2023 Update to Myeloid Neoplasms

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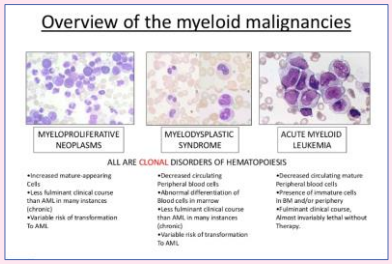
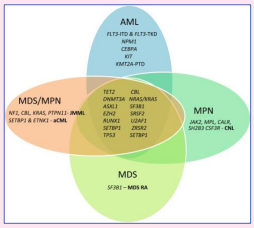
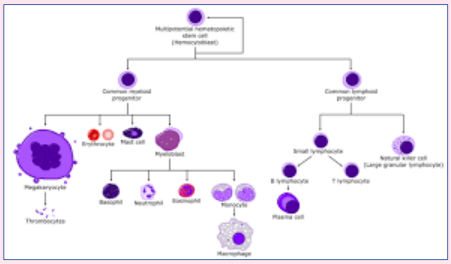
2022-2023 FCDS EDUCATIONAL WEBCAST SERIES

4/20/2023

STEVEN PEACE, CTR







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CDC & Florida DOH Attribution

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FCDS would also like to acknowledge the Florida Department of Health for its support of the Florida Cancer Data System, including the development, printing and distribution of materials for the 2022 Virtual FCDS Annual Conference and the 2022-2023 FCDS Webcast Series under state contract COHAW. The findings and conclusions in this series are those of the author(s) and do not necessarily represent the official position of the Florida Department of Health.

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FLccSC LMS – CEU Quiz – FCDS IDEA

3

FLccSC
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NO CEU QUIZ FOR THIS WEBCAST

NCRA CEU# is 2022-162

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3

Outline

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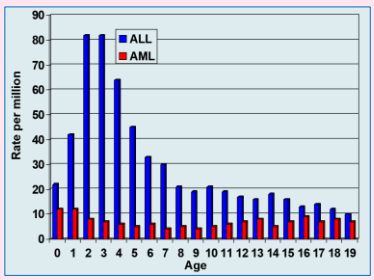
- Introduction to Myeloid Neoplasms
- Who Gets Myeloid Neoplasms & Why So Many Types
- Pediatric versus Adult Myeloid Neoplasms
- Inaugural WHO Classification of Pediatric Tumors
- Blood, Bone Marrow and Circulatory System - Anatomy
- Milestones in the Classification of Tumors of Hematopoietic Tissues
- "Overlap Syndromes" – What is the Diagnosis? How Many Primaries?
- WHO Classification of Hematolymphoid Tumors, 5th ed – BETA Version
- Molecular Genetics and Tumor Markers for Myeloid Neoplasms
- The 2022 Hematopoietic Manual and Hematopoietic Data Base
- Diagnostic Confirmation for Myeloid Neoplasms & "Transformations"
- Workup and Staging Myeloid Neoplasms – Never N/A or No Staging
- Treatment Guidelines for Myeloid Neoplasms
- Blood and Marrow Stem Cell Transplant Procedures
- Documentation Needed for Myeloid Neoplasms
- 2022 FCDS Audit of Lymphoid and Myeloid Neoplasms – June 30, 2023
- Questions



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Hematopoiesis - Myeloid

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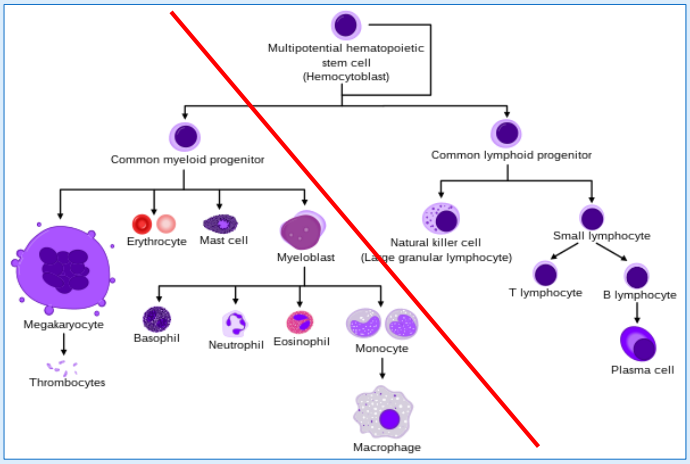
Myeloid



Lymphoid

Image:Hematopoiesis (human) diagram.png by A. Rad

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Introduction to Myeloid Neoplasms

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- Myeloid malignancies are clonal disorders of the progenitor cells or hematopoietic stem cells, which are comprised of chronic phases including myeloproliferative neoplasms, myelodysplastic disorders, chronic myelomonocytic leukemia, and acute stages, i.e., acute myeloid leukemia.
- Chronic phases of myeloid neoplasms all carry a risk of disease evolution or 'transformation' to acute myeloid leukemia of on variety or another – there are many subtypes of acute myeloid leukemia
- There are many carcinogenic exposures related to development of myeloid disease and many genetic mutations associated with disease
- An individual may even develop a myeloid malignancy due to genetics, post cytotoxic therapy, exposure to petrochemicals like benzene or radiation

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Pediatric versus Adult Myeloid Neoplasms

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- Myeloproliferative (MPN) and Myelodysplastic (MDS) Conditions are exceedingly rare in children but fairly common in older adults
- The drivers/causes for MPN and MDS and the genetic makeup are different in children than in adults and probably different diseases
- CMML and JMML (myelomonocytic leukemias) are also probably different types of MML diseases – juvenile and chronic in elderly
- CMML is not CML – be careful delineating the differences
- AML occurs most frequently in adults over age 60
- AML is much less common in children - as young as a few days old
- Pediatric AML is entirely different genetically than adult AML
- Knowing that pediatric myeloid and older adult myeloid neoplasms are totally different diseases that happen to have the same name is confusing
- The primary reason molecular pathology now plays a huge role in distinguishing differences in myeloid neoplasms – not just pediatric versus adult but differentiating the numerous subtypes and requiring different diagnostic/treatment approaches

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Inaugural WHO Classification of Pediatric Tumors

8

A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era

Stefan M. Pfister[1,2,3], Miguel Reyes-Múgica[4,5], John K.C. Chan[6], Henrik Hasle[7], Alexander J. Lazar[8], Sabrina Rossi[9], Andrea Ferrari[10], Jason A. Jarzembowski[11], Kathy Pritchard-Jones[12], D. Ashley Hill[13], Thomas S. Jacques[14,15], Pieter Wesseling[16,17], Dolores H. López Terrada[18], Andreas von Deimling[19,20], Christian P. Kratz[21], Ian A. Cree[22], and Rita Alaggio[9]

ABSTRACT Pediatric tumors are uncommon, yet are the leading cause of cancer-related death in childhood. Tumor types, molecular characteristics, and pathogenesis are unique, often originating from a single genetic driver event. The specific diagnostic challenges of childhood tumors led to the development of the first World Health Organization (WHO) Classification of Pediatric Tumors. The classification is rooted in a multilayered approach, incorporating morphology, IHC, and molecular characteristics. The volume is organized according to organ sites and provides a single, state-of-the-art compendium of pediatric tumor types. A special emphasis was placed on "blastomas," which variably recapitulate the morphologic maturation of organs from which they originate.

Significance: In this review, we briefly summarize the main features and updates of each chapter of the inaugural WHO Classification of Pediatric Tumors, including its rapid transition from a mostly microscopic into a molecularly driven classification systematically taking recent discoveries in pediatric tumor genomics into account.

