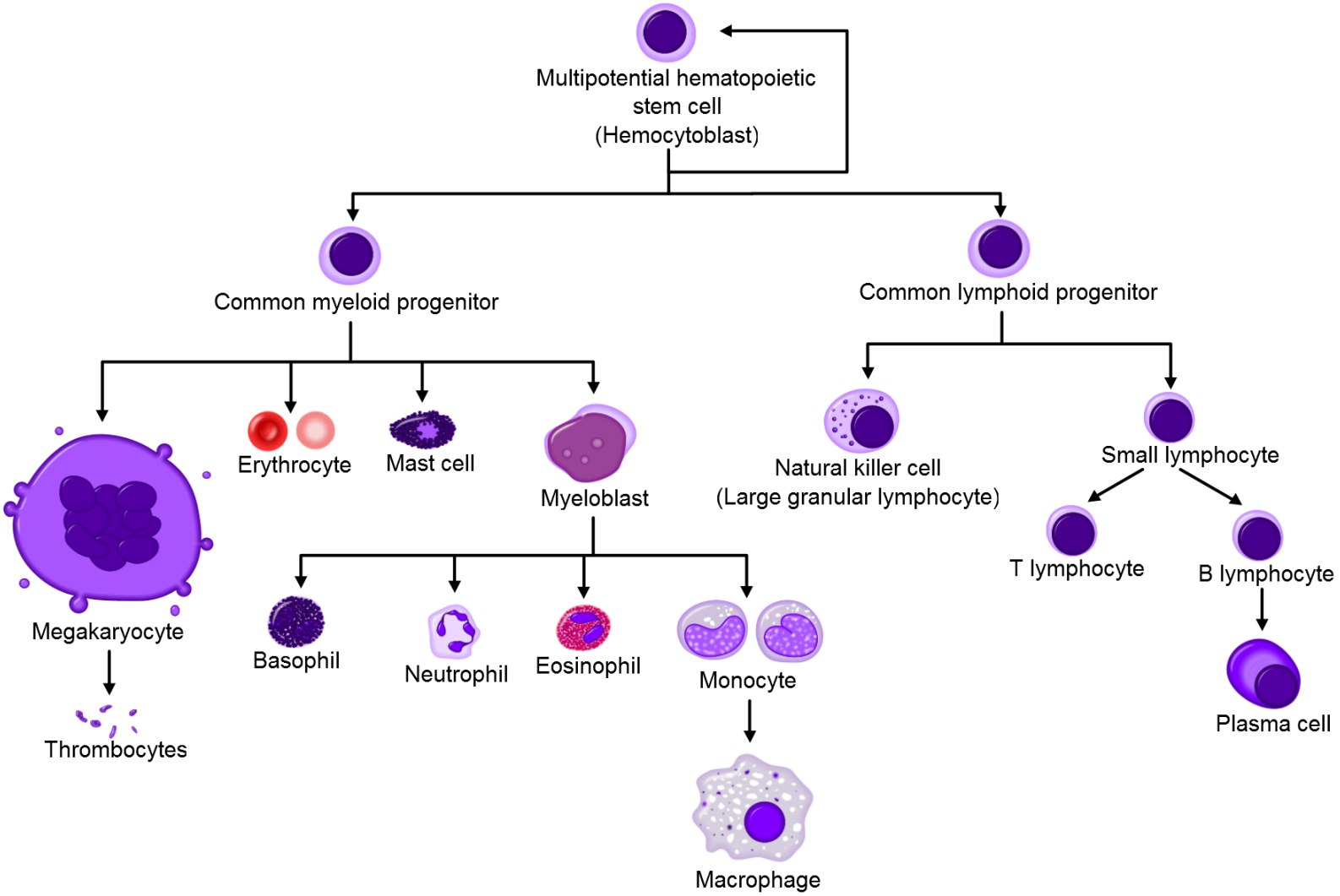
DREAM9: predicting therapeutic response and overall survival in AML

