State of Hematopathology:

The past, present and the future

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Disclosures

- None

Agenda

Evolution of hematopathology

And then there were 2 classifications…

Integrated reporting

Evolution of hematopathology

A brief history of hematopathology classification

Clinical Morphology

- 1860s: Virchow and Cohnheim: lymphosarcoma
- 1920s: Oberling and Brill and Symmers: “reticulum cell sarcoma” and giant follicular lymphoma.
- 1950s and 1960s: Rappaport, Winter, Hicks,: based on architectural organization and cell size.

Clinical Morphology Immunophenotype

- 1974: Lukes and Collins’ classifications: B or T, site of origin, cell size, and nuclear shape
- 1974: Kiel classification: tumour grade; centrocytic, centroblastic and immunoblastic
- 1974: British National Lymphoma Investigation (BNLI) classification
- 1978: NCI working formulation: low- and high-grade groups, an intermediate grade.
- 1994: Stein and Isaacson: Revised European-American Lymphoma (REAL) classification

Clinical Morphology Microbes Immunophenotype Genetics

- 2001: World Health Organization classifications of haematopoietic and lymphoid tissue tumours
- 2008: World Health Organization classifications of haematopoietic and lymphoid tissue tumours

Clinical Morphology Microbes Immunophenotype Genetics

- 2017: World Health Organization classifications of haematopoietic and lymphoid tissue tumours
- 2022: World Health Organization classifications of haematopoietic and lymphoid tissue tumours
- 2022: ICC

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- 1920s: Oberlin
- 1950s and 196

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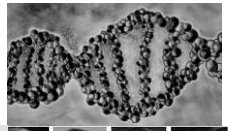
- 2022: ICC

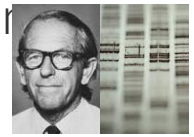
Greater importance of Genet
and molecular phenotyping

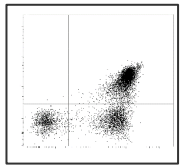
1950s: DNA discovered; Humans have 46 chromosomes

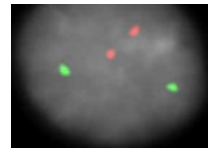


1960s: 1 color flow cytometry; simple IHC

1970s: Sanger sequencing; Q&C and G bandi
Improved IHC; Immuno-EM

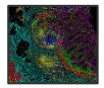






1980s: 4 color flow cytometry; PCR; interphase FISH
1990s: 8 color flow cytometry; CGH

2000s: Mass cytometry; Human genome sequenced; Roche 4
2010s: Imaging mass cytometry; 30+ color flow cytometry, Nanopore, Pacbio
"single molecular real-time" sequencer; Metagenomic



2020s: Artificial Intelligence and machine learning

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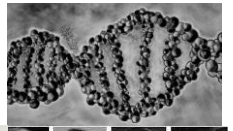
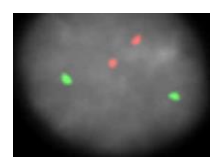
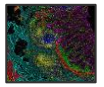
2020s: Artificial Intelligence and machine learning