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Inaugural WHO Classification of Pediatric Tumors

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Myeloid neoplasms
Myeloproliferative neoplasms
Chronic myeloid leukemia, *BCR::ABL1* positive
Myelodysplastic/myeloproliferative neoplasms
Juvenile myelomonocytic leukemia
Myelodysplastic syndromes
Refractory cytopenia of childhood
Myelodysplastic syndrome with excess blasts
Myeloid neoplasms with germline predisposition
Myeloid proliferations associated with Down syndrome
Acute myeloid leukemia and related neoplasms
Acute myeloid leukemia, NOS
Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1::RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB::MYH11*
APL with t(15;17)(q24.1;q21.2); *PML::RARA*
AML with *KMT2A*-rearrangement *new*
AML with t(6;9)(p23;q34.1); *DEK::NUP214*
AML with inv(3)(q21q26)/t(3;3)(q21;q26); *GATA2, RPN1::MECOM*
AML with *ETV6*-fusion *new*
AML with t(8;16)(p11.2;p13.3); *KAT6A::CREBBP new*
AML with t(1;22)(p13.3;q13.1); *RBM15::MKL1*
AML with *CBFA2T3::GLIS2* (inv(16)(p13q24)) *new*
AML with *NUP98*-fusion *new*
AML with t(16;21)(p11;q22); *FUS::ERG new*
AML with mutated *NPM1*
AML with bZIP mutated *CEBPA*

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Adult Myeloid and Lymphoid Neoplasms

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Figure 3. Leading Sites of New Cancer Cases and Deaths – 2022 Estimates

Estimated New Cases

Male			Female		
Prostate	268,490	27%	Breast	287,850	31%
Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
Pancreas	32,970	3%	Leukemia	24,840	3%
All sites	983,160		All sites	934,870	

Estimated Deaths

Male			Female		
Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
Prostate	34,500	11%	Breast	43,250	15%
Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
Pancreas	25,970	8%	Pancreas	23,860	8%
Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
Leukemia	14,020	4%	Uterine corpus	12,550	4%
Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
Urinary bladder	12,120	4%	Leukemia	9,980	3%
Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
All sites	322,090		All sites	287,270	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

2022 Cancer Facts & Figures – American Cancer Society

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Pediatric Myeloid and Lymphoid Neoplasms

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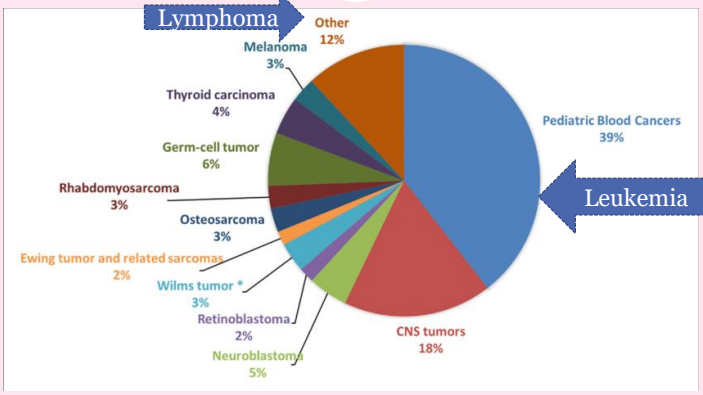

Frequency of pediatric cancers in patients younger than 19 years. The figure shows the prevalence of the main pediatric cancer types among patients younger than 19 years of age, calculated from Centers for Disease Control and Prevention (CDC) data (United States Cancer Statistics Data, https://wonder.cdc.gov/ cancer.html) and based on incidence in United States for the years 1999-2016.

Source: CDC NPCR United States Cancer Statistics

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Blood, Bone Marrow, Circulatory System - Anatomy

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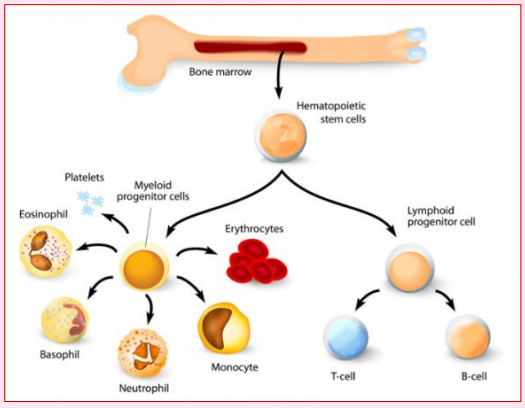
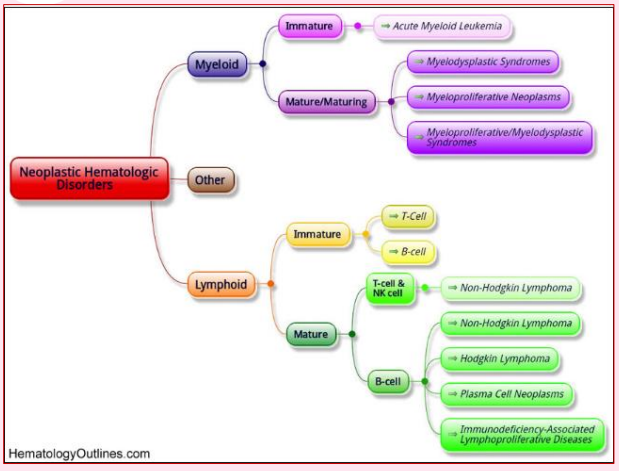


https://www.medicalnewstoday.com/articles/285666.php



https://HematologyOutlines.com

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Blood, Bone Marrow, Circulatory System - Anatomy

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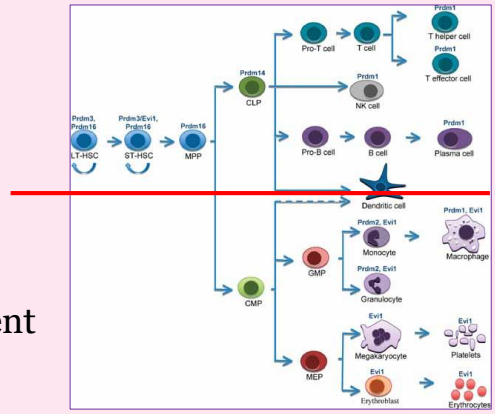
- Cell differentiation
- Regulation of proliferation
- Regulation of differentiation
- Turn on/Turn off
  - Growth factors
  - Genes (including mutations)
  - Proteins
- Dysregulation disrupts normal development
- Oncogenesis – becoming malignant
- Shows up in genetic mutations of all sorts



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Blood, Bone Marrow, Circulatory System - Anatomy

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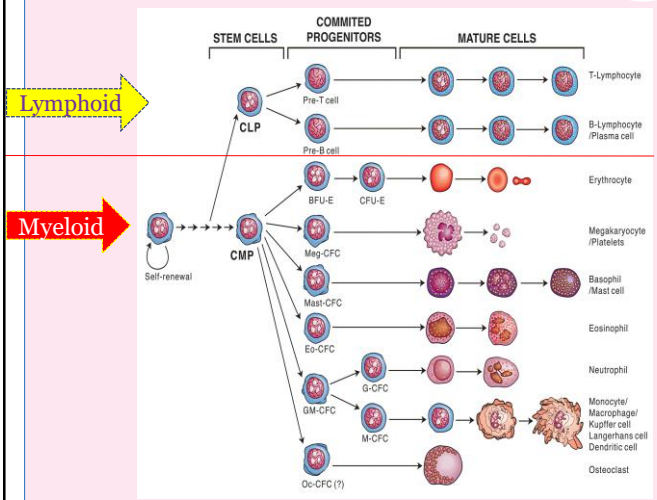

- Cellular differentiation is the process by which an immature cell becomes a more mature cell
- Differentiation changes a cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals or signal pathways
- Regulatory function of cells (regulates cell line proliferation and cell line differentiation) so you have right mix of different types of hematopoietic cells being produced by the bone marrow…and circulating in the blood and/or lymph.
- Over/Under Production by bone marrow of one cell line
- Too many/too few cells leads to chronic/acute disease

Blood Lines – Donald Metcalf, Alpha from MED Press, 2005

Figure 3.2 The eight major hematopoietic lineages generated by self-renewing multipotential stem cells

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Why are cell line, proliferation, differentiation and function important?

