AML: WHO classification, biology and prognosis

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Ziekenhuis Netwerk Antwerpen
Acute myeloid leukemia

- Clonal expansion of undifferentiated myeloid precursors
- Impaired hematopoiesis and bone marrow failure
- Heterogeneous response to treatment and prognosis

Morphology
Acute myeloid leukemia

- Clonal expansion of undifferentiated myeloid precursors
- Impaired hematopoiesis and bone marrow failure
- Heterogeneous response to treatment and prognosis

Morphology

Myeloperoxidase staining
# Acute myeloid leukemia
## Prognosis according age

<table>
<thead>
<tr>
<th>Age</th>
<th>Complete remission</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 - 60 years</td>
<td>80%</td>
<td>40% at 5 years</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>65%</td>
<td>28% at 2 years</td>
</tr>
</tbody>
</table>
FAB classification of acute myeloblastic leukaemia

M0: Acute myeloblastic leukaemia with minimal differentiation
- Morphology:
  - Can resemble LL/L2 blasts. Medium-sized blasts, rounded nucleus, fine chromatin, basophilic non-granular cytoplasm, prominent nucleoli.
- Immunophenotype:
  - CD15 +
  - CD33 +
  - CD10 +
  - CD11c +
  - CD14 +
  - CD15 +

M1: Acute myeloblastic leukaemia without maturation
- Morphology:
  - Medium-sized blasts with high nuclear:cytoplasm (n:cyt) ratio, rounded nuclei with immature, dispersed chromatin with one or more prominent nucleoli. Blasts can show fine azurophilic granulation or isolated Auer rods in the cytoplasm in 5% to 10% of cases.
- Immunophenotype:
  - MPO +
  - CD13 +
  - CD33 +
  - CD4 +

M2: Acute myeloblastic leukaemia with maturation
- Morphology:
  - Small to medium-sized blasts with high nuclei:cytoplasm (n:cyt) ratio and rounded nuclei sometimes located in a corner of the cytoplasm. The nucleus shows dispersed immature chromatin with one or more nucleoli. The cytoplasm is basophilic and can contain traces of primary azurophilic granulation or isolated Auer rods.
- Immunophenotype:
  - MPO +
  - CD34 +
  - CD13 +
  - CD15 +
  - HLA-DR +
  - Sulfur black +
  - CD117 +

M3: Promyelocytic leukaemia
- Morphology:
  - Abundant, intensely azurophilic granulation.
  - The nucleus is usually monomeric in appearance (xenomorphic) and is either irregular or lobulated with a deep cleft. Slightly basophilic cytoplasm due to the proliferation of azurophilic granulation. Some promyelocytes also contain elongated or splinter-shaped crystalline cytoplasmic inclusions specific to this type of leukaemia. These usually form dumbs, but differ from Auer rods in that they show a tubular substructure on electronic microscopy.
- Immunophenotype:
  - CD13 +
  - CD33 +
  - HLA-DR +
  - CD34 +

M4: Acute monomyelo-monocytic leukaemia
- Morphology:
  - Large blasts, moderate nucleocytoplasmic ratio and variable basophilia. The nucleus may be rounded, kidney-shaped or irregular. Nucleoli are usually prominent.
- Immunophenotype:
  - CD13 +
  - CD15 +
  - CD33 +
  - CD11b +
  - CD14 +
  - CD64 +

M5: Acute monocytic leukaemia
- M5a acute monocytic leukaemia:
  - Large blasts with rounded nucleus and dispersed, immature chromatin (1-3 nuclei) and moderately large, intensely basophilic cytoplasm. The cytoplasm may show some Auer rods and/or pseudoiclusions and granulations.
  - M5b acute monocytic leukaemia
  - Promonocytes have a rounded or kidney-shaped nucleus with a less basophilic cytoplasm that is more highly granulated than monoblasts and contains some vacuoles. A finding of erythrophagocytosis together with monocytic blasts suggests a t(6;16) translocation.
- Immunophenotype:
  - CD14 +
  - CD64 +
  - CD4 +
  - CD11c +
  - HLA-DR +