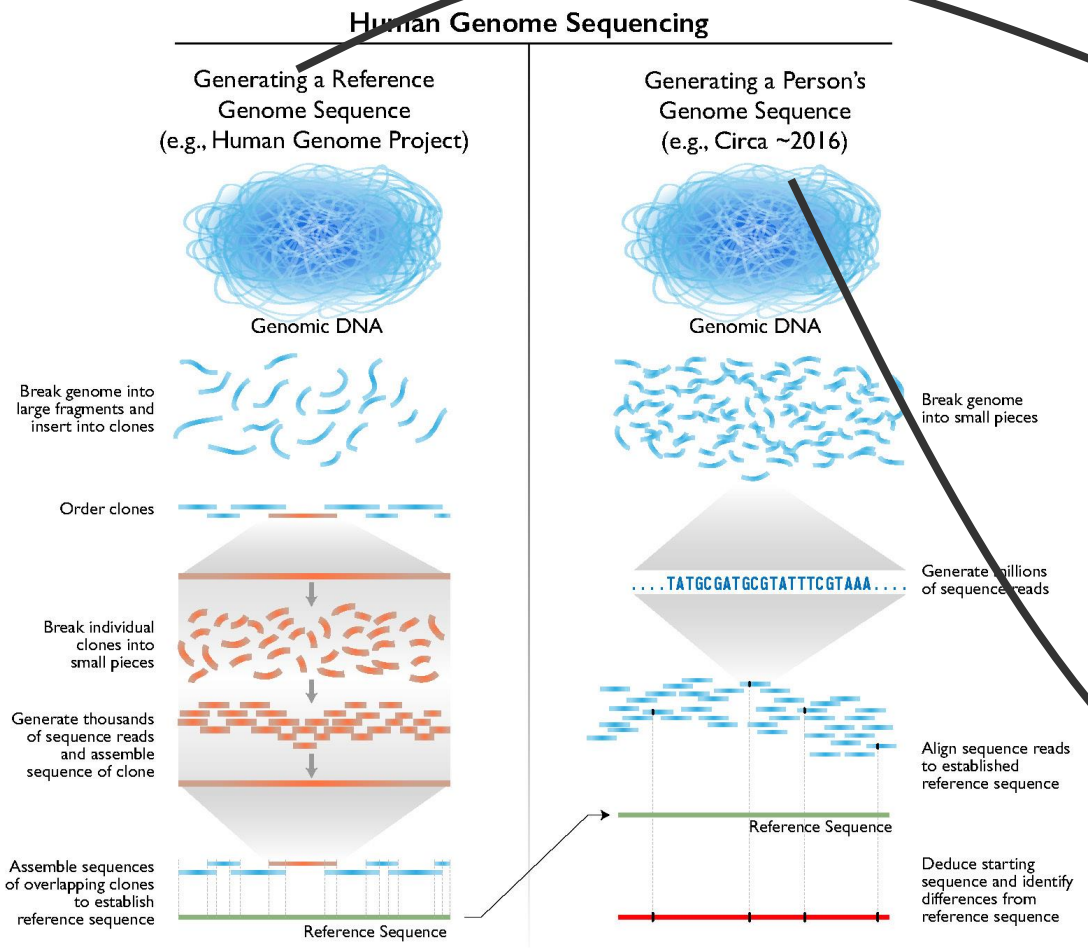
Technology Drives Medicine

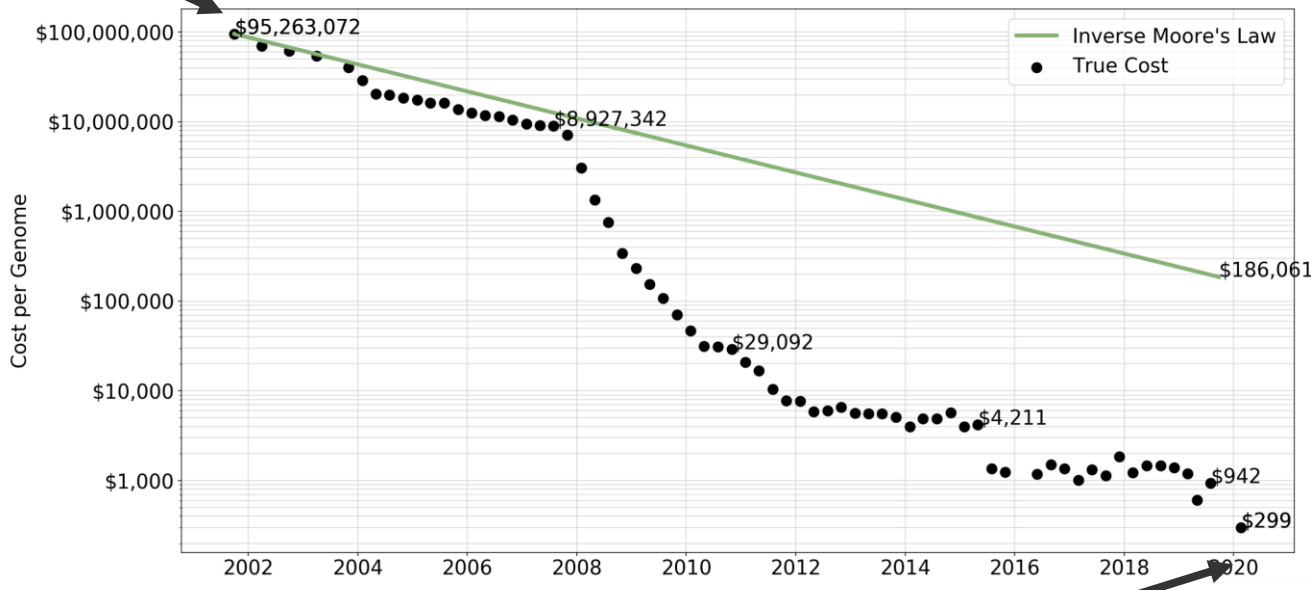





Whole genome sequencing





Whole Genome sequencing in AML

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Acute Myeloid Leukemia (Age ≥18 years)

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 3.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 2.2023 include:

MS-1

- The BPDCN section of the discussion has been updated.

Updates in Version 2.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 1.2023 include:

AML-3

- Erratum: Re-induction for significant residual disease without a hypocellular BM, regimen added back after inadvertent removal: 7+3 (mitoxantrone) (for age ≥60 y)
- Erratum: Re-induction for significant cytoreduction, regimen added back after inadvertent removal: 7+3 (mitoxantrone) (for age ≥60 y)

AML-E 1 of 9

- Erratum: FLAG-IDA + venetoclax regimen: HiDAC dosing modified from 2 g/m^2 to 1.5 g/m^2

Updates in Version 1.2023 of the NCCN Guidelines for Acute Myeloid Leukemia from Version 3.2022 include:

Global

- Terminologies modified to be more inclusive, including of all sexual orientations and gender identities.

EVAL-1

- Evaluation, bullet 5 modified: Bone marrow (BM) core biopsy and aspirate analyses, including immunophenotyping by immunohistochemistry (IHC) stains + flow cytometry, and ~~cytogenetic analyses (karyotype + FISH)~~ the analysis of chromosomal structural variations by cytogenetics, fluorescence in situ hybridization (FISH), or whole genome sequencing (See AML-A)

EVAL-1 2

- Footnote a modified: A variety of genetic lesions are associated with specific prognoses (category 2A) and may guide medical decision-making (category 2B). Other genetic lesions may have therapeutic significance. The field of genomics in myeloid malignancies and related implications in AML are evolving rapidly. Mutations should be tested in all patients. Multiplex gene panels and ~~comprehensive~~ targeted next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. (Papaemmanuil E, et al. N Engl J Med 2016;374:2209-2221; Lindsley RC, et al. Blood 2015;125:1367-1376; Dohner H, et al. Blood 2017;129:424-447) (see Discussion). If a test is not available at your institution, consult the pathology team (prior to performing the BM evaluation) about preserving material from the original diagnostic sample for future testing at an outside reference lab. Peripheral blood may alternatively be used to detect molecular abnormalities in patients with disease with morphologically detectable, circulating leukemic blasts.
- Footnote removed: The WHO 2016 classification defines acute leukemia as ≥20% blasts in the marrow or blood. In an appropriate clinical setting, a diagnosis of AML may be made with less than 20% in patients with the following cytogenetic abnormalities: t(15;17), t(8;21), t(16;16), inv(16). AML evolving from MDS (AML-MDS) is often more resistant to cytotoxic chemotherapy than AML that arises without antecedent hematologic disorder and may have a more indolent course. Some clinical trials designed for highgrade MDS may allow enrollment of patients with AML-MDS.
- Footnotes added:
  - d: Khoury JD, et al. Leukemia 2022;36:1703-1719.
  - j:Arber DA, et al. Blood 2022;140:1200-1228.
  - i: Kim K, et al. Am J Hematol. 2022;97:885-894.