15

- All cells contain the full complement of biomolecules that are necessary for survival, proliferation, differentiation, cell death, and expression of many cell type–specific functions. These functions are controlled in normal cells and one or more of the functions operate out of control in cancer cells.
- Regulatory function of cells (proliferation and differentiation) ensure you have right mix/balance of hematopoietic cells produced by the bone marrow…and circulating in the blood and/or lymph.
- Failure to regulate the functions properly (dysregulation) results in an altered phenotype and cancer.
- Cell Lines show which major group of disease the malignancy occurs – lymphoid/myeloid
- Proliferation is the process when the body/bone marrow makes too many of a specific type of cells
- Differentiation is the process of an immature cell becoming a mature cell with a specific function.
- Mutations can occur during proliferation & differentiation – pathways to neoplastic development

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Blood, Bone Marrow, Circulatory System - Anatomy

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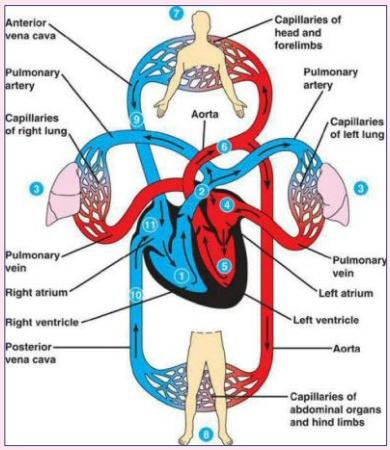

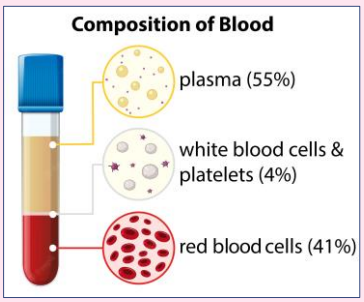

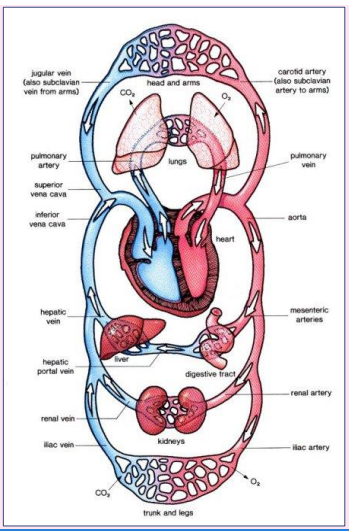

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Milestones - Classification of Hematopoietic Neoplasms

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- 1951, William Dameshek described the concept of 'myeloproliferative disorders' by grouping together chronic myelogenous leukemia, polycythemia vera, essential thrombocythemia, primary myelofibrosis and erythroleukemia
- 1960, Nowell and Hungerford discovered the Philadelphia (Ph) chromosome in CML.
- 1967, Fialkow and colleagues used X-linked polymorphisms to establish CML as a clonal stem cell disease.
- 1967, the PV Study Group was summoned by Louis Wasserman to study the natural history of Polycythemia Vera and conduct large-scale clinical trials.
- 1972, Janet Rowley deciphered the Ph chromosome as a reciprocal translocation between chromosomes 9 and 22, thus paving the way for its subsequent characterization as an oncogenic BCR–ABL mutation.
- 1996, Brian Druker discovered imatinib (Gleevec) —a small molecule ABL inhibitor with exceptional therapeutic activity in CML.
- 2005, a gain-of-function JAK2 mutation (JAK2V617F) was described in BCR–ABL-negative MPDs, raising the prospect of a CML-like treatment strategy in PV, ET and PMF.

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Milestones - Classification of Hematopoietic Neoplasms

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- 1951 – Dameshek – clinical phenotype
- 1960 – Philadelphia (Ph1) chromosome
- 1966 – Rappaport Classification
- 1974 – Kiel Classification System
- 1974 – Lukes and Collins System
- 1976 – Revised Rappaport Classification
- 1976 – French/American/British (FAB) Classification
- 1982 – Working Formulation
- 1994 –Revised European-American Classification of Lymphoid Neoplasms
- 2001 – WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, 3rd edition, 2001
- 2008 – WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, 4th edition, October 2008
- 2016 – Revision to 4th edition, 2017
- 2022 – WHO Classification of Hematolymphoid Tumors, 5th ed

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"Overlap Myeloid Syndromes" – Number of Primaries

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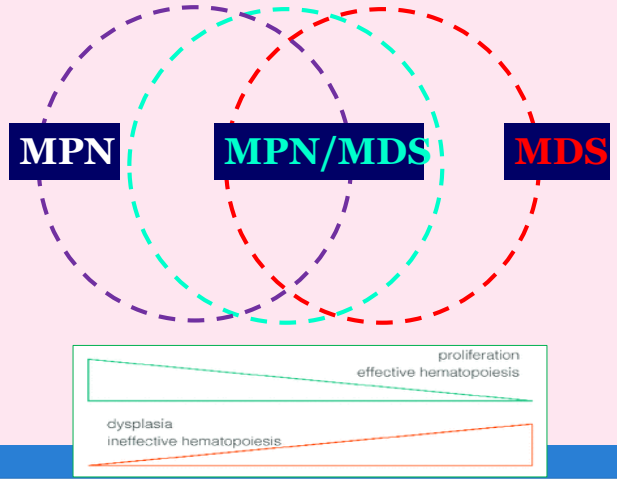

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"Overlap Myeloid Syndromes" – Number of Primaries

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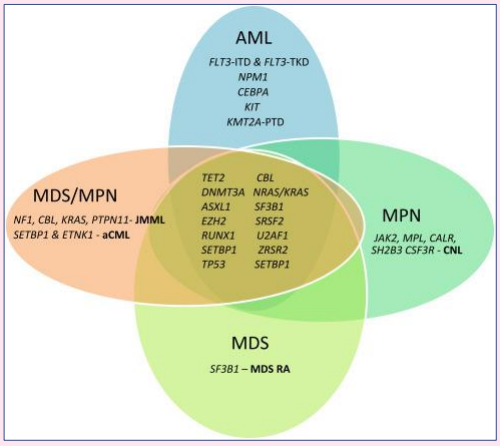

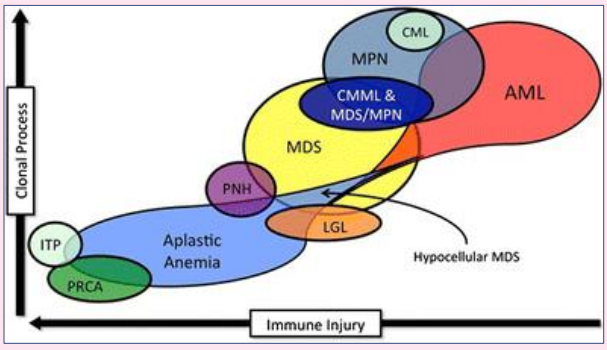

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Chronic versus Acute – In Remission Does Not Mean Cured

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Note: Patients with 'chronic' neoplastic conditions *such as chronic leukemia, myelodysplastic syndromes and myeloproliferative diseases, or other lymphoid/myeloid neoplasms designated as 'chronic' disease always have some level of active disease and must be reported. Treatment for these neoplasms may achieve a state of 'clinical remission'. However, these conditions cannot be cured without aggressive therapy including high-dose chemotherapy plus bone marrow transplant or stem cell transplant. The chronic nature of their disease makes these cases always reportable, regardless of clinical status.*

Remission Means Different Things to Different People

Clinical Remission, Complete Remission, Partial Remission, Clinical Response to Treatment, Measurable Response to Treatment, Stable Disease, Durable Remission, A Reduction, Resolution or Remission of Symptoms Complete Molecular Remission

MPN, MDS, Chronic Leukemia, Myeloma – ARE CHRONIC CONDITIONS
They CAN be **Potentially** Cured with High-Dose Chemo and **Allogeneic** Bone Marrow Transplant
They may have 'clinical remission' but not 'total remission/cure' with BMT (not auto-SCT)
ICD-10-CM Codes may indicate 'in remission' – but this remission is rarely a 'cure'

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Is 'In Remission' the Same as 'Cancer Free'?