M6: Acute erythroid leukaemia
- M6a erythroid leukaemia with proliferation of mixed blasts:
  - Over 50% erythroid precursors and around 30% myeloblasts. Morphology of erythroblasts in peripheral blood is greatly shrunken, with schistocytes, “pinched” or mushroom-shaped cells, and spicular echinocytes and acanthocytes. M5b pure erythroid leukaemia:
  - Erythroblasts make up 80% of bone marrow cells, with less than 5% myeloblasts. Erythroblasts in peripheral blood consist of macrocytes, basophilic stippling, Howell-Jolly bodies or Cabot rings.
- Immunophenotype:
  - CD13 +
  - CD33 +
  - CD15 +
  - Glycoprotein A +
  - Glycoprotein C +

M7: Acute megakaryocytic leukaemia
- Morphology:
  - Highly immature, polymorphic blasts. The nucleus is eccentric with dispersed, reticulated chromatia and 1-3 prominent nucleoli. The cytoplasm is non-granular, basophilic and very similar in appearance to platelets, with pseudopods or granulations. Megakaryocytes and fragments of megakaryoblasts are seen in peripheral blood (plump platelets, some highly degranulated).
- Immunophenotype:
  - CD41 +
  - CD61 +
  - CD42 +
  - CD13 +
  - CD30 +
  - CD34 +

Bennett et al et al, BJH, 1976
# FAB classification of AML

<table>
<thead>
<tr>
<th>FAB subtype</th>
<th>% of Cases</th>
<th>Morphology</th>
<th>Cytoschemistry</th>
<th>Flow Cytometry</th>
<th>Cytogenetic Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1: Myeloblastic leukemia without maturation</td>
<td>20</td>
<td>Few blasts with azurophilic granules, Auer rods, or both</td>
<td>Peroxidase / Sudan Black 3% or more</td>
<td>-</td>
<td>CD13, 33, 34, HLA-DR+</td>
</tr>
<tr>
<td>M2: Myeloblastic leukemia with maturation</td>
<td>25-30</td>
<td>Azurophilic granules, Auer rods are often present</td>
<td>Nonspecific Esterase +</td>
<td>-</td>
<td>CD13, 15, 33, 34, HLA-DR+ T(8;21) (q22;q22)(^e)</td>
</tr>
<tr>
<td>M3: Hypergranular promyelocytic leukemia</td>
<td>8-15</td>
<td>Hypergranular promyelocytes with multiple Auer rods; Variant: hypogranular</td>
<td>CD13, 15, 33, HLA-DR+</td>
<td>+</td>
<td>T(15;17) (q22;q11-12)</td>
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## FAB classification of AML

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<tr>
<td>maturation</td>
<td></td>
<td>present</td>
<td></td>
<td>HLA-DR+</td>
<td></td>
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<td>T(15;17) (q22;q11-12)</td>
</tr>
<tr>
<td>M4: Myelomonocytic leukemia</td>
<td>20-25</td>
<td>Granulocytic and monocytic blasts; Variant: M4Eo: increase in abnormal marrow eosinophils</td>
<td>+/-</td>
<td>CD11b, 13, 14f, 15, 33, HLA-DR+</td>
<td>M4Eo: inv(16)(p13q22)</td>
</tr>
<tr>
<td>M5: Monocytic leukemia</td>
<td>20-25</td>
<td>M5a undifferentiated; M5b differentiated</td>
<td>-</td>
<td>CD11b, 13, 14f, 15, 33, HLA-DR+</td>
<td>11q23 translocation</td>
</tr>
<tr>
<td>M6: Erythroleukemia (Di Guglielmo's disease)</td>
<td>5</td>
<td>Erythroblasts &gt;50% of nucleated cells, myeloblasts &gt;30% of nonerythroid cells</td>
<td>+/-</td>
<td>CD33, HLA-DR+</td>
<td></td>
</tr>
<tr>
<td>M7: Megakaryoblastic leukemia</td>
<td>1-2</td>
<td>Megakaryoblasts &gt;30% of all nucleated cells</td>
<td>-</td>
<td>CD33</td>
<td></td>
</tr>
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</table>
**FAB classification of AML**