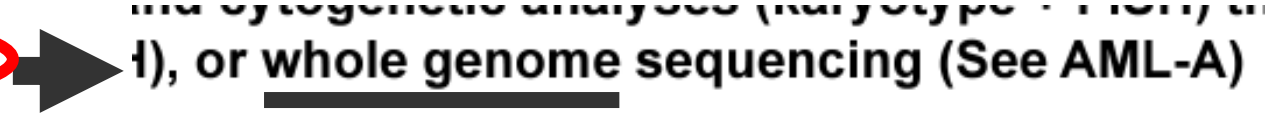
Acute Promyelocytic Leukemia

APL-1

- Footnote a modified: Therapy-related APL is treated the same as de novo APL. FLT3 inhibitors are not recommended for FLT3-positive APL. Gale RE, et al. Blood 2005;106:3768-3776.

Continued

UPDATES



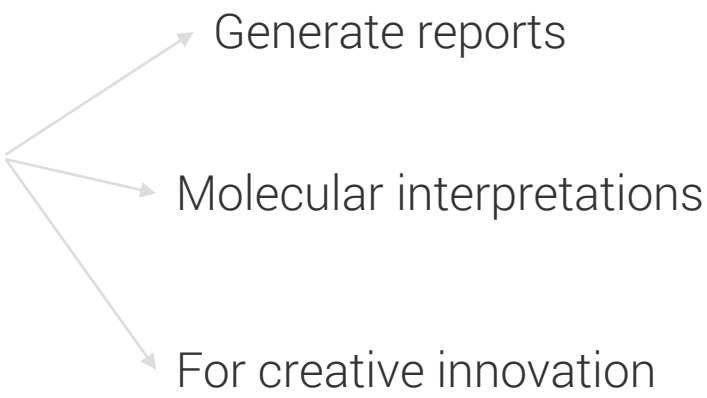
The Future is Now with AI

ChatGPT

Examples	Capabilities	Limitations
"Explain quantum computing in simple terms" →	Remembers what user said earlier in the conversation	May occasionally generate incorrect information
"Got any creative ideas for a 10 year old's birthday?" →	Allows user to provide follow-up corrections	May occasionally produce harmful instructions or biased content
"How do I make an HTTP request in Javascript?" →	Trained to decline inappropriate requests	Limited knowledge of world and events after 2021

Applied Artificial Intelligence

- Humans using and APPLYING artificial intelligence (AI) to work
- Example: NGS pipelines which filter and use decision tree analyses are under the larger umbrella of “AI”
- AI will need to help analyze singular data (molecular, digital, clinical, immunohistochemistry…)
- Human integration of applied AI (deeper subtle analyses) will be critical



The WHO and the ICC:

A story of 2 classifications

WHO/IARC Revised 4th edition

WHO/IARC 5th edition

1. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022 Jul;36(7):1720-1748.

2. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719.

International consensus classification

- **CAC-clinical advisory committee**
- **EAHP & SH ended their association with IARC**

1. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022 Sep 15;140(11):1200-1228

2. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood. 2022 Sep 15;140(11):1229-1253.

3. Guide to the Diagnosis of Myeloid Neoplasms. A Bone Marrow Pathology Group Approach. Am J Clin Pathol 2023.

Myeloid Neoplasms

Chronic Myeloid Neoplasms

WHO REVISED 4th EDITION	WHO 5th EDITION	ICC
Myeloproliferative Neoplasms		
Chronic myeloid leukemia, *BCR-ABL1* positive • Chronic phase • Accelerated phase • Blast phase	Chronic myeloid leukemia • Chronic phase • Omits accelerated phase but defines high risk features in chronic phase • Blast phase	Chronic myeloid leukemia • Chronic phase • Accelerated phase • Blast phase
Chronic neutrophilic leukemia	Chronic neutrophilic leukemia	Chronic neutrophilic leukemia • WBC ≥ $13x10^9$/L if *CSF3R* present • WBC ≥ $25x10^9$/L if *CSF3R not* present
Polycythemia vera	Polycythemia vera	Polycythemia vera
Primary myelofibrosis (PMF) • Prefibrotic/early PMF • Overt PMF	Primary myelofibrosis (PMF) • Prefibrotic PMF • Fibrotic PMF	Primary myelofibrosis (PMF) • PMF, early/prefibrotic stage (prePMF) • PMF, overt fibrotic stage
Essential thrombocythemia (ET)	Essential thrombocythemia (ET)	Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified	Chronic eosinophilic leukemia	Chronic eosinophilic leukemia, not otherwise specified
Myeloproliferative neoplasm, unclassifiable	Myeloproliferative neoplasm, not otherwise specified (NOS)	Myeloproliferative neoplasm, unclassifiable
JMML classified with MDS/MPN	Juvenile myelomonocytic leukemia (JMML) classified as a Myeloproliferative Neoplasm	JMML classified with Pediatric Disorders and/or Germline Mutation-Associated Disorders

- JMML- requires *RAS* pathway (mutations in *NF1, PTPN11, NRAS, KRAS, CBL*) etc.
- JMML like-Absence of *RAS* pathway mutations (ICC)

Mastocytosis

Systemic Mastocytosis Diagnostic Criteria 2022

Major	Multifocal dense aggregates of mast cells*
Minor	1. >25% mast cells with atypical morphology 2. *KIT* D816V or other activating *KIT* mutation 3. CD2, CD25 or CD30 expression on mast cells 4. Serum total tryptase >20 ng/mL ** (unless associated myeloid disorder)

*1 major + 1 minor OR 3 minor criteria per WHO;1 major OR 3 minor criteria per ICC.
**Adjust for HαT per WHO.