Kevin Emmett

Sakellarios Zairis

Normal Hematopoiesis

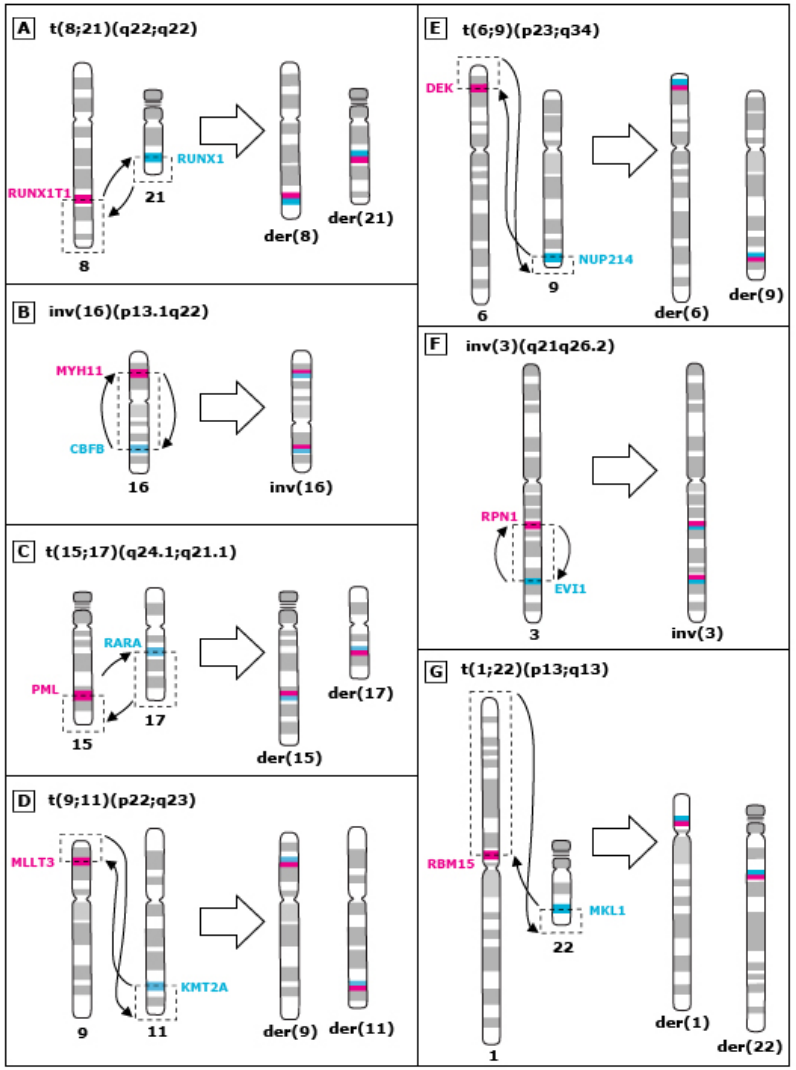


French-American-British (FAB) classification of acute myeloid leukemia

FAB type	Blasts, percent		Erythroid progenitors	Morphology	Cytochemistry
	All cells	NEC			
M0	>30	>90	<50	Blasts resemble L2 variant of ALL; cytoplasmic granules and Auer rods are not seen.	<3 percent PXase+ or SBB+
M1	>30	>90	<50	>30 percent type 1 and type 2 blasts; <10 percent differentiated myeloid cells; Auer rods seen in about 50 percent of cases	>3 percent PXase+ or SBB+
M2	>30	>30-89	<50	>30 percent type 1 and type 2 blasts; >10 percent differentiated myeloid cells; Auer rods seen in about 70 percent of cases	PXase+ SBB+ NSE+<20 percent PAS-
M3	>30*	>30-89	<50	>20 percent abnormal hypergranular progranulocytes; blast count may be <30 percent; Auer rods and faggot cells seen in virtually all cases	PXase+ SBB+ PAS- NSE±
M3V	>30*	>30-89	<50	>20 percent abnormal hypogranular progranulocytes; blast count may be <30 percent; Auer rods and faggot cells seen in virtually all cases	PXase+ SBB+ PAS- NSE±
M4	>30	>30-79	<50	>20 percent promonocytes and monocytes; >20 percent granulocytic cells; peripheral monocytosis (>5 x 10^9) ± elevated serum or urine lysozyme; Auer rods seen in about 65 percent of cases	PXase+ >20 percent NSE+
M4eo	>30	>30-79	<50	>5 percent eosinophils and cells with mixed basophilic and eosinophilic granules, plus M4 features	PXase+ >20 percent NSE+
M5a		>80	<50	>80 percent of nonerythroid cells are monoblasts; Auer rods usually not seen	NSE+
M5b		>80	<50	>80 percent of nonerythroid cells are monocytes, promonocytes, and monoblasts; Auer rods can be seen in a minor population of myeloblasts (30 percent of cases)	NSE+
M6		>30	>50	Erythroid predominance and dysplasia; >30 percent blasts among non-erythroid cells; Auer rods present in blasts in 60 percent of cases	PAS+ (erythroid cells); blasts are PXase+
M7	>30		<50	Blasts with cytoplasmic blebbing ± platelet shedding; marrow fibrosis; Auer rods are not seen	Platelet PXase+ on EM