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</thead>
<tbody>
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<td>M0: Minimally differentiated leukemia</td>
<td>2-3</td>
<td>Immature morphology</td>
<td>-</td>
<td>CD13 or 33</td>
<td></td>
</tr>
<tr>
<td>M1: Myeloblastic leukemia without maturation</td>
<td>20</td>
<td>Few blasts with azurophilic granules, Auer rods, or both</td>
<td>3% or more</td>
<td>CD13, 33, 34, HLA-DR+</td>
<td></td>
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<td>T(8;21) (q22;q22)*</td>
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<td>T(15;17) (q22;q11-12)</td>
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Modern diagnosis of AML

- Morphology
- Immunophenotyping
- Cytogenetics
- Cytochemistry
- FISH
- Molecular Biology
Cytogenetic distribution of AML

Based on Grimwade et al, Blood 1998; Grimwade et al, Blood, 2001
Impact of specific genetic aberrations on survival in AML

Grimwade et al, Blood 2010
Impact of karyotype complexity on survival for AML patients not belonging to favourable subgroups

MRC/NCRI AML Trials: Overall Survival
Ages 16–59 excluding known prognostic abnormalities

- 0–3 abnormalities
- >3 abnormalities

0–3 abnormalities:
- Patients: 3194
- Events: 1789

>3 abnormalities:
- Patients: 102
- Events: 76

2P < 0.00001

Years from entry

% alive

0 25 50 75 100

0 1 2 3 4 5 6 7 8 9 10

Grimwade et al, Blood 2010
Overall survival in AML patients categorized into favourable, intermediate, adverse and very adverse cytogenetic risk groups

Overall survival in AML patients categorized into three groups based on cytogenetic abnormalities:

- **inv(16), t(8;21)**: 66%
- **normal karyotype, -X, -Y**: 41%
- **other abnormal karyotype**: 26%
- **monosomal karyotype***: 4%

Two or more autosomal monosomy or 1 auto monosomy with structural abn (n=184) = monosomal karyotype*

### Prognostic value of cytogenetics in acute myeloid leukemia

Cytogenetic analysis of 1975 patients, 18-60 years

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Number of patients (%)</th>
<th>Four-year overall survival, % (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, -X, -Y</td>
<td>1001 (51)</td>
<td>41 (2)</td>
</tr>
<tr>
<td>inv(16)/t(16;16)</td>
<td>120 (6)</td>
<td>70 (4)</td>
</tr>
<tr>
<td>t(8;21)</td>
<td>134 (7)</td>
<td>63 (4)</td>
</tr>
<tr>
<td>Abnormal, no monosomalic karyotype</td>
<td>535 (27)</td>
<td>26 (2)</td>
</tr>
<tr>
<td>Monosomalic karyotype</td>
<td>184 (9)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

Mutational complexity of AML

Two cooperating classes of mutations in AML

Class I Mutations
- FLT3-ITD
- FLT3-TKD
- RAS
- JAK2
- KIT
- SHP2

proliferative and/or survival advantage

Class II Mutations
- PML/RARA
- RUNX1/CBFA2T1
- CBFB/MYH11
- MLL fusions
- CEBPA
- NPM1

impaired hematopoietic differentiation

molecular therapy, e.g. with FLT3, KIT inhibitors

molecular therapy, e.g. with ATRA

Adapted from Speck & Gilliland, Nat Rev Cancer. 2002
Comprehensive mutational profiling for risk stratification and clinical management of AML.