WHO REVISED 4th EDITION	WHO 5th EDITION	ICC
Indolent systemic mastocytosis (SM)	Indolent SM	Indolent SM • Bone marrow mastocytosis
Bone marrow mastocytosis	Bone marrow mastocytosis	
Smoldering SM	Smoldering SM*	Smoldering SM
SM with an associated hematological neoplasm (SM-AHN)	SM with an associated hematological neoplasm (SM-AHN)	SM with an associated myeloid neoplasm (AM-AMN)
Aggressive SM	Aggressive SM	Aggressive SM
Mast cell leukemia	Mast cell leukemia • ≥20% mast cells on BM aspirate	Mast cell leukemia • ≥20% atypical immature mast cells on BM aspirate smears • If inadequate BM aspirate smear, can be diagnosed on BM biopsy

*Additional B-finding: *KIT* D816V with VAF 10% or greater per WHO 5th Edition

Clonal hematopoiesis and cytopenia

Clonal hematopoiesis and cytopenias

WHO 4th Ed.	WHO 5th Ed.	ICC
Idiopathic cytopenia of undetermined significance (ICUS)	Not included	Not included
Not included	Clonal cytopenias of undetermined significance (CCUS)	Clonal cytopenia of undetermined significance (CCUS)
Clonal hematopoiesis of indeterminate potential (CHIP)	Clonal hematopoiesis	Clonal hematopoiesis of indeterminate potential (CHIP)
Not included	Not included	Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome

Clonal hematopoiesis and cytopenias

ICC	WHO		CYTOPENIA	DYSPLASIA	
+	+	**CHIP** (Clonal hematopoiesis of undetermined significance)	-	-	≥1 mutation at ≥2% VAF
+	+	**CCUS** (Clonal cytopenia of undetermined significance)	+	-	• 4 mths cytopenia • No corbid condition to explain cytopenia
+	-	CMUS (ICC) (Clonal monocytosis of undetermined significance)	-	-	• Unexplained monocytosis (Persistent monocytosis ≥10% and ≥0.5x10 ^{9} /L WBC
+	-	CCMUS (ICC) (Clonal cytopenia and monocytosis of undetermined significance)	+	-	• Unexplained monocytosis • cytopenia
+	-	VEXAS (**V**acuoles, **E**1 ubiquitin enzyme, **X**-chromosome UBA1 gene, **A**utoinflammation, **S**omatic)	+	**vacuoles**	• Anemia • CH • Autoimmune • UBA1 mutation

Cytopenia definitions (CCUS, CCMUS, MDS, and MDS/MPN):

1. Hb <13 g/dL in males and <12 g/dL in females
2. Absolute neutrophil count <1.8 ×10^9/L
3. Platelets<150 × 10^9/L

Myelodysplastic syndrome/neoplasms (MDS)

Myeloid neoplasms with mutated TP53

ICC

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

WHO

MDS with biallelic *TP53* inactivation (MDS-bi*TP*53)	Any	<20% BM and PB <30% erythroblasts	An exact VAF not defined Evidence of cnLOH or loss of TP53 locus

<u>Definition of TP53 mutation</u>:

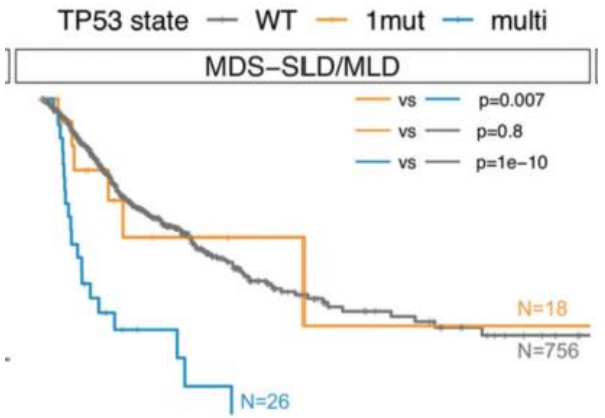
1) **2** distinct TP53 mutations (each VAF >10%) **OR**

2) **Single** TP53 mutation with

(a) 17p del on cytogenetics or complex

(b) VAF >50%; or

(c) Copy-neutral LOH at 17p TP53 locus



Monoallelic patients (MDS with low blasts) did not differ from TP53 WT patients in outcomes and response to therapy

Bernard, 2020, Nat Med

MDS with increased blasts

- ICC introduces concept of MDS/AML (10-19% blasts)

WHO Revised 4th Edition	WHO 5th Edition	ICC
MDS with excess blasts (EB) • **MDS-EB-1** • **MDS-EB-2**	MDS with increased blasts (MDS-IB) • MDS with increased blasts-1 (MDS-IB1) 5-9% BM or 2-4% PB • MDS with increased blasts-2 (MDS-IB2) 10-19% BM or 5-19% PB • MDS with increased blasts and fibrosis (MDS-F) 5-19% BM or 2-19% PB	• MDS with excess blasts (EB) 5-9% BM or 2-9% PB • MDS/AML (adults only) 10-19% BM or PB

MDS

WHO Revised 4th Edition	WHO 5th Edition	ICC
MDS with single lineage dysplasia **MDS with multilineage dysplasia**	MDS with low blasts (single vs. multilineage optional)	MDS, NOS • MDS, NOS with single lineage dysplasia • MDS, NOS with multilineage dysplasia • MDS, NOS without dysplasia ➢ Cytopenias ➢ +/-7, del(7q) or complex cytogenetics ➢ Excludes multihit *TP53*
Not included	MDS, hypoplastic (MDS-h)	• Not included

MDS

WHO Revised 4th Edition	WHO 5th Edition	ICC
MDS with ring sideroblasts (RS) • **MDS-RS-SLD** • **MDS-RS-MLD**	• MDS with **low blasts** and *SF3B1* mutation (MDS-SF3B1) (**≥ 5%** VAF) • MDS with low blasts and RS ➢ no *SF3B1* mutation ➢ ≥15% RS	MDS with mutated *SF3B1* **(≥ 10% VAF)**
MDS with isolated del(5q)	MDS with **low blasts** and 5q deletion (MDS-5q)	MDS with del(5q)

- ICC allows for these diagnoses without dysplasia while WHO requires dysplasia

ICC

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics†	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex	*SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1	Thrombocytosis allowed	<5% BM <2% PB§	del(5q), with up to 1 additional, except −7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS without dysplasia	0	≥1	0	<5% BM <2% PB§	−7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF)
MDS, NOS with single lineage dysplasia	1	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥1	0	5-9% BM, 2-9% PB§	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1‡	≥1	0	10-19% BM or PB‖	Any, except AML-defining¶	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

*Cytoses: Sustained white blood count ≥ 13 × 10^9/L, monocytosis (≥0.5 × 10^9/L and ≥10% of leukocytes) or platelets ≥450 × 10^9/L; thrombocytosis is allowed in MDS-del(5q) or in any MDS case with inv(3) or t(3;3) cytogenetic abnormality.