22

What does it mean when cancer is 'in remission'?

A decrease in or disappearance of signs and symptoms of cancer.
The signs and symptoms of your cancer are reduced.
Remission can be partial or complete.

In **partial remission**, some, but not all, signs and symptoms of cancer have disappeared.

In **complete remission**, all signs and symptoms of cancer have disappeared,
although cancer still may be in the body.

A **complete remission for 5 years or more**, ***some*** doctors ***may say*** that you are ***cured***.

SUMMARY: 'in remission' is not 'cured of cancer'...especially for the myeloid neoplasms.

People can go into remission for many years.

22

Molecular Genetics and Tumor Markers for Myeloid Neoplasms

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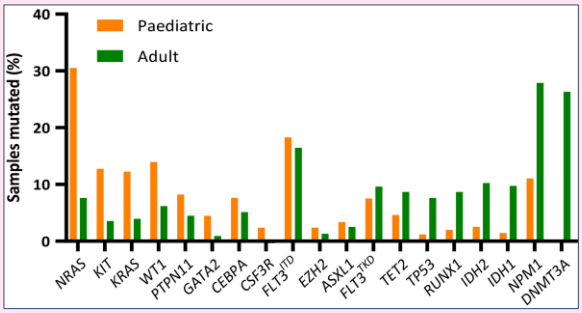

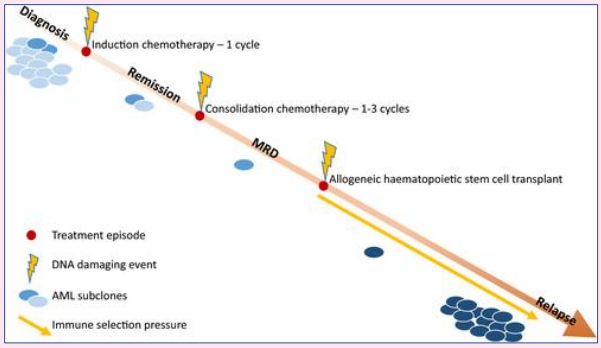

Prevalence of somatic mutations in adult versus paediatric AML. Adapted from Bolouri et al., 2018.

23

Molecular Genetics and Tumor Markers for Myeloid Neoplasms

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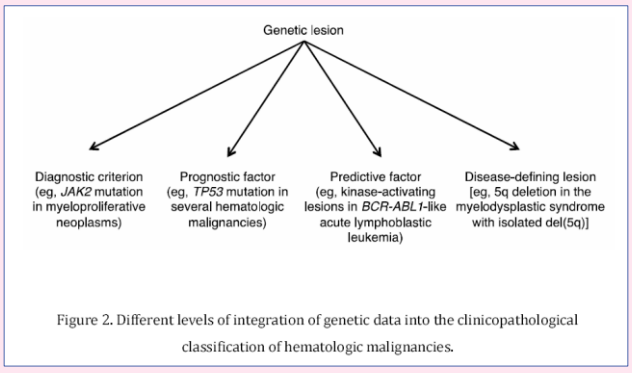

Figure 2. Different levels of integration of genetic data into the clinicopathological classification of hematologic malignancies.

24

Integrated Diagnosis, Essential & Desirable Diagnostic Criteria

25

- The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of diagnostic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. Using the classification to its fullest extent requires specialized techniques, which at a minimum should include immunophenotyping, conventional karyotyping, fluorescence in situ hybridization (FISH), and mutation profiling.
- **Diagnostic Integration or Integrated Diagnosis** - this classification is predicated on **integrating morphologic** (cytology and histology), **immunophenotypic**, **molecular and cytogenetic data**.
- The **essential and desirable diagnostic criteria** are intended to facilitate distilling the key diagnostic components needed to classify a particular disease type.
- **Essential diagnostic criteria** are considered must-have features
- **Desirable diagnostic criteria** are 'nice-to-have' features (they support a diagnosis but are not mandatory).

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Integrated Diagnosis, Essential & Desirable Diagnostic Criteria

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- Even the pathologists and oncologists are struggling with information overload from all of these tests – and their responsibility to interpret a complex set of literally hundreds of results from molecular testing while knowing only some of the results 'might' be important to Dx or Tx. So some Dx end up 'generic'.
- All of these new tests are new. It is not an exact science yet – and may never be…it is rapidly evolving.
- Not every case will fit neatly into a word-match like our traditional microscopic histology did
- Every case is individualized with some level of unique individual mutation(s)
- Cases will have some 'in common' mutations – but there is always something unique – that's what genetics is all about – molecular tests are drawing lines around 'families' of malignancies
- If each case required full interpretation of the entire set of mutations for each individual tumor we would have thousands of new histology codes to account for each tumor's unique genetic makeup
- That is why we have to rely on the pathologist and oncologist to give us the integrated diagnosis
- It is up to us to document the integrated diagnosis and which tests led the pathologist and/or oncologist to the conclusion that it was xyz lymphoma or 123 leukemia – but they still have to make the statement

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What Type of Test Do I Look for in Myeloid Neoplasms?

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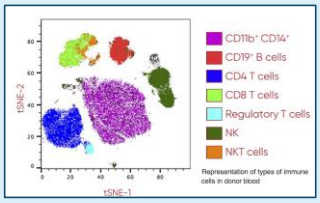
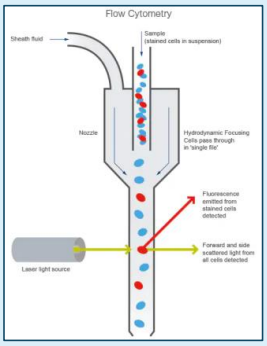
1. Did the patient have one or more of the following tests performed on blood, lymph, bone marrow or tissue biopsy or resection (traditional microscopic anatomic pathology)?

- Immunophenotype
  - Flow cytometry (cell sorting/counting) for cluster of designation or CD marker analysis,
  - IHC (immunohistochemistry) for CD marker analysis,
  - PCR testing (polymerase chain reaction) for CD marker analysis,
- Molecular pathology studies to analyze DNA or other genetic material using;
  - Single gene test,
  - Genetic panel test,
  - Multi-gene panel test,
  - DNA Microarray,
  - Biomolecular marker(s),
  - FISH (fluorescent in-situ hybridization),
  - Other Immunofluorescence testing,
  - Next-generation sequencing (NGS) gene panel, or
  - Other DNA/RNA/gene testing





2. Did any of the additional test results; confirm the diagnosis, clarify the type of neoplasm (histologic type or subtype), or identify a target drug or specific biological, molecular or immunotherapy (BRM)?