Evolution of mutations in AML

M1 initiating mutations
(NPM1, DNM3A, IDH1, TET2 & others)

cooperating mutations
(FLT3 and others)

HSPC

X: age-dependent passenger mutations pre-existing in HSPC

Y: passenger mutations gained between initiating and cooperating mutations

Z: passenger mutations gained during progression to subclones

Welch et al, Cell, 2012
Patterns of relapse in AML

Cell type:
- Normal
- AML

Mutations:
- Founding (cluster 1)
- Primary specific (cluster 2)
- Relapse enriched (cluster 3)
- Relapse specific (cluster 5)
- Random mutations in HSCs

Model 1 (UPNs 400220, 573988, 804168)

Chemotherapy

Model 2 (UPNs 426980, 452198, 758168, 869586, 933124)

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

Contents

Chapter 7: Myeloid neoplasma with germline predisposition

Chapter 8: Acute myeloid leukemia and related precursor neoplasms

Chapter 9: Blastic plasmacytoid dendritic neoplasm

Chapter 10: Acute leukemias of ambiguous lineage
            Mixed phenotype acute leukemia (MPAL)
Principles WHO classification

- Integration of all available information
  - Definition, ICD-O Code, Synonyms
  - Epidemiology
  - Clinical features
  - Microscopy
  - Immunophenotype
  - Genetic profile
  - Prognosis and predictive factors
# Tests/procedures

<table>
<thead>
<tr>
<th>For a patient with AML</th>
<th>Additional tests/procedures at diagnosis (cont'd)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tests to establish the diagnosis</strong></td>
<td><strong>Analysis of comorbidities</strong></td>
</tr>
<tr>
<td>Complete blood count and differential count</td>
<td>Biochemistry, coagulation tests, urine analysis††</td>
</tr>
<tr>
<td>Bone marrow aspirate</td>
<td>Serum pregnancy test††</td>
</tr>
<tr>
<td>Bone marrow trephine biopsy‡</td>
<td>Information on oocyte and sperm cryopreservation‡‡</td>
</tr>
<tr>
<td>Immunophenotyping</td>
<td>Eligibility assessment for allogeneic HCT (including HLA typing)a</td>
</tr>
<tr>
<td><strong>Genetic analyses</strong></td>
<td>Hepatitis A, B, C; HIV-1 testing</td>
</tr>
<tr>
<td>Cytogenetics†</td>
<td>Chest radiograph, 12-lead electrocardiogram, and echocardiography or MUGA (on indication)</td>
</tr>
<tr>
<td>Screening for gene mutations including‡</td>
<td>Lumbar punctureb</td>
</tr>
<tr>
<td><strong>NPM1, CEBPA, RUNX1, FLT3, TP53, ASXL1</strong></td>
<td>Biobankingc</td>
</tr>
<tr>
<td>Screening for gene rearrangements§</td>
<td>Sensitive assessment of response by RT-qPCR or MFCd</td>
</tr>
<tr>
<td><strong>PML-RARA, CBFB-MYH11, RUNX1-RUNX1T1, BCR-ABL1, other fusion genes (if available)</strong></td>
<td>RT-qPCRe,f for NPM1 mutation, CBFB-MYH11, RUNX1-RUNX1T1, BCR-ABL1, other fusion genes (if available)d</td>
</tr>
<tr>
<td><strong>Demographics and medical history¶</strong></td>
<td>MFCf,g</td>
</tr>
<tr>
<td><strong>Detailed family history¶</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Patient bleeding history#</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Performance status (ECOG/WHO score)</strong></td>
<td></td>
</tr>
</tbody>
</table>
# Markers for the diagnosis of AML and MPAL

<table>
<thead>
<tr>
<th>Expression of cell-surface and cytoplasmic markers</th>
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</thead>
<tbody>
<tr>
<td><strong>Diagnosis of AML</strong>†</td>
</tr>
<tr>
<td>Precursors†</td>
</tr>
<tr>
<td>Granulocytic markers‡</td>
</tr>
<tr>
<td>Monocytic markers§</td>
</tr>
<tr>
<td>Megakaryocytic markersǁ</td>
</tr>
<tr>
<td>Erythroid markers</td>
</tr>
<tr>
<td><strong>Diagnosis of MPAL</strong>¶</td>
</tr>
<tr>
<td>Myeloid lineage</td>
</tr>
<tr>
<td>T-lineage</td>
</tr>
<tr>
<td>B-lineage‡</td>
</tr>
</tbody>
</table>