†*BCR*::*ABL1* rearrangement or any of the rearrangements associated with myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions exclude a diagnosis of MDS, even in the context of cytopenia.

‡Although dysplasia is typically present in these entities, it is not required.

§Although 2% PB blasts mandates classification of an MDS case as MDS-EB, the presence of 1% PB blasts confirmed on 2 separate occasions also qualifies for MDS-EB.

‖For pediatric patients (<18 y), the blast thresholds for MDS-EB are 5% to 19% in BM and 2% to 19% in PB, and the entity MDS/AML does not apply.

¶AML-defining cytogenetics are listed in the AML section.

MDS/MPN

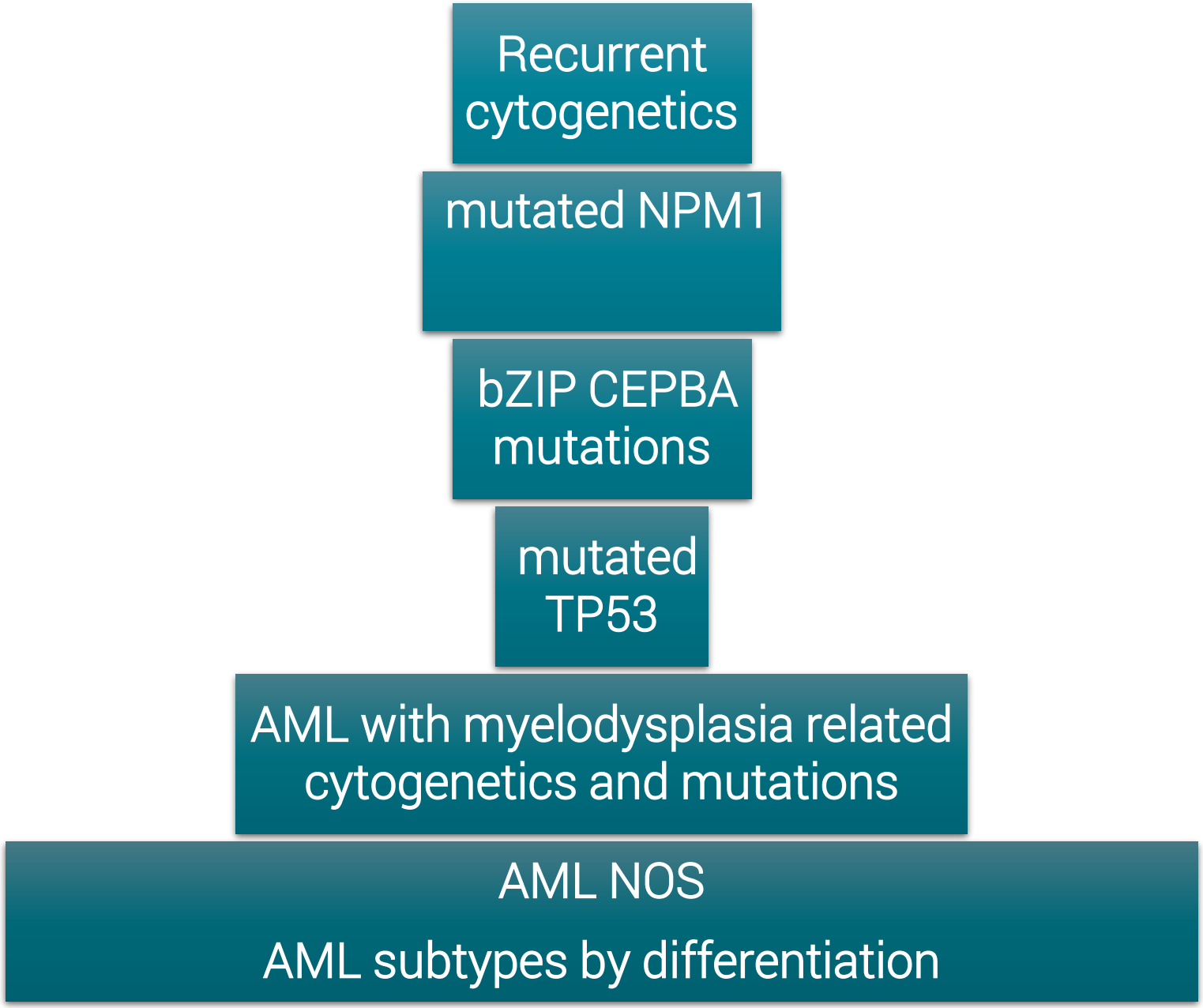
WHO REVISED 4th EDITION	WHO 5th EDITION	ICC
Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN)		
Chronic myelomonocytic leukemia (CMML) • CMML-0 • CMML-1 • CMML-2	Chronic myelomonocytic leukemia (CMML1) • Subtypes ○ Myelodysplastic CMML (MD-CMML) ○ Myeloproliferative CMML (MP-CMML) • Subgroups ○ CMML-1 ○ CMML-2	Chronic myelomonocytic leukemia (CMML) • CMML-1 • CMML-2
Atypical chronic myeloid leukemia, *BCR-ABL1* negative	MDS/MPN with neutrophilia	Atypical chronic myeloid leukemia
Juvenile myelomonocytic leukemia (JMML)	JMML classified with MPN	JMML classified with Pediatric Disorders and/or Germline Mutation-Associated Disorders
MDS/MPN with ring sideroblasts and thrombocytosis	MDS/MPN with *SF3B1* and thrombocytosis	• MDS/MPN with thrombocytosis and SF3B1 mutation • MDS/MPN with ring sideroblasts and thrombocytosis, NOS
MDS/MPN, unclassifiable	MDS/MPN, NOS	MDS/MPN, NOS • MDS/MPN with isolated i(17q) (provisional)