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Flow Cytometry – How it Works

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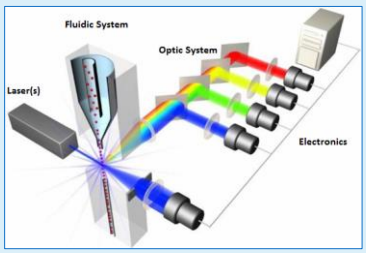

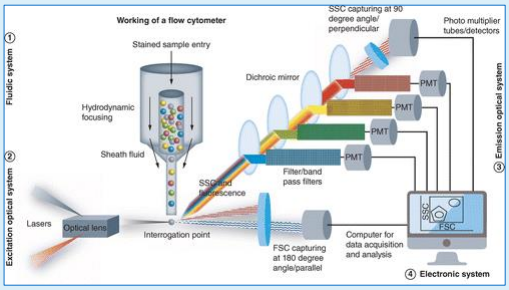

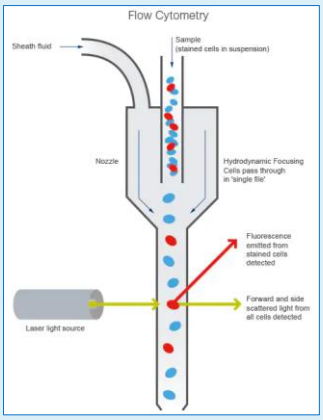

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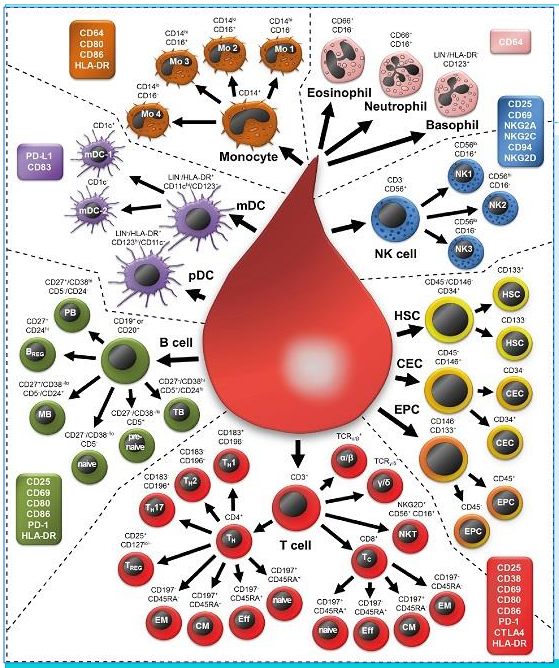

Flow Cytometry Assays and Reports

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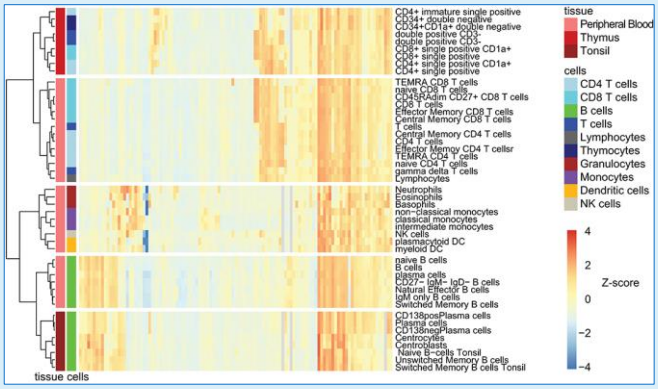

Int. J. Mol. Sci. **2016**, *17*(8), 1316; https://doi.org/10.3390/ijms17081316

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Molecular Genetics and Tumor Markers for Myeloid Neoplasms

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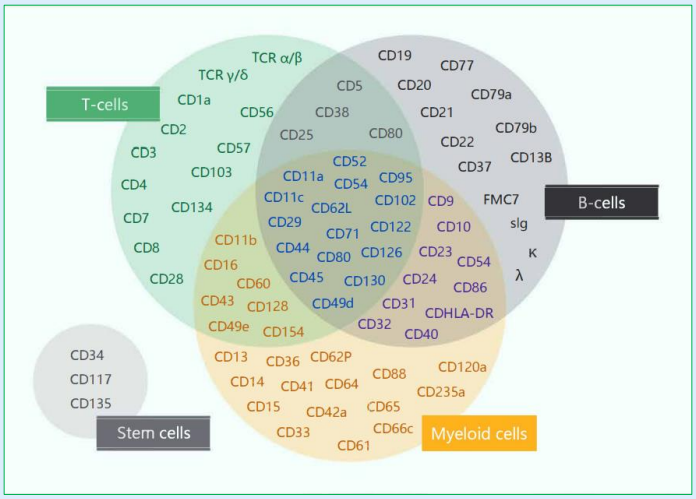

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What about Molecular Pathology

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	Early detection	Cancer diagnosis	Workup	Treatment	Monitoring recurrence	Relapse
Standard of care	Imaging, protein testing (i.e. PSA)	Tissue biopsy	Tissue testing	Late stage: systemic Early stage: curative	Imaging, protein testing (i.e. PSA)	Tissue biopsy
Liquid biopsy opportunity	Early detection of cancer in higher risk individuals		Therapy selection in advanced stage cancer patients		Minimal residual disease and recurrence detection in cancer survivors	
Market size	~ $18 billion (for higher risk individuals)		~$6 billion		~$15 billion	
# of Patients	35 million		0.7 million		15 million	
Products	LUNAR - 2		GUARDANT360 GUARDANT OMNI		LUNAR - 1	

https://www.guardantcomplete.com/guardant-portfolio/cdx

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What about Molecular Pathology

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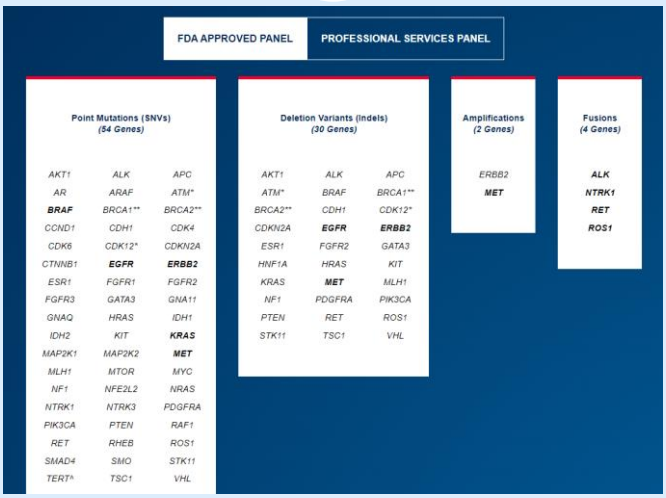

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Integrating Anatomic and Molecular Pathology Service

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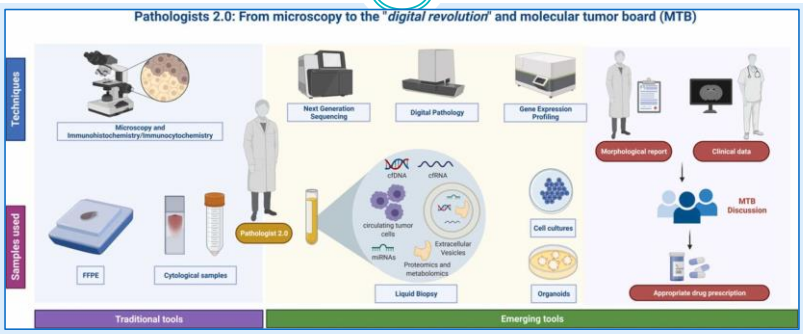

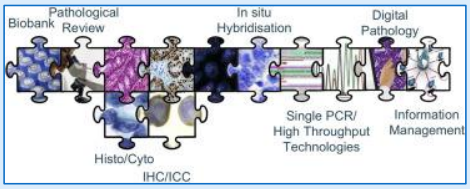

Science Direct – The Evolving Landscape of Anatomic Pathology

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WHO Classification of Hematolymphoid Tumors, 5th ed

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BETA Version – so, there are no 'final' codes or preferred terms.

