MDS/MPN are required for diagnosing AML-MR. ○ The defining somatic mutations are *ASXL1, BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2.* ○ The defining cytogenetic abnormalities are the same as the unbalanced abnormalities. Balanced translocations are no longer AML, MR defining. ○ In AML, **defined by differentiation**, ▪ Acute monocytic leukaemia is used instead of Acute monocytic and monoblastic leukaemia. ▪ Acute erythroid leukaemia is used instead of Pure erythroid leukaemia. New subtypes: • AML with NUP98 rearrangement ○ May be cryptic on conventional karyotyping. • AML with other defined genetic alterations ○ AML with inv(16)(p13.3q24.3)/*CBFA2T3::GLIS2* ○ AML with *KAT6A::CREBBP* ○ AML with *FUS::ERG* ○ AML with *MNX1::ETV6* ○ AML with *NPM1::MLF1* Removed subtypes: • AML with mutated *RUNX1* • Acute panmyelosis with myelofibrosis	New subtypes: • AML with mutated *TP53* ○ Define a distinctly aggressive AML category, whether they present de novo, as progression of MDS, or as therapy-related disease. ○ Cytopenias not required. ○ Any somatic TP53 mutation (VAF >10%). • APL with other RARA rearrangements ○ t(1;17)(q42.3;q21.2)/*IRF2BP2::RARA* ○ t(5;17)(q35.1;q21.2)/*NPM1::RARA* ○ t(11;17)(q23.2;q21.2)/*ZBTB16::RARA* ○ cryptic inv(17q) or del(17)(q21.2q21.2)/*STAT5B::RARA, STAT3::RARA* ○ Other genes rarely rearranged with RARA: ○ *TBL1XR1* (3q26.3), *FIP1L1* (4q12), *BCOR* (Xp11.4) • AML with other KMT2A rearrangements ○ t(4;11)(q21.3;q23.3)/*AFF1::KMT2A* ○ t(6;11)(q27;q23.3)/*AFDN::KMT2A* ○ t(10;11)(p12.3;q23.3)/*MLLT10::KMT2A* ○ t(10;11)(q21.3;q23.3)/*TET1::KMT2A* ○ t(11;19)(q23.3;p13.1)/*KMT2A::ELL* ○ t(11;19)(q23.3;p13.3)/*KMT2A::MLLT1* • AML with other MECOM rearrangements ○ t(2;3)(p11∼23;q26.2)/*MECOM::?* ○ t(3;8)(q26.2;q24.2)/*MYC, MECOM* ○ t(3;12)(q26.2;p13.2)/*ETV6::MECOM* ○ t(3;21)(q26.2;q22.1)/*MECOM::RUNX* • AML with other rare recurring translocations ○ AML with t(11;12)(p15.4;p13.3)/*NUP98::KMD5A* ○ AML with t(5;11)(q35.2;p15.4/*NUP98::NSD1* ○ AML with NUP98 and other partners ○ AML with t(1;3)(p36.3;q21.3)/*PRDM16::RPN1*

		○ AML with t(3;5)(q25.3;q35.1)/*NPM1::MLF1* ○ AML with t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* ○ AML (megakaryoblastic) with t(1;22)(p13.3;q13.1)/*RBM15::MRTF1* ○ AML with t(7;12)(q36.3;p13.2)/*ETV6::MNX1* ○ AML with t(10;11)(p12.3;q14.2)/*PICALM::MLLT10* ○ AML with t(16;21)(p11.2;q22.2)/*FUS::ERG* ○ AML with t(16;21)(q24.3;q22.1)/*RUNX1::CBFA2T3* ○ AML with inv(16)(p13.3q24.3)/*CBFA2T3::GLIS2* • The classification identifies prior therapy, antecedent myeloid neoplasms (MDS or MDS/MPN or MPN), or underlying germline genetic disorders as qualifiers to the diagnosis, rather than as specific disease categories. Diagnostic qualifier: • AML, therapy-related ○ Prior chemotherapy, radiotherapy, immune interventions. ○ e.g. AML with myelodysplasia-related cytogenetic abnormality, therapy-related. • AML, progressing from MDS ○ MDS should be confirmed by standard diagnostics. • AML, progressing from MDS/MPN ○ MDS/MPN should be confirmed by standard diagnostics. • AML, germline predisposition ○ e.g. AML with myelodysplasia-related gene mutation, germline *RUNX1* mutation.