CMML

- ICC and WHO: CMML-0 (blast count <2% PB, <5% BM) eliminated
- ICC and WHO: Threshold for CMML diagnosis is ≥0.5 x 10^9 /L and ≥10% monocytes
- ICC includes cytopenia in the criteria now (not included in WHO)
- ICC: cases lacking clonality, diagnosis possible if 1) persistent monocytosis 2) increased blasts (>2% PB, >5% BM) or dysplasia or abnormal immunophenotype
- Myeloproliferative type (≥13 x 10^9/L): adverse prognosis, (*RAS*, *JAK2* and *SETPB1* mutations)

Acute Myeloid Leukemia

WHO Revised 4th Edition	WHO 5th Edition	ICC
AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1	AML with RUNX1::RUNX1T1 fusion	AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 ≥10%
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	AML with CBFB::MYH11 fusion	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11 ≥10%
APL with PML-RARA	Acute promyelocytic leukemia (APL) with PML::RARA fusion	APL with t(15;17)(q24.1;q21.2)/PML::RARA ≥10%
Not included	Currently mentioned in text	APL with other RARA rearrangements[1] ≥10%
AML with t(9;11)(p21.3;q23.3); KMT2A-MLLT3	Included in AML with KMT2A rearrangement	AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A ≥10%
Not included	AML with KMT2A rearrangement	AML with other KMT2A rearrangements[2] ≥10%
AML with t(6;9)(p23;q34.1); DEK-NUP214	AML with DEK::NUP214 fusion	AML with t(6;9)(p22.3;q34.1)/DEK::NUP214 ≥10%
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM	Included in AML with MECOM rearrangement	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2; MECOM(EVI1) ≥10%
Mentioned in text	AML with MECOM rearrangement	AML with other MECOM rearrangements[3] ≥10%
AML with t(1;22)(p13.3;q13.1); RBM15-MKL1	AML with RBM15::MRTFA fusion	Included in AML with other rare recurring translocations ≥10%
AML with BCR-ABL 1	AML with BCR::ABL1 fusion (≥20% blasts)	AML with t(9;22)(q34.1;q11.2)/BCR::ABL1 ≥20% blasts
Not included	**AML with NUP98 rearrangement**	Included in AML with other rare recurring translocations ≥10%
Not included	**AML with other defined genetic alterations**	**AML with other rare recurring translocations**
AML with mutated NPM1	AML with NPM1 mutation	AML with mutated NPM1 ≥10%
AML with biallelic mutation of CEBPA	AML with **CEBPA mutation (both bZIP and biallelic) (>20% blast count)**	AML with **in-frame bZIP** CEBPA mutations ≥10%
AML with mutated RUNX1	**Not included**	**Not included**
Not included	Not included	**AML and MDS/AML with mutated TP53 10-19% (MDS/AML) and ≥ 20% (AML): at least one TP53 mutation with VAF >10%**



Diagnostic qualifiers

ICC

Prior history of therapy

Prior history of MDS or MDS/MPN

Germline predisposition

AML major updates

AML with defining genetic abnormalities

- ICC: 10% blast threshold for AMLs defined by translocations and mutations (*CEPBA* and *NPM1*)
- WHO: AML with CEPBA and BCR-ABL (only AMLs that require 20% blast count)
- ICC: 20% blast threshold for AML with *TP53* (10% for MDS/AML)
- ICC and WHO: 20% blast threshold for AML with *BCR::ABL1*

•AML based on differentiation

- ICC merged AML defined by differentiation markers into AML NOS
- WHO maintains AML subtyping based on differentiation

•AML with myelodysplasia-related changes has been replaced

- Morphologic dysplasia no longer a criteria
- ICC: AML (and AML/MDS) with myelodysplasia-related gene
- mutations and/or cytogenetic abnormalities
- WHO: AML, myelodysplasia-related

AML major updates

Therapy-related myeloid neoplasm:

- No longer a subtype
- ICC recommends using this as a diagnostic qualifier
- WHO has combined into one category "Secondary myeloid neoplasms" but recommends using as qualifer
  1) prior therapy (specify if its cytotoxic)
  2) germline predisposition

AML myelodysplasia related

ICC

WHO 4th Revised Edition

AML with myelodysplasia-related changes

AML with myelodysplasia-related gene mutations RUNX1

Defined by mutations in ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2

AML with myelodysplasia-related cytogenetic abnormalities +8 Del (20q)

Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities

AML not otherwise specified (AML NOS)