Blood, 2017, Döhner et al.
8: Acute myeloid leukemia and related precursor neoplasms

- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML not otherwise specified
- Myeloid sarcoma
- Myeloid proliferations associated with Down syndrome
AML with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1;1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- Acut promyelocytic leukemia with PML-RARA FAB M3
- AML with t(9;11)(p21.3;q23.3); KMT2A-MLLT3
- AML with t(6;9)(p23;q34.1); DEK-NUP214
- AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM (=EVI1)
- AML (megakaryoblastic) with t(1;22)(p13.3;q13.1); RBM15-MKL1
- AML with BCR-ABL1
- AML with with gene mutations
  - AML with mutated NPM1
  - AML with biallelic mutation of CEBPA
  - AML with mutated RUNX1
AML with recurrent genetic abnormalities favorable prognosis

- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1;1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
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AML with recurrent genetic abnormalities adverse prognosis

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  - AML with mutated \textit{RUNX1}
<table>
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<tr>
<th>Risk category</th>
<th>Genetic abnormality</th>
</tr>
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<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22.1); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITD_{low}†</td>
</tr>
<tr>
<td></td>
<td>Biallelic mutated CEBPA</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Mutated NPM1 and FLT3-ITD_{high}†</td>
</tr>
<tr>
<td></td>
<td>Wild-type NPM1 without FLT3-ITD or with FLT3-ITD_{low}† (without adverse-risk genetic lesions)</td>
</tr>
<tr>
<td></td>
<td>t(9;11)(p21.3;q23.3); MLLT3-KMT2A‡</td>
</tr>
<tr>
<td></td>
<td>Cytogenetic abnormalities not classified as favorable or adverse</td>
</tr>
<tr>
<td>Adverse</td>
<td>t(6;9)(p23;q34.1); DEK-NUP214</td>
</tr>
<tr>
<td></td>
<td>t(v;11q23.3); KMT2A rearranged</td>
</tr>
<tr>
<td></td>
<td>t(9;22)(q34.1;q11.2); BCR-ABL1</td>
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<td>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)</td>
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<td></td>
<td>−5 or del(5q); −7; −17/abn(17p)</td>
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<tr>
<td></td>
<td>Complex karyotype,§ monosomal karyotype‖</td>
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<td></td>
<td>Wild-type NPM1 and FLT3-ITD_{high}†</td>
</tr>
<tr>
<td></td>
<td>Mutated RUNX1¶</td>
</tr>
<tr>
<td></td>
<td>Mutated ASXL1¶</td>
</tr>
<tr>
<td></td>
<td>Mutated TP53#</td>
</tr>
</tbody>
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Blood, 2017, Döhner et al.
AML with myelodysplasia-related changes

- ≥ 20% blasts in PB or BM
- AND one of the following:
  - History of MDS or MDS/MPN
  - Myelodysplasia-related cytogenetic abnormality
    - Complex karyotype: 3 or more chromosomal abnormalities
    - Unbalanced abnormalities: -7, del(7q), -5, del(5q), i(17q), t(17q), -13, del(13q), del(11q), del(12p), t(12p) or idic(X)(q13)
    - Balanced abnormalities: t(11;16)(q23.3;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23.3), t(5;12)(q32;p13.2), t(5;7)(q32;q11.2), t(5;17)(q32;p13.2), t(5;10)(q32;q21.2) or t(3;5)(q25.3;q35.1)
  - Multilineage dysplasia: dysplasia in ≥50% of cells in ≥2 myeloid lineages
- AND absence of both prior cytotoxic therapy for unrelated disease and aforementioned recurring genetic abnormalities
Therapy-related myeloid neoplasms