NEC: nonerythroid cells; PXase: peroxidase; SBB: Sudan black; NSA: nonspecific esterase; PAS: periodic acid-Schiff.
* Abnormal progranulocytes and blasts.

Chromosomal abnormalities in acute myeloid leukemia



UpToDate®

UpToDate®

Standardized reporting for correlation of cytogenetic and molecular genetic data in acute myeloid leukemia (AML) in adults with clinical data*

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD (normal karyotype)
	Mutated CEBPA (normal karyotype)
Intermediate-I•	Mutated NPM1 and FLT3-ITD (normal karyotype)
	Wild type NPM1 and FLT3-ITD (normal karyotype)
	Wild type NPM1 without FLT3-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLLT3-MLL
	Cytogenetic abnormalities not classified as favorable or adverseΔ
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
	t(6;9)(p23;q34); DEK-NUP214
	t(v;11)(v;q23); MLL rearranged
	-5 or del(5q); -7; abnl(17p); complex karyotype◇

* Frequencies, response rates and outcome measures should be reported by genetic group, and, if sufficient numbers are available, by specific subsets indicated; excluding cases of acute promyelocytic leukemia.
• Includes all AMLs with normal karyotype except for those included in the favorable subgroup; most of these cases are associated with poor prognosis, but they should be reported separately because of the potential different response to treatment.
Δ For most abnormalities, adequate numbers have not been studied to draw firm conclusions regarding their prognostic significance.
◇ Three or more chromosome abnormalities in the absence of one of the WHO designated recurring translocations or inversions, ie, t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23), t(6;9), inv(3)/t(3;3); indicate how many complex karyotype cases have involvement of chromosome arms 5q, 7q, and 17p.
This research was originally published in Blood. Dohner, H, Estey, EH, Amadori, S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel on behalf of the European LeukemiaNet. Blood 2009. Copyright © American Society of Hematology.

UpToDate®

Response criteria in acute myeloid leukemia

Category	Definition
Complete remission (CR)*	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1.0 x 10^9/L (1000/µL); platelet count >100 x 10^9/L (100,000/µL); independence of red cell transfusions
CR with incomplete recovery (CRi)•	All CR criteria except for residual neutropenia (<1.0 x 10^9/L (1000/µL)) or thrombocytopenia (<100 x 10^9/L (100,000/µL))
Morphologic leukemia-free stateΔ	Bone marrow blasts <5 percent; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	Relevant in the setting of phase I and II clinical trials only; all hematologic criteria of CR; decrease of bone marrow blast percentage to 5 to 25 percent; and decrease of pretreatment bone marrow blast percentage by at least 50 percent
Cytogenetic CR (CRc) ◇	Reversion to a normal karyotype at the time of morphologic CR (or CRi) in cases with an abnormal karyotype at the time of diagnosis; based on the evaluation of 20 metaphase cells from bone marrow
Molecular CR (CRm)§	No standard definition; depends on molecular target
Treatment failure	
Resistant disease (RD)	Failure to achieve CR or CRi (general practice; phase II/III trials), or failure to achieve CR, CRi or PR (phase I trials); only includes patients surviving ≥7 days following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination
Death in aplasia	Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available
Relapse¥	Bone marrow blasts ≥5 percent; or reappearance of blasts in the blood; or development of extramedullary disease