	Myeloid neoplasm, secondary	
	○ Myeloid neoplasms that arise secondary to exposure to cytotoxic therapy or germline predisposition (new) are grouped in this category. ○ AML transformation of MPN is retained in the MPN category. ○ AML transformation of MDS and MDS/MPN is kept under AML-MR. • Myeloid neoplasms post cytotoxic therapy (MN-pCT) • Myeloid neoplasms associated with germline predisposition • Myeloid proliferations associated with Down syndrome	
Myeloid neoplasms with germline predisposition and Paediatric and/or germline mutation-associated disorders		
The category is called: "Myeloid neoplasms with germline predisposition (MNGP)" Organisation: • **MNGP without a pre-existing disorder or organ dysfunction** • **MNGP and pre-existing platelet disorders** • **MNGP associated with other organ dysfunction** • **MNGP associated with inherited bone failure syndromes and telomere biology disorders** Subtypes: • **MNGP without a pre-existing disorder or organ dysfunction** ○ AML with germline *CEBPA* mutation	"Myeloid neoplasms with germline predisposition" is a subcategory of the **Myeloid neoplasms, secondary**. New organisation: • **MNGP without a pre-existing platelet disorder or organ dysfunction** • **MNGP and pre-existing platelet disorder** • **MNGP and potential organ dysfunction** Five new subtypes were added: • Germline *TP53* P/LP variant (Li-Fraumeni syndrome) was added to **MNGP without a pre-existing disorder** or organ dysfunction. • The following conditions are specified under **MNGP and potential organ dysfunction**: ○ RASopathies (Neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disorders)	The category is included in a group named "Paediatric and/or germline mutation-associated disorders" This group contains: • Juvenile myelomonocytic leukaemia ○ Diagnostic criteria refined. • Juvenile myelomonocytic leukaemia-like neoplasms ○ Clonal conditions that mimic JMML, but have an absence of RAS-pathway mutations. • Noonan syndrome-associated myeloproliferative disorder (new, specified as RASopathies in WHO-HAEM5) ○ These conditions are transient in the first year of life but may be indistinguishable from JMML. There are no acquired somatic mutations. • Refractory cytopenia of childhood

○ Myeloid neoplasms with germline *DDX41* mutation • **MNGP and pre-existing platelet disorders** ○ Myeloid neoplasms with germline *RUNX1* mutation ○ Myeloid neoplasms with germline *ANKRD26* mutation ○ Myeloid neoplasms with germline *ETV6* mutation • **MNGP associated with other organ dysfunction** ○ Myeloid neoplasms with germline *GATA2* mutation • **MNGP associated with inherited bone failure syndromes and telomere biology disorders**	○ Germline *SAMD9* P/LP variant: MIRAGE Syndrome ○ Germline *SAMD9L* P/LP variant: SAMD9L-related Ataxia ○ Biallelic germline *BLM* P/LP variant: Bloom syndrome The following three conditions were specified elsewhere and have now been specified under **MNGP and potential organ dysfunction**: • Bone marrow failure syndromes ○ Severe congenital neutropenia (SCN) ○ Shwachman-Diamond syndrome (SDS) ○ Fanconi anaemia (FA) - Distinguishes 5 haematologic categories depending on blast percentage cytopenia and chromosomal abnormalities. - Dysgranulopoiesis and dysmegakaryopoiesis are histologic indicators of progression. • Telomere biology disorders • Down syndrome P/LP: pathogenic/likely pathogenic	• **Hematologic neoplasms with germline predisposition (HNGP)** **HNGP** has a similar organisation: • **HNGP without a constitutional disorder affecting multiple organ systems** • **HNGP associated with a constitutional platelet disorder** • **HNGP associated with a constitutional disorder affecting multiple organ systems** • **Acute lymphoblastic leukaemia with germline predisposition** Three new subtypes were added: • Myeloid or lymphoid neoplasms with germline *TP53* mutation was added to **HNGP without a constitutional disorder affecting multiple organ systems**. • The following conditions were specified under **HNGP associated with a constitutional disorder affecting multiple organ systems**. • Myeloid neoplasms with germline *SAMD9* mutation. The following two conditions were specified elsewhere and have now been specified under **HNGP associated with a constitutional disorder affecting multiple organ systems**: • Myeloid neoplasms associated with bone marrow failure syndromes. • Myeloid or lymphoid neoplasms associated with Down Syndrome. Two conditions were recognised under the new category **Acute lymphoblastic leukaemia with germline predisposition**: • ALL with germline *PAX5* mutation