- t-AML, t-MDS or t-MDS/MPN
- Excluded: progression from MPN or evolution of primary MDS or MDS/MPN to AML (secondary AML)
- Cytotoxic agents implicated in therapy-related myeloid neoplasms
  - Alkylating agents
  - Ionizing radiation therapy
  - Topoisomerase II inhibitors
  - Others
AML not other specified

- AML with minimal differentiation FAB M0
  - MPO negative, CD13+, CD117+, CD33+ (60%)
- AML without maturation FAB M1
  - >90% blasts of NEC
- AML with maturation FAB M2
- Acute myelomonocytic leukemia FAB M4
- Acute monoblastic/monocytic leukemia FAB M5a/b
- Acute erythroid leukemia FAB M6
- Acute megakaryoblastic leukemia FAB M7
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
Myeloid sarcoma

- Tumor mass consisting of myeloid blasts with or without maturation
- Occurring in other anatomical site than bone marrow
- Not: Infiltration of any site of the body by myeloid blasts in a patient with AML
- Localization, any site, most frequent:
  - Skin, lymph nodes, GI tract, bone, soft tissue, testes
Molecular classes of AML and concurrent gene mutations in adult patients ≤65 years

Döhner et al. Blood 2017
Genomic classification and prognosis in AML

11 discrete genetic subsets of AML on the basis of the expression and coexpression of particular mutations

Molecular subclassification and overall survival

- 11 discrete genetic subsets of AML on the basis of the expression and coexpression of particular mutations.