Definitions of response criteria are based primarily on those given by Cheson et al[2].
* All criteria need to be fulfilled; marrow evaluation should be based on a count of 200 nucleated cells in an aspirate with spicules; if ambiguous, consider repeat exam after 5 to 7 days; flow cytometric evaluation may help to distinguish between persistent leukemia and regenerating normal marrow; a marrow biopsy should be performed in cases of dry tap, or if no spicules are obtained; no minimum duration of response required.
• The criterion of CRi is of value in protocols using intensified induction or double induction strategies, in which hematologic recovery is not awaited, but intensive therapy will be continued. In such protocols, CR may even not be achieved in the course of the entire treatment plan. In these instances, the overall remission rate should include CR and CRi patients. Some patients may not achieve complete hematologic recovery upon longer observation times.
Δ This category may be useful in the clinical development of novel agents within phase I clinical trials, in which a transient morphologic leukemia-free state may be achieved at the time of early response assessment.
◇ Four studies showed that failure to convert to a normal karyotype at the time of CR predicts inferior outcome.[3-6]
§ As an example, in CBF AML low-level PCR-positivity can be detected in patients even in long-term remission. Normalizing to 10^4 copies of ABL1 in accordance with standardized criteria, transcript levels below 10 to 12 copies appear to be predictive for long-term remission.[7-9]
¥ In cases with low blast percentages (5 to 10 percent), a repeat marrow should be performed to confirm relapse. Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

1. This research was originally published in Blood. Dohner, H, Estey, EH, Amadori, S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel on behalf of the European LeukemiaNet. Blood 2009. Copyright © American Society of Hematology.
2. Cheson, BD, Bennett, JM, Kopecky, KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003; 21:4642.
3. Freireich, EJ, Cork, A, Stass, SA, et al. Cytogenetics for detection of minimal residual disease in acute myeloblastic leukemia. Leukemia 1992; 6:500.
4. Grimwade, D, Walker, H, Oliver, F, et al. What happens subsequently in AML when cytogenetic abnormalities persist at bone marrow harvest? Results of the 10th UK MRC AML trial. Bone Marrow Transplant 1997; 19:1117.
5. Marcucci, G, Mrózek, K, Ruppert, AS, et al. Abnormal cytogenetics at date of morphologic complete remission predicts short overall and disease-free survival, and higher relapse rate in adult acute myeloid leukemia: results from Cancer and Leukemia Group B study 8461. J Clin Oncol 2004; 22:2410.
6. Balleisen, S, Kuendgen, A, Hildebrandt, B, et al. Prognostic relevance of achieving cytogenetic remission in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome following induction chemotherapy. Leuk Res 2009; 33:1189.
7. Freeman, SD, Jovanovic, JV, Grimwade, D. Development of minimal residual disease-directed therapy in acute myeloid leukemia. Semin Oncol 2008; 35:388.
8. Perea, G, Lasa, A, Aventín, A, et al. Prognostic value of minimal residual disease (MRD) in acute myeloid leukemia (AML) with favorable cytogenetics [t(8;21) and inv(16)]. Leukemia 2006; 20:87.
9. Martinelli, G, Rondoni, M, Buonamici, S, et al. Molecular monitoring to identify a threshold of CBFβ/MYH11 transcript below which continuous complete remission of acute myeloid leukemia inv(16) is likely [letter]. Haematologica 2004; 89:495.

UpToDate®

DREAM9

Online Description of Dataset:

https://www.synapse.org/#!Synapse:syn2455683/wiki/64621

Online Visualization Tool:

https://www.synapse.org/#!Synapse:syn2455683/wiki/64622

DREAM9 Subchallenges

1. Predict which patients will achieve CR
   - Binary Classification
2. Predict remission duration in the CR cases
   - Censored Regression
3. Predict overall survival of all patients
   - Censored Regression

Performance Metrics

a) Balanced Accuracy:
   - 0.5 * (sensitivity + specificity)
b) AUROC
   - Area under the receiver-operator characteristic
c) Concordance Index
d) Pearson Correlation Coefficient