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury[1✉], Eric Solary[2✉], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52✉]

Leukemia (2022) 36:1703–1719; https://doi.org/10.1038/s41375-022-01613-1

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WHO Classification of Hematolymphoid Tumors, 5th ed

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BETA Version – so, there are no 'final' codes or preferred terms.

- We have organization and 'families' and diagnostic criteria in the specific entities
- But we do not have 'histology' codes or finalized 'preferred terms'
- "Histology" is now a misnomer – histology indicates microscopic diagnosis – most myeloid neoplasms are now diagnosed based on microscopic findings, molecular pathology, immunophenotype, other tests
- We still call it a 'histology code' – but in fact it is now an 'INTEGRATED DIAGNOSIS' based on much more than just the microscopic findings or a blood smear or a bone marrow analysis.
- When the pathology report just lists all of the tests they performed either with or without a result – the pathologist still should provide you with a "Final Diagnosis" that is an "Integrated Diagnosis" that takes into account all of the 'parts' to come up with a final diagnosis.
- When all they do is list the tests and the results without a final diagnosis – there are still codes that are NOS codes for microscopic diagnosis only – the additional tests must prove something else to be used.
- If all of the tests are negative – there is only an NOS diagnosis – I will show you how this is structured.

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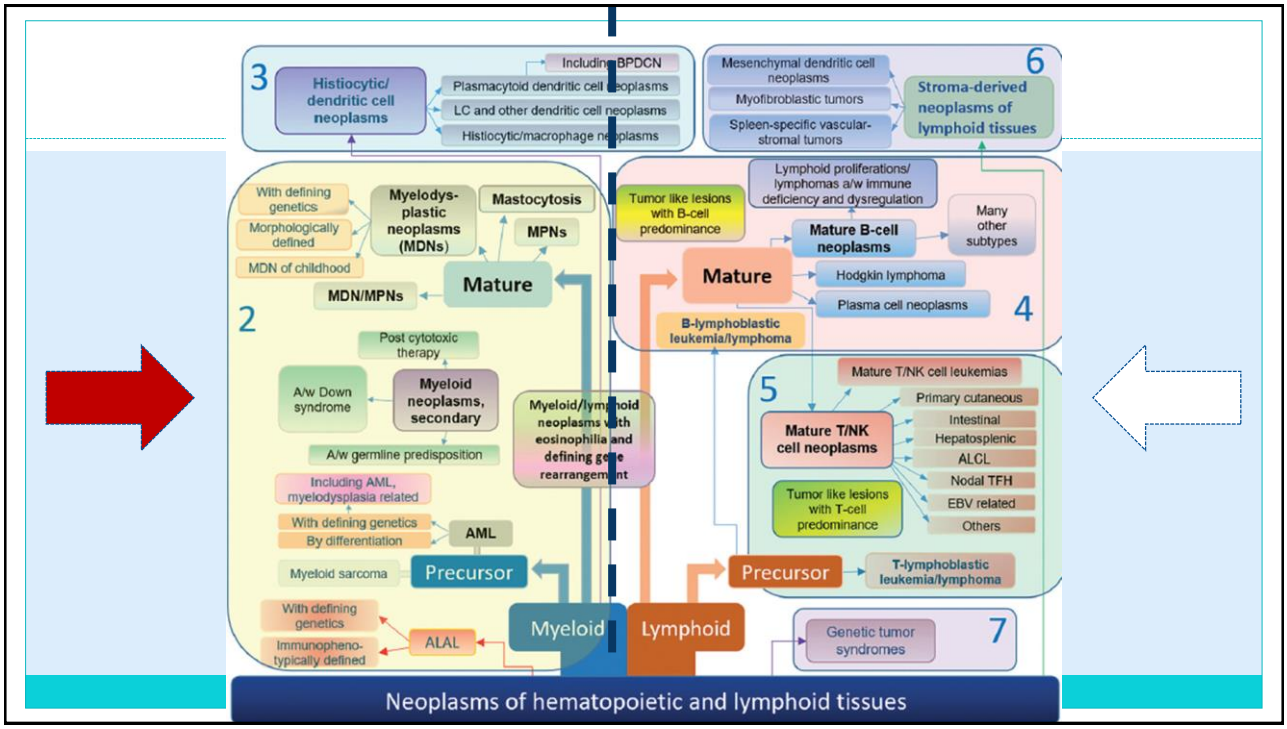

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WHO Classification of Hematolymphoid Tumors, 5th ed

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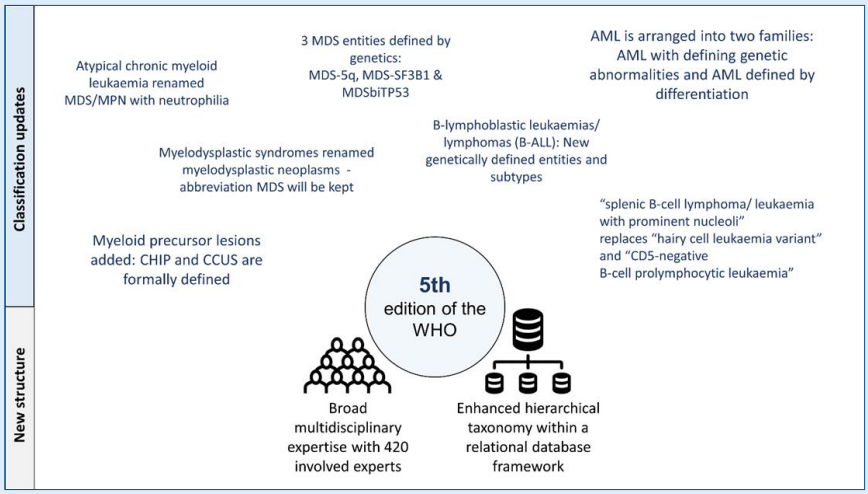

MLL Magazine – http://mll.com/en/the-new-who-classification-2022

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Table 1: Myeloproliferative neoplasms.
Chronic myeloid leukaemia
Polycythaemia vera
Essential thrombocythaemia
Primary myelofibrosis
Chronic neutrophilic leukaemia
Chronic eosinophilic leukaemia
Juvenile myelomonocytic leukaemia
Myeloproliferative neoplasm, not otherwise specified

BCR-ABL Fusion Gene
Philadelphia Chromosome

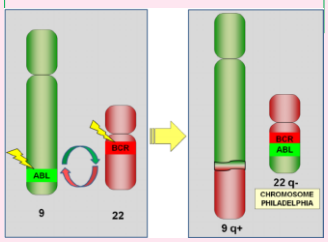

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Table 2. Mastocytosis types and subtypes.

Cutaneous mastocytosis
Urticaria pigmentosa/Maculopapular cutaneous mastocytosis
Monomorphic
Polymorphic
Diffuse cutaneous mastocytosis
Cutaneous mastocytoma
Isolated mastocytoma
Multilocalized mastocytoma
Systemic mastocytosis
Bone marrow mastocytosis
Indolent systemic mastocytosis
Smoldering systemic mastocytosis
Aggressive systemic mastocytosis
Systemic mastocytosis with an associated haematologic neoplasm
Mast cell leukemia
Mast cell sarcoma
Note: Well-differentiated systemic mastocytosis (WDSM) represents a morphologic variant that may occur in any SM type/subtype, including mast cell leukaemia.