		• ALL with germline *IKZF1* mutation
Myeloid/lymphoid neoplasms with eosinophilia		
• Myeloid/lymphoid neoplasms with *PDGFRA*, *PDGFRB* and *FGFR1* rearrangement.	Modified subtypes: • Myeloid/lymphoid neoplasm with *JAK2* rearrangement. New subtypes: • Myeloid/lymphoid neoplasm with *FLT3* rearrangement • Myeloid/lymphoid neoplasm with *ETV6::ABL1* fusion • Myeloid/lymphoid neoplasms with other tyrosine kinase fusion genes ○ *ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; FGFR1OP::RET*	Modified subtypes: • Myeloid/lymphoid neoplasm with *JAK2* rearrangement. New subtypes: • Myeloid/lymphoid neoplasm with *FLT3* rearrangement • Myeloid/lymphoid neoplasm with *ETV6::ABL1*
Acute leukaemias of ambiguous lineage (ALAL) and mixed phenotype acute leukaemia (MPAL)		

	Two new subtypes:
	• MPAL with *ZNF384* rearrangement
	  ○ Commonly B/myeloid MPAL.
	  ○ Multiple partners, but similar transcriptional profile.
	  ○ *ZNF384*-rearranged B/myeloid MPAL and B-ALL have similar transcriptional profile.
	• ALAL with *BCL11B* rearrangement
	  ○ Seen in AUL and T/myeloid MPAL.
	  ○ Also seen in AML with minimal differentiation or without differentiation and ETP-ALL.
		Categories unchanged.
		
		Comment on subtypes not included in this section, but is included elsewhere:
		• *ZNF384*-rearranged leukaemia – discussed in the B-ALL section. Often myeloid antigen expression – insufficient to result in classification as MPAL or does meet B/myeloid MPAL. But treated as one entity because lineage may shift with disease evolution.
		• *ZNF362*-rearranged leukaemia has similar features.
		• *BCL11B* rearrangement – discussed in Early T-cell precursor ALL section.

Lineage assignment	Lineage assignment: emphasis on intensity of expression	

• Myeloid lineage:
  ○ MPO positive OR
  ○ Monocytic differentiation: ≥2 of: NSE, CD11c, CD14, CD64, lysozyme.
  ○ Using flow cytometry, ICH or cytochemistry.
• T-lineage:
  ○ cCD3 or sCD3.
  ○ Using flow cytometry to CD3ε chain or non-zeta chain IHC reagent.
• B-lineage:
  ○ CD19 + ≥1 of the following if CD19 is strongly expressed or ≥2 if CD19 is weakly expressed: CD79a, cCD22, CD10.
	• Myeloid lineage:
	  ○ MPO intensity exceeds 50% of mature neutrophil level.
	  ○ Monocytic differentiation remains the same.
	• T-lineage:
	  ○ CD3 intensity exceeds 50% of mature T-cell level by flow cytometry.
	  ○ IHC criteria remains the same.
	• B-lineage:
	  ○ Same criteria as WHO-HAEM4R, but emphasis that CD19 is considered strong if the intensity exceeds 50% of normal B-cell progenitors by flow cytometry.
	  ○ CD79a cannot be used if T-lineage is under consideration.	