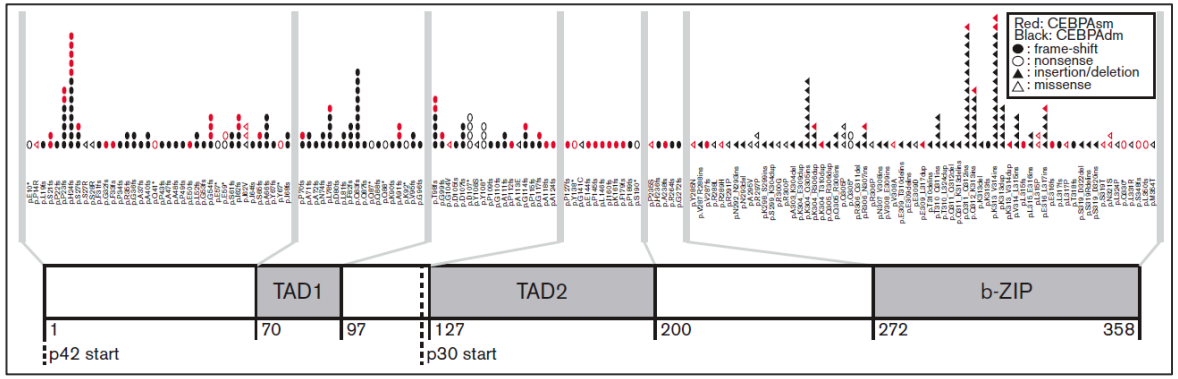
AML with mutated *TP53*

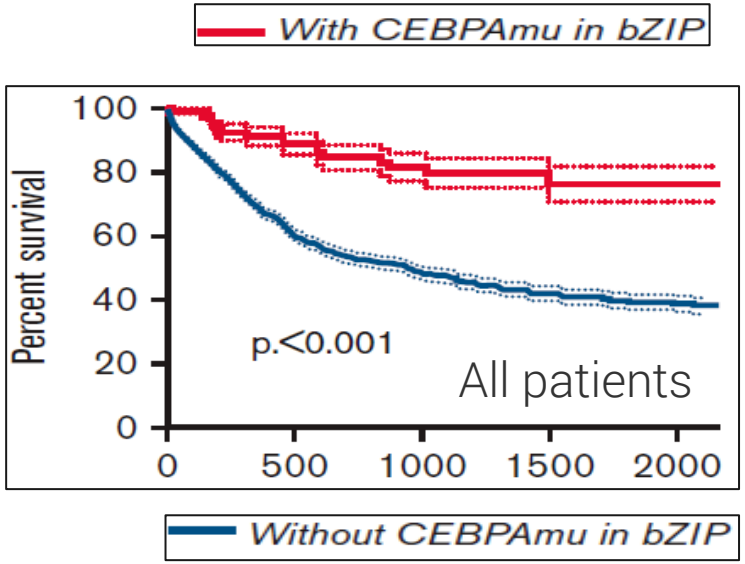
WHO

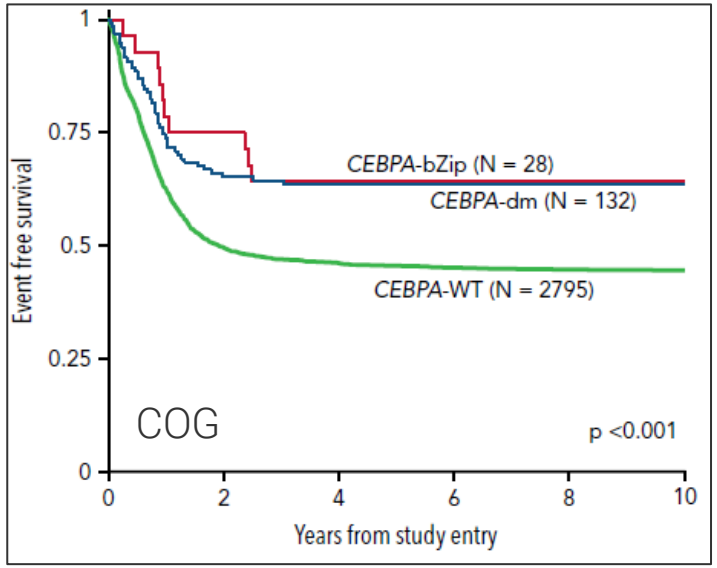
Defining cytogenetic abnormalities
Complex karyotype (≥3 abnormalities)
5q deletion or loss of 5q due to unbalanced translocation
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation
11q deletion
12p deletion or loss of 12p due to unbalanced translocation
Monosomy 13 or 13q deletion
17p deletion or loss of 17p due to unbalanced translocation
Isochromosome 17q
idic(X)(q13)
Defining somatic mutations
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