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Myeloid precursor lesions

Clonal Haematopoiesis

Clonal haematopoiesis

Clonal cytopenias of undetermined significance

Myeloproliferative neoplasms

Myeloproliferative neoplasms

Chronic myeloid leukemia

Chronic neutrophilic leukemia

Chronic eosinophilic leukemia

Polycythemia vera

Essential thrombocythemia

Primary myelofibrosis

Juvenile myelomonocytic leukemia

Myeloproliferative neoplasm, NOS

Mastocytosis

Cutaneous mastocytosis

Systemic mastocytosis

Mast cell sarcoma

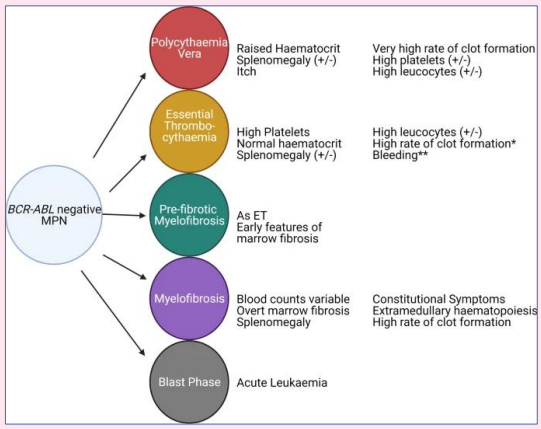

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Table 3. Classification and defining features of myelodysplastic neoplasms (MDS)

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

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Table 5. Myelodysplastic/myeloproliferative neoplasms.

Chronic myelomonocytic leukaemia
Myelodysplastic/myeloproliferative neoplasm with neutrophilia
Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

- CMML diagnostic criteria undergo major revisions, including lowering the cutoff for absolute monocytosis, adopting MD-CMML and MPCMML subtypes, and eliminating CMML-0.
- Atypical chronic myeloid leukaemia renamed MDS/MPN with neutrophilia.
- MDS/MPN with ring sideroblasts and thrombocytosis redefined based on SF3B1 mutation and renamed MDS/MPN with SF3B1 mutation and thrombocytosis.

Table 6. Diagnostic criteria of chronic myelomonocytic leukaemia.

Prerequisite criteria
1. Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]
Supporting criteria
1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]
Requirements for diagnosis
- Pre-requisite criteria must be present in all cases.
- If monocytosis is ≥ 1 × 10^9/L: one or more supporting criteria must be met.
- If monocytosis is ≥0.5 and <1 × 10^9/L: supporting criteria 1 and 2 must be met.
Subtyping criteria
- Myelodysplastic CMML (MD-CMML): WBC < 13 × 10^9/L
- Myeloproliferative CMML (MP-CMML): WBC ≥ 13 × 10^9/L
Subgrouping criteria (based on percentage of blasts and promonocytes)
CMML-1: <5% in peripheral blood and <10% in bone marrow
CMML-2: 5–19% in peripheral blood and 10-19% in bone marrow
[a]Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes.

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Myelodysplastic neoplasms

Myelodysplastic neoplasms, with defining genetic abnormalities

- Myelodysplastic neoplasm with low blasts and 5q deletion
- Myelodysplastic neoplasm with low blasts and SF3B1 mutation
- Myelodysplastic neoplasm with biallelic TP53 inactivation

Myelodysplastic neoplasms, morphologically defined

- Myelodysplastic neoplasm with low blasts
- Myelodysplastic neoplasm, hypoplastic
- Myelodysplastic neoplasm with increased blasts

Myelodysplastic neoplasms of childhood

- Childhood myelodysplastic neoplasm with low blasts
- Childhood myelodysplastic neoplasm with increased blasts

Myelodysplastic/myeloproliferative neoplasms

Chronic myelomonocytic leukemia

- Myelodysplastic/myeloproliferative neoplasm with neutrophilia
- Myelodysplastic/myeloproliferative neoplasm with SF3B1 mutation and thrombocytosis
- Myelodysplastic/myeloproliferative neoplasm, NOS

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Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML::RARA* fusion
Acute myeloid leukaemia with *RUNX1::RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB::MYH11* fusion
Acute myeloid leukaemia with *DEK::NUP214* fusion
Acute myeloid leukaemia with *RBM15::MRTFA* fusion
Acute myeloid leukaemia with *BCR::ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Mutations in the FL3T3, TP53, RUNX1, and ASXL1 genes are linked with a worse outlook.

Mutations in the NPM1 gene and in both copies of CEBPA gene linked to a better outcome

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Acute myeloid leukemia

Acute myeloid leukemia with defining genetic abnormalities
- Acute promyelocytic leukemia with PML::RARA fusion
- Acute myeloid leukemia with RUNX1::RUNX1T1 fusion
- Acute myeloid leukemia with CBFB::MYH11 fusion
- Acute myeloid leukemia with DEK::NUP214 fusion
- Acute myeloid leukemia with RBM15::MRTFA fusion
- Acute myeloid leukemia with BCR::ABL1 fusion
- Acute myeloid leukemia with KMT2A rearrangement
- Acute myeloid leukemia with MECOM rearrangement
- Acute myeloid leukemia with NUP98 rearrangement
- Acute myeloid leukemia with NPM1 mutation
- Acute myeloid leukemia with CEBPA mutation
- Acute myeloid leukemia, myelodysplasia-related
- Acute myeloid leukemia with other defined genetic alterations

Acute myeloid leukemia, defined by differentiation
- Acute myeloid leukemia with minimal differentiation
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute basophilic leukemia
- Acute myelomonocytic leukemia
- Acute monocytic leukemia
- Acute erythroid leukemia
- Acute megakaryoblastic leukemia

Myeloid sarcoma
- Myeloid sarcoma

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WHO Classification of Hematolymphoid Tumors, 5th ed

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Table 8. Cytogenetic and molecular abnormalities defining acute myeloid leukaemia, myelodysplasia-related.

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

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Demonstration Hematopoietic Manual and Hematopoietic Data Base

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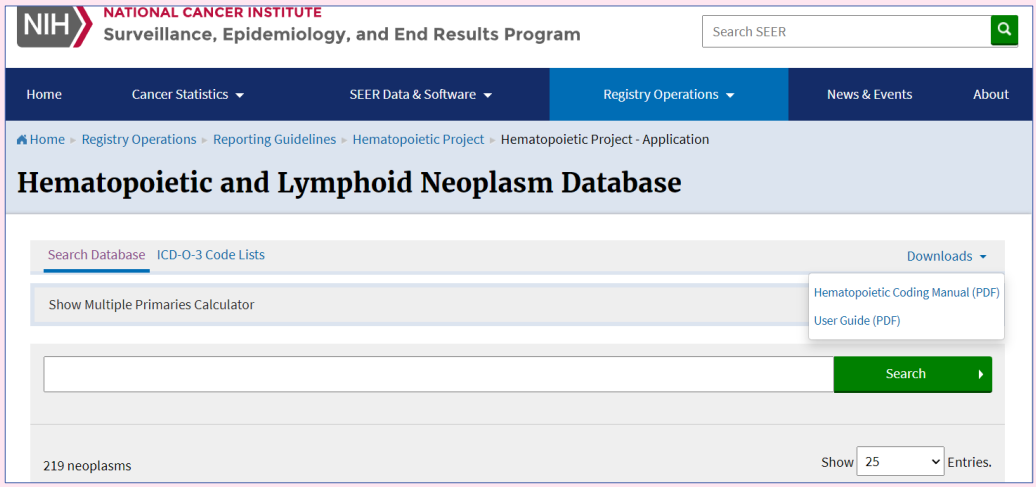

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Coding Primary Site

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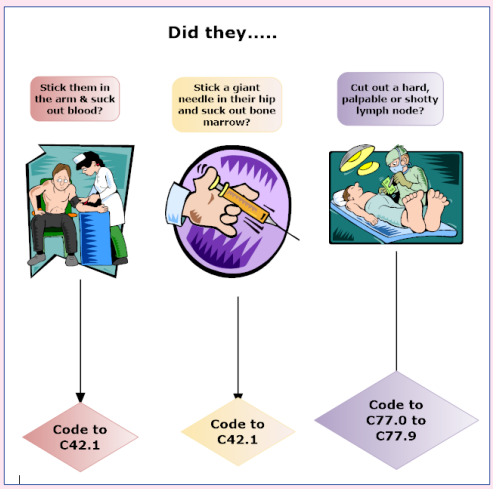

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The 2022 Hematopoietic Manual and Hematopoietic Data Base

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Hematopoietic and Lymphoid Neoplasm Coding Manual

Effective with Cases Diagnosed 1/1/2010 and Forward

Published August 2021

SEER

Editors: Jennifer Ruhl, MSHCA, RHIT, CCS, CTR, NCI SEER
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Suggested citation: Ruhl J, Adamo M, Dickie L., Negoita, S. (August 2021). Hematopoietic and Lymphoid Neoplasm Coding Manual. National Cancer Institute, Bethesda, MD, 2021.