Histiocytic and dendritic cell (DC) neoplasms		

Histiocytic and DC neoplasms consist of:
• Histiocytic sarcoma
• Langerhans cell histiocytosis
• Langerhans cell sarcoma
• Indeterminate DC tumour
• Interdigitating DC sarcoma
• Follicular DC sarcoma
• Inflammatory pseudo tumour-like
• follicular/fibroblastic DC sarcoma
• Fibroblastic reticular cell tumour
• Disseminated juvenile xanthogranuloma
• Erdheim-Chester disease
	The category is positioned to follow myeloid neoplasms in view of the close ontology.
	
	Recognition of convergence of pathways between this group of malignancies with activation of MAPK pathway.
	
	Neoplasms were organised into:
	• **Plasmacytoid DC neoplasms**
	• **Langerhans cell neoplasms**
	• **Other DC neoplasms**
	• **Histiocytic neoplasms**
	
	Two new subtypes (same as ICC):
	• ALK-positive histiocytosis
	  ○ Added to **Histiocytic neoplasms**.
		The category is found following the classification of Mature Lymphoid Neoplasms.
		Recognition of convergence of pathways between this group of malignancies with activation of MAPK pathway or PI3K pathway.
		
		No organisation of histiocytic and DC neoplasms
		Two new subtypes (same as WHO-HAEM5):
		• ALK-positive histiocytosis
		  ○ Mature histiocytic phenotype with foamy cytoplasm.
		• Rosai-Dorfman-Destombes (RDD) disease
		  ○ A subset of RDD is identified as neoplastic based on clonal genetic alternations.
		
		Naming convention changed for:
		• Indeterminate DC histiocytosis

	○ Presence of *ALK* gene translocations, commonly *KIF5B::ALK.* • Rosai-Dorfman-Destombes (RDD) disease ○ Added to **Histiocytic neoplasms**. ○ RDD with gain-of-function mutations in genes of MAPK pathway – indicate neoplastic process. Inclusion of **Plasmacytoid DC neoplasms** in this category (only in WHO-HAEM5): • Mature plasmacytoid DC proliferation associated with myeloid neoplasm (new) ○ Seen in CMML with activating RAS pathway mutations. ○ Seen in AML frequently with *RUNX1* mutations. • Blastic plasmacytoid DC neoplasm Removal of two subtypes from this category to be included in "stromal-derived neoplasms of lymphoid tissues": • Follicular DC sarcoma • Fibroblastic reticular cell tumour	○ Histiocytosis is preferred over tumour. • Fibroblastic reticular cell sarcoma ○ Sarcoma is preferred over tumour. • EBV–positive inflammatory follicular DC/fibroblastic reticular cell tumour ○ EBV added to the name. ○ Tumour is preferred over sarcoma, because of the indolent nature. Unchanged: • Blastic plasmacytoid DC neoplasm. • Follicular DC sarcoma and Fibroblastic reticular cell sarcoma.
Tumour-like lesions with B-cell predominance		
	• Included as a new category. • Subtypes: ○ **Reactive B-cell rich lymphoid proliferations that can mimic lymphoma** ○ **IgG4-related disease** ○ **Unicentric Castleman disease** ○ **Idiopathic multicentric Castleman disease** ○ **KSHV/HHV8-associated multicentric Castleman disease**	