Presence of 1+ above and/or history of MDS or MDS/MPN required for dx

CEBPA mutant AML – b-zip domain



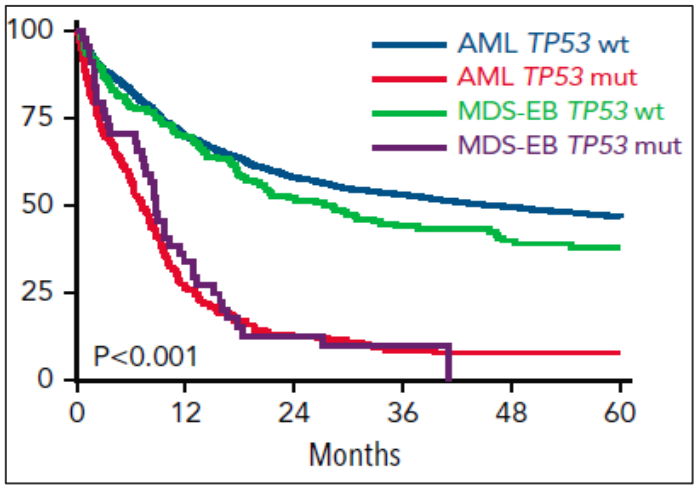


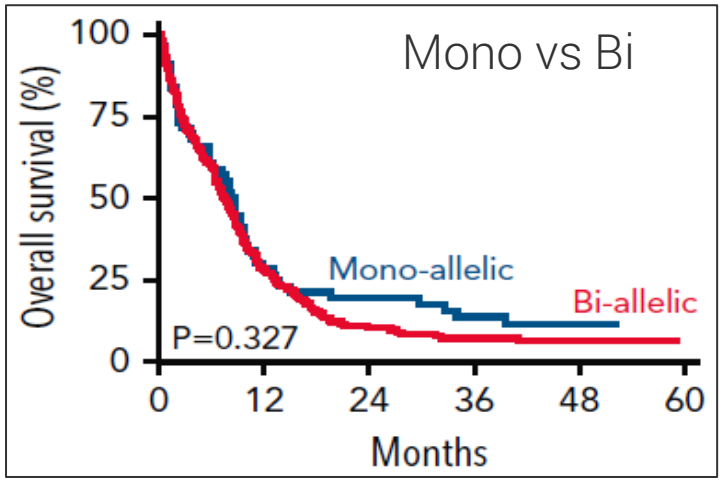


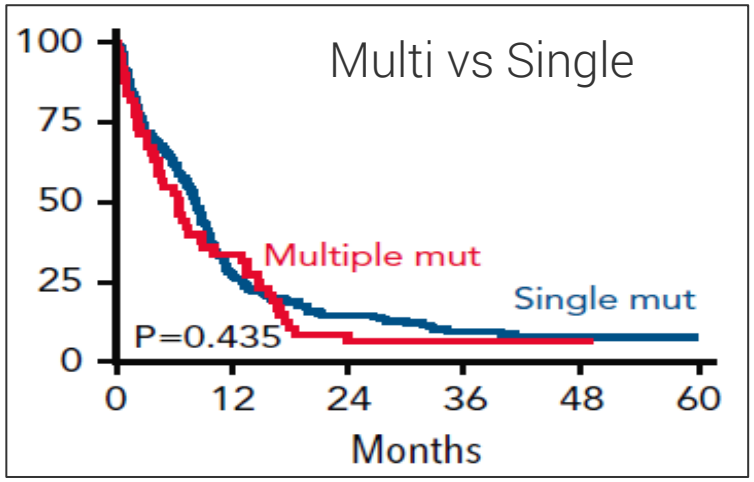
- CEBPA-bZip domain mutations – favorable OS
- Single or double mutations – **similar OS**

Tarlock, 2021, Blood; Wakita, 2022, Blood Advances

MDS/AML AND AML – *TP53* mutations







- Blast count is not relevant i.e. excess blasts vs. AML
- Single *TP53* mutation sufficient (VAF>10%)
- Concurrent mutation doe not matter

Grob, 2022, Blood

Hematologic neoplasms with germline predisposition

ICC

Hematologic neoplasms with germline predisposition without a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *CEBPA* mutation
Myeloid or lymphoid neoplasms with germline *DDX41* mutation
Myeloid or lymphoid neoplasms with germline *TP53* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional platelet disorder
Myeloid or lymphoid neoplasms with germline *RUNX1* mutation
Myeloid neoplasms with germline *ANKRD26* mutation
Myeloid or lymphoid neoplasms with germline *ETV6* mutation
Hematologic neoplasms with germline predisposition associated with a constitutional disorder affecting multiple organ systems
Myeloid neoplasms with germline *GATA2* mutation
Myeloid neoplasms with germline *SAMD9* mutation
Myeloid neoplasms with germline *SAMD9L* mutation
Myeloid neoplasms associated with bone marrow failure syndromes
Fanconi anemia
Shwachman-Diamond syndrome
Telomere biology disorders including dyskeratosis congenita
Severe congenital neutropenia
Diamond-Blackfan anemia
JMML associated with neurofibromatosis
JMML associated with Noonan-syndrome-like disorder (CBL-syndrome)
Myeloid or lymphoid neoplasms associated with Down syndrome
Acute lymphoblastic leukemia with germline predisposition*
Acute lymphoblastic leukemia with germline *PAX5* mutation
Acute lymphoblastic leukemia with germline *IKZF1* mutation

*Down syndrome and germline mutations in *ETV6* or *TP53* also predispose to acute lymphoblastic leukemia.

- A novel scalable model (1) presence or absence of multiple organ involvement 2) platelet disorder
- ICC and WHO are similar except ICC also included lymphoblastic leukemias under this broad umbrella

Integrated reporting

Challenges of Integrated reporting

Logistics

- Addendum
- Amendment
- Separate integrated (final) report

Including

- Specimen and site
- Procedure
- Histologic type and extent of tumor
- Immunophenotype
- Cytogenetic and molecular genetic findings
- Other ancillary types
- Classification(s)
- Synoptic reporting
- AI algorithms
- Prognostic scoring system

Ohgami, Arber. Surg Pathol Clin 2013

Challenges of Integrated reporting

Logistics	Including
• Addendum • Amendment • Separate integrat report	extent of tumor ecular genetic findings s ng tic scoring system

Pathology-generated

Ohgami, Arber. Surg Pathol Clin 2013

From: **Combined Pathology-Driven Algorithmic Testing and Integrated Reporting for Bone Marrow Examination**

Arch Pathol Lab Med. 2019;143(6):732-737. doi:10.5858/arpa.2018-0161-OA

PATHOLOGY SUMMARY REPORT

Name: **Name, Patient** Accession#:
DOB: MRN#:

Location:
Provider: Collect Date:
Copy to: Receive Date:

FINAL DIAGNOSIS: ACUTE MYELOID LEUKEMIA, NORMAL KARYOTYPE, NPM1 POSITIVE, FLT3-ITD NEGATIVE

DIAGNOSTIC COMMENT:
This patient has acute myeloid leukemia with normal karyotype, presence of an NPM1 mutation, and absence of a FLT3-ITD mutation. This combination of findings is associated with a favorable prognosis in acute myeloid leukemia. The prognostic significance of FLT3-TKD mutations is not well defined but in general patients with FLT3-TKD mutations have a less favorable prognosis than those without.

Cytogenetics: normal karyotype
FLT3-ITD: NEGATIVE
FLT3-TKD: POSITIVE
NPM1: POSITIVE
CEBPA: NEGATIVE

Peripheral Blood: WBC 32,480/cmm, Blasts 11,060/cmm, Hgb 9.6 gm/dl, Platelets 138,000/cmm

Bone Marrow: Acute myeloid leukemia (69% blasts)
Flow Cytometry: Acute myeloid leukemia
Cytogenetics: 46, XX[30] no abnormalities of MLL (KMT2A)
FISH PML/RARA: No PML-RARA gene fusion by FISH

Document reviewed and electronically signed by:

Report Date:
By the signature above, the attending physician certifies that he/she has personally conducted a gross and/or microscopic examination of the described specimens and rendered or confirmed the above diagnosis.

Integrated reporting: WHO diagnosis (94%) vs hematopathology report (64%)
Test utilization: Unnecessary testing decreased from 45% to 0.7% using pathology-driven algorithmic testing

Thank you Madhu Menon and Robert Ohgami!

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