## Proposed genomic classification of AML

### Table 1. Proposed Genomic Classification of Acute Myeloid Leukemia (AML).

<table>
<thead>
<tr>
<th>Genomic Subgroup</th>
<th>Frequency in the Study Cohort (N=1540)</th>
<th>Most Frequently Mutated Genes*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>gene (%)</td>
</tr>
<tr>
<td>AML with <em>NPM1</em> mutation</td>
<td>418 (27)</td>
<td><em>NPM1</em> (100), <em>DNMT3A</em> (54), <em>FLT3</em>&lt;sub&gt;ITD&lt;/sub&gt; (39), <em>NRAS</em> (19), <em>TET2</em> (16), <em>PTPN11</em> (15)</td>
</tr>
<tr>
<td>AML with mutated chromatin, RNA-splicing genes, or both†</td>
<td>275 (18)</td>
<td><em>RUNX1</em> (39), <em>MLL</em>&lt;sub&gt;PTD&lt;/sub&gt; (25), <em>SRSF2</em> (22), <em>DNMT3A</em> (20), <em>ASXL1</em> (17), <em>STAG2</em> (16), <em>NRAS</em> (16), <em>TET2</em> (15), <em>FLT3</em>&lt;sub&gt;ITD&lt;/sub&gt; (15)</td>
</tr>
<tr>
<td>AML with <em>TP53</em> mutations, chromosomal aneuploidy, or both‡</td>
<td>199 (13)</td>
<td>Complex karyotype (68), −5/5q (47), −7/7q (44), <em>TP53</em> (44), −17/17p (31), −12/12p (17), +8/8q (16)</td>
</tr>
<tr>
<td>AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <em>CBFB</em>–<em>MYH11</em></td>
<td>81 (5)</td>
<td>inv(16) (100), <em>NRAS</em> (53), +8/8q (16), +22 (16), <em>KIT</em> (15), <em>FLT3</em>&lt;sub&gt;ITD&lt;/sub&gt; (15)</td>
</tr>
<tr>
<td>AML with bialelic <em>CEBPA</em> mutations</td>
<td>66 (4)</td>
<td><em>CEBPA</em>&lt;sup&gt;biallelic&lt;/sup&gt; (100), <em>NRAS</em> (30), <em>WT1</em> (21), <em>GATA2</em> (20)</td>
</tr>
<tr>
<td>AML with t(15;17)(q22;q12); <em>PML</em>–<em>RARA</em></td>
<td>60 (4)</td>
<td>t(15;17) (100), <em>FLT3</em>&lt;sub&gt;ITD&lt;/sub&gt; (35), <em>WT1</em> (17)</td>
</tr>
<tr>
<td>AML with t(8;21)(q22;q22); <em>RUNX1</em>–<em>RUNX1T1</em></td>
<td>60 (4)</td>
<td>t(8;21) (100), <em>KIT</em> (38), −Y (33), −9q (18)</td>
</tr>
<tr>
<td>AML with <em>MLL</em> fusion genes; t(x;11)(x;q23)‡</td>
<td>44 (3)</td>
<td>t(x;11q23) (100), <em>NRAS</em> (23)</td>
</tr>
<tr>
<td>AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); <em>GATA2</em>, <em>MECOM</em> (EV11)</td>
<td>20 (1)</td>
<td>inv(3) (100), −7 (85), <em>KRAS</em> (30), <em>NRAS</em> (30), <em>PTPN11</em> (30), <em>ETV6</em> (15), <em>PHF6</em> (15), <em>SF3B1</em> (15)</td>
</tr>
<tr>
<td>AML with <em>IDH2</em>&lt;sup&gt;R172&lt;/sup&gt; mutations and no other class-defining lesions</td>
<td>18 (1)</td>
<td><em>IDH2</em>&lt;sup&gt;R172&lt;/sup&gt; (100), <em>DNMT3A</em> (67), +8/8q (17)</td>
</tr>
<tr>
<td>AML with t(6;9)(p23;q34); <em>DEK</em>–<em>NUP214</em></td>
<td>15 (1)</td>
<td>t(6;9) (100), <em>FLT3</em>&lt;sub&gt;ITD&lt;/sub&gt; (80), <em>KRAS</em> (20)</td>
</tr>
<tr>
<td>AML with driver mutations but no detected class-defining lesions</td>
<td>166 (11)</td>
<td><em>FLT3</em>&lt;sub&gt;ITD&lt;/sub&gt; (39), <em>DNMT3A</em> (16)</td>
</tr>
<tr>
<td>AML with no detected driver mutations</td>
<td>62 (4)</td>
<td></td>
</tr>
<tr>
<td>AML meeting criteria for ≥2 genomic subgroups</td>
<td>56 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Genomic classification and prognosis in AML

- The driver landscape in AML reveals distinct molecular subgroups that reflect discrete paths in the evolution of AML, informing disease classification and prognostic stratification.

- Prospective studies may elucidate distinct approaches to their management.
Prognostic value of minimal residual disease detection in AML with flowcytometry

- 517 AML patients, 18-60 years
- 85% of all AMLs:
  - Leukemia-associated phenotype by immunoflow cytometry is determined at diagnosis
  - Minimal residual disease assessment in complete remission:
    - After chemotherapy induction cycle 1
    - After chemotherapy cycle 2
    - After consolidation treatment

Terwijn et al. J Clin Oncol 2013
Relapse incidence by minimal residual disease

A: After chemotherapy induction cycle 1
B: After chemotherapy cycle 2
C: After consolidation treatment
Relapse incidence by minimal residual disease

After chemotherapy cycle 2
D: Good risk
C: Intermediate risk
F: Poor risk
Populatie A
CD45+ HLADR+ CD56+ CD4+(LD) CD123+
CD34- CD19- CD3- cytCD3- cytCD79a- cytTdT- cytMPO-
9: Blastic plasmacytoid dendritic cell neoplasm

- Very rare
- 75% male
- Median age range at diagnosis 60-70 years
- Bone marrow involvement in 80-90% of cases
- Skin lesions 85-90% of cases
- Lymphnodes and viscera may also be involved
- Signature marker triad: CD123, CD4, CD56
- BPDCN rapid progression like acute leukemia
- Median survival 8-14 months after diagnosis
Literature AML