Mature B-cell neoplasms		
• Organisation: ○ Hodgkin Lymphoma includes both classical and nodular lymphocyte predominant. ○ *Hodgkin Lymphoma* and *Immunodeficiency associated lymphoproliferative disorders* are in a separate category to Mature B-cell neoplasms. ○ Mature B-cell neoplasms are listed without sub-organisation. ○ Plasma cell neoplasms are included in the mature B-cell neoplasms.	• Organisation: ○ Mature B-cell neoplasms have organisational structure. *Hodgkin Lymphoma* and *Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation* are sub-categories of Mature B-cell neoplasms. ○ *Plasma cell neoplasms and diseases with paraproteins* are a separate category to Mature B-cell neoplasms. • Categories for organisation within Mature B-cell neoplasms: ○ **Pre-neoplastic and neoplastic small lymphoproliferations** ○ **Splenic B-cell lymphomas and leukaemias** ○ **Lymphoplasmacytic lymphoma** ○ **Marginal zone lymphoma** ○ **Follicular lymphoma** ○ **Mantle cell lymphoma** ○ **Transformations of indolent B-cell lymphomas** ○ **Large B-cell lymphomas** ○ **Burkitt lymphoma** ○ **KSHV/HHV8 associated B-cell lymphoid proliferations and lymphomas** ○ **Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation** ○ **Hodgkin Lymphoma** New subtypes: • Transformations of indolent B-cell lymphomas • Splenic B-cell lymphoma/leukaemia with prominent nucleoli	• Organisation: ○ *Classical Hodgkin Lymphoma* (but not NLP-HL) and *Immunodeficiency associated lymphoproliferative disorders* are in a separate category to Mature B-cell neoplasms. ○ Mature B-cell neoplasms are listed with little organisation. ○ Plasma cell neoplasms are included in the mature B-cell neoplasms. • Classification of multiple myeloma (plasma cell myeloma) into: ○ Multiple myeloma, NOS ○ Multiple myeloma (MM) with recurrent genetic abnormalities ➢ MM with *CCND* family translocation ➢ MM with *MAF* family translocation ➢ MM with *NSD2* translocation ➢ MM with hyperdiploidy New subtypes: • Primary cutaneous marginal zone lymphoproliferative disease • Testicular lymphoma • EBV-positive polymorphic B-cell lymphoproliferative disorder, NOS • Primary LBCL of testis (new entity) • HGBCL with *MYC* and *BCL6* rearrangements (provisional entity) • DLBCL or HGBCL with expression of TdT • Primary cold agglutinin disease

	○ Encompasses hairy cell leukaemia variant and some cases of B-cell prolymphocytic leukaemia. • Primary cutaneous marginal zone lymphoma • Primary large B-cell lymphoma (LBCL) of immune-privileged sites ○ Includes primary LBCL of the CNS and also Primary LBCL of testis and Primary LBCL of the vitreoretinal. • Fluid overload-associated LBCL • DLBCL or HGBCL with *MYC* and *BCL2* rearrangement with expression of TdT is a subtype of DLBCL/HG-BCL with *MYC* and *BCL2* rearrangement • Cold agglutinin disease • Monoclonal gammopathy of renal significance Removed subtypes: • B-cell prolymphocytic leukaemia • Testicular follicular lymphoma Renamed subtypes: • High-grade B-cell lymphoma with 11q aberrations (changed from Burkitt-like lymphoma with 11q aberration). • EBV+ DLBCL. • Mediastinal grey zone lymphoma (changed from *B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma*). • Diffuse large B-cell lymphoma/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements. • KSHV/HHV8-positive diffuse large B-cell lymphoma. • Immunoglobulin-related (AL) amyloidosis.	• Primary cutaneous marginal zone lymphoproliferative disorder • EBV-positive polymorphic B-cell lymphoproliferative disorder, NOS • Provisional entity: BCL2-R-negative, CD23-positive follicle centre lymphoma • Provisional entity: HHV8- and EBV-negative primary effusion-based lymphoma Renamed subtypes: • LBCL with 11q aberrations. • Mediastinal grey zone lymphoma. • HGBCL with *MYC* and *BCL2* rearrangements (with or without *BCL6* rearrangement. • Primary effusion lymphoma (PEL) and extracavitary primary effusion lymphoma . • Immunoglobulin light chain amyloidosis (AL). Expanded subtypes: IgM MGUS subtyped into *IgM MGUS, plasma cell type* and *IgM MGUS, NOS.*

	Expanded subtypes: • Lymphoplasmacytic lymphoma subtyped into IgM-LPL/Walderstrom macroglobulinaemia and non-IgM-LPL/Walderstrom macroglobulinaemia. • Fibrin-associated LBCL.	
Hodgkin Lymphoma		**Classic Hodgkin Lymphoma**
• Both classical Hodgkin Lymphoma and Nodular-lymphocyte predominant Hodgkin Lymphoma (NLPHL).		• The four morphological subtypes of classical Hodgkin Lymphoma. • NLPHL part of Mature B-cell Lymphoma.
	Plasma cell neoplasms and other diseases with paraproteins	
	Categories for organisation within Mature B-cell neoplasms: • **Monoclonal gammopathies** • **Diseases with monoclonal immunoglobulin deposition** • **Heavy chain diseases** • **Plasma cell neoplasms** New subtype: • AESOP syndrome (Adenopathy and Extensive Skin patch Overlying a Plasmacytoma)	
Precursor Lymphoid Neoplasms	**B-lymphoblastic lymphoma/leukaemia (B-ALL)**	

• B-ALL and T-ALL are part of the category **Precursor Lymphoid Neoplasms.**
• Nomenclature: Subtypes of B-ALL with balanced translocations/inversions are described using cytogenetics and gene fusion.
• Gene fusions are separated by a -
• Subcategories are:
  ○ **B-ALL, NOS**
  ○ **B-ALL with recurrent genetic abnormalities**
	• B-ALL is in its own category separate from T-ALL.
	• Nomenclature: Subtypes of B-ALL with balanced translocations/inversions are described using gene fusion.
	• Gene fusions are separated by a ::
	• Subcategories are:
	  ○ **B-ALL, NOS**
	  ○ **B-ALL with defining genetic abnormalities**
		• B-ALL is in its own category separate from T-ALL.
		• Nomenclature: Subtypes of B-ALL with balanced translocations/inversions are described using cytogenetics and gene fusion.
		• Gene fusions are separated by a ::
		• Subcategories are:
		  ○ **B-ALL, NOS**
		  ○ **B-ALL with recurrent genetic abnormalities**

○ **T-ALL** - One subcategory: **Early T-cell Precursor lymphoblastic leukaemia/lymphoma (ETP-ALL)** ○ **NK-ALL**	New subtypes: • B-ALL with *ETV6::RUNX1*-like features ○ Enriched with ETV6 fusions including: *IKZF1:ETV6* and *ETV6:ELMO1.* • B-ALL with *TCF3::HLF* fusion. Clarified subtype: • B-ALL with high hyperdiploid	New subtypes: • B-ALL with *MYC* rearrangement ○ Poor prognosis. • B-ALL with *DUX4* rearrangement ○ Very good prognosis • B-ALL with *MEF2D* rearrangement ○ Poor prognosis. • B-ALL with *NUTM1* rearrangement ○ Good prognosis. • B-ALL with *ZNF384*(*362*) rearrangement • B-ALL with *HLF* rearrangement ○ Very poor prognosis • B-ALL with *UBTF::ATXN7L3/PAN3,CDX2* • B-ALL with mutated *IKZF1* N159Y • B-ALL with mutated *PAX5* P80R • Provisional entity: B-ALL, *ETV6::RUNX1*-like • Provisional entity: B-ALL, with *PAX5* alteration • Provisional entity: B-ALL, with mutated *ZEB2* (p.H1038R)/IGH::CEBPE • Provisional entity: B-ALL, *ZNF384* rearranged-like • Provisional entity: B-ALL, *KMT2A* rearranged-like Expanded subtypes: • B-ALL with hypodiploidy is divided into B-ALL, low hypodiploid and B-ALL, near haploid. • B-ALL with t(9;22)/*BCR::ABL1* is divided into those with lymphoid involvement only and those with multilineage involvement.. • B-ALL, *BCR::ABL1*-like is divided into ABL1-class rearranged, JAK-STAT activated and NOS.

	T-lymphoblastic leukaemia/lymphoma(T-ALL)	
	• T-ALL is in its own category separate from B-ALL. Modified: • T-ALL, NOS – addition of NOS if does not meet criteria for ETP-ALL.	• T-ALL is in its own category separate from B-ALL. New subtype: • Early T-cell precursor ALL with *BCL11B* rearrangement. Modified: • T-ALL, NOS – addition of NOS if does not meet criteria for other subtypes.
Tumour-like lesions with T-cell predominance		

	• Included as a new category.
	• Three entities:
	  ○ **Kikuchi-Fujimoto disease**
	  ○ **Indolent T-lymphoblastic proliferation Autoimmune lymphoproliferative syndrome**	

Mature T-cell and NK-cell Neoplasms		

The following categories/organisation:
• T-cell prolymphocytic leukaemia
• T-cell large granular lymphocytic (LGL) leukaemia
• Chronic lymphoproliferative disorder of NK cells
• Aggressive NK-cell leukaemia
• EBV-positive T-cell and NK-cell LPDs of childhood
• Adult T-cell leukaemia/lymphoma (ATLL)
• Extranodal NK/T-cell lymphoma, nasal type
• Intestinal T-cell lymphoma
• Hepatosplenic T-cell lymphoma
• Subpanniculitis-like T-cell LPDs
• Mycosis fungoides
• Sezary syndrome
	Organisation change:
	• Mature T-cell and NK-cell leukaemias
	This includes:
	  ○ T-prolymphocytic leukaemia
	  ○ T-LGL leukaemia
	  ○ NK-LGL leukaemia
	  ○ ATLL
	  ○ Sezary syndrome
	  ○ Aggressive NK-cell leukaemia
	• Anaplastic large cell lymphoma is a subcategory.
	• Nodal T-follicular helper (TFH) cell lymphoma
	  ○ New category that includes angioimmunoblastic T-cell lymphoma as a subtype.
	  ○ The three subtypes are:
		New subtypes:
		• Follicular helper T-cell (FHT) cell lymphoma
		  ○ New category and three with slight difference of name: *FHT* instead of *nodal TFH*
		• Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
		• Primary nodal EBV-positive T-cell/NK-cell lymphoma
		
		Modified:
		• Primary cutaneous acral CD8+ lymphoproliferative disorder: .
		• Chronic active EBV disease, systemic (T-cell and NK-cell phenotypes).

• Primary cutaneous T-cell lymphomas • Peripheral T-cell lymphoma, NOS • Angioimmunoblastic T-cell lymphoma • Anaplastic large cell lymphoma, ALK-positive • Anaplastic large cell lymphoma, ALK-negative • Breast-implant associated anaplastic large cell lymphoma	➢ Nodal TFH cell lymphoma, angioimmunoblastic-type ➢ Nodal TFH cell lymphoma, follicular-type ➢ Nodal TFH cell lymphoma, NOS . New subtypes: • Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract. • EBV positive nodal T- and NK-cell lymphoma • Primary cutaneous peripheral T-cell lymphoma, NOS – added if criteria for other categories are not met. Modified: • Primary cutaneous acral CD8+ lymphoproliferative disorder: . • Indolent T-cell lymphoma of the gastrointestinal tract. • Extranodal NK/T-cell lymphoma. . • Systemic chronic active EBV disease.	
Genetic predisposition syndromes in lymphoid neoplasms		
	• Included as a new category. • Two entities: ○ **Ataxic telangiectasia** ○ **Nijmegen-breakage syndrome**	
Stroma-derived neoplasms of lymphoid tissue		
	• Included as a new category. Entities moved from dendritic cell neoplasms: • Follicular dendritic cell sarcoma • EBV-positive inflammatory follicular dendritic cell sarcoma • Fibroblastic reticular cell tumour	

	New entities: • Intranodal palisaded myofibroblastoma • Littoral cell angioma • Splenic hamartoma • Sclerosing angiomatoid nodular transformation of spleen	