Steps for Using the Heme DB and Hematopoietic Coding Manual

Note: The search function for the Hematopoietic Database has recently changed. For most users, there will not be a noticeable difference. Information regarding the search function has been updated below.

Follow each step in the order listed

1. Identify the working (preliminary) **histology code(s)**
   a. Search the Heme DB using any of the methods below
      i. Search using a **unique word** in the diagnosis; for example, "precursor" if the diagnosis is precursor acute lymphoblastic leukemia
         - Avoid searching on general terms such as "leukemia" or "lymphoma." This type of search will return too many results.
      ii. Search on the **complete name** (diagnosis). For example, "acute myelomonocytic leukemia". Two different results will appear
         - 107 neoplasms match any term. The words may appear in any part of the entry (alternate names, abstractor notes, transformations, etc.)
         - 10 neoplasms match all terms. This is when all three words occur together
      iii. You can also search on **abbreviations** such as AMML for acute myelomonocytic leukemia, DLBCL for diffuse large B-cell lymphoma, or AML for acute myeloid leukemia.
   b. "Show Alternate Names": This box appears under the Search box. If this box is checked, the results will include an additional column that shows where alternate names include the words being search
   c. Search on histology code if desired, i.e., 9867/3.
   d. When multiple results are displayed, click on the desired term (e.g. acute myelomonocytic leukemia) to display the record.
2. Use the Multiple Primary Rules to determine the number **of primaries** using the working histology code(s)
   a. Start with rule M1, move through the rules in consecutive order and stop at the first rule that applies. The M rule references in the Heme DB are to be used as a guide only.
   b. Use the Hematopoietic Multiple Primaries Calculator in the Heme DB **only** when instructed by the rules in the Hematopoietic Manual.
3. Verify or revise the working histology code(s) using the Primary Site and Histology (PH) Rules
   a. When the PH rules lead you to a different histology code, enter that code in the Heme DB search box and display the record for that histology
   b. The PH rules referenced in the Heme DB are the most common rule(s) used to code Primary Site and Histology for the selected histology. More than one Module/PH Rule may be needed to code Primary Site and Histology.
4. Determine **primary site using the Primary Site and Histology Rules in this manual** *(see Note on next page)*
   a. See Primary Site Coding Instructions.
   b. For certain histologies, only one primary site code is displayed in the Heme DB
      i. The primary site code displayed under **Primary Site(s)** is the **only** site code to be used for that histology

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Diagnostic Confirmation for Myeloid Neoplasms

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Example: Peripheral blood flow cytometry report: Flow cytometry express HLA-DR, CD5, CD19, moderate CD20, CD22, bright CD45, bright CD200 and exhibit lambda immunoglobin light chain restriction by intracellular staging. These cells lack expression of CD38. Taken together, these results demonstrate the presence of a clonal population of B-cell, immonphenotypically diagnostic of CLL/SLL

2. NOS histology diagnosed and not a provisional diagnosis and genetics/immunophenotyping was performed.

Example 1 (Identifying a more specific histology): Bone marrow biopsy positive for acute myeloid leukemia (9861/3). Genetic testing positive for AML with inv (16)(p13.1q22) (9871/3). Code Diagnostic Confirmation code 3, positive histology and positive genetic testing, which identified a more specific histology.

Example 2 (Identifying a more specific histology): Peripheral blood smear with lymphoblastic lymphoma (9671/3). Bone marrow biopsy with immunophenotyping showing CD5 negative and IgM positive, diagnosis Waldenstrom Macroglobulinemia (9761/3). Code Diagnostic Confirmation code 3, positive histology and positive immunophenotyping testing which identified a more specific histology.

Example 3 (Confirming the histologic diagnosis): Bone marrow biopsy diagnosis is plasma cell dyscrasia. Peripheral blood smear is compatible with plasma cell leukemia. FISH and chromosome analysis revealed plasma cell myeloma. Both plasma cell leukemia and plasma cell myeloma are coded to the same ICD-O code, 9732/3, so there is only one disease process. The peripheral blood smear is histologic diagnosis for the plasma cell leukemia and FISH confirmed the diagnosis of multiple myeloma/plasma cell myeloma. Code Diagnostic Confirmation 3, positive histology and positive genetic testing.

Example 4 (Histologic confirmation plus genetic and immunophenotyping confirmation): Patient diagnosed with CLL by CBC and flow cytometry that was positive for both the genetic and CD antigens (immunophenotyping) for CLL. A bone marrow biopsy not performed. Since this is leukemia, the CBC is histologic confirmation, so this patient had histologic confirmation, genetic, and immunophenotyping positive for CLL. Code Diagnostic Confirmation 3, positive histology and positive genetic testing/immunophenotyping.

Example 5 (Ambiguous terminology used with immunophenotyping): Bone marrow biopsy shows B lymphoblastic leukemia. Abnormal FISH results most likely represent a hyperdiploid clone. Code the histology to 9811 (B-ALL, NOS) and assign a diagnostic confirmation code of 1. Neither Diagnostic confirmation code 3 nor the more specific hyperdiploidy histology is coded because the associated FISH result is preceded by ambiguous terminology.

: Positive microscopic confirmation, method not specified
rarely used for Hematopoietic and Lymphoid neoplasms.
Assign code 4 when there is information that the diagnosis of cancer was microscopically confirmed, but the type of confirmation is unknown

Code 5: Positive laboratory test/marker study
Assign code 5 when the diagnosis of cancer is based on laboratory tests, tumor marker studies, genetics or immunophenotyping that are diagnostic for that specific cancer. Laboratory tests are listed under Definitive Diagnostic Methods in the Hematopoietic Database. Do not assign code 5 when there is histologic confirmation (See code 1).

NEVER ASSIGN DX CONFIRMATION = 9 FOR MYELOID NEOPLASMS – IT IS 1 or 3 - PERIOD

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Diagnostic Confirmation for Myeloid Neoplasms

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- Note 1: Other than microscopic confirmation (1-4) taking priority over clinical diagnosis only (5-8), there is no priority order or hierarchy for coding the Diagnostic Confirmation for hematopoietic or lymphoid neoplasms. Most commonly the bone marrow provides several provisional diagnoses and the specific histologic type is determined through immunophenotyping or genetic testing.
- Note 2: Use code 1 when ONLY the tissue, bone marrow, or blood was used to diagnose the specific histology. Do not use code 1 if the provisional diagnosis was based on tissue, bone marrow, or blood and the immunophenotyping or genetic testing on that same tissue, bone marrow, or blood identified the specific disease (see Code 3).
- Note 3: If a neoplasm is originally confirmed by histology (code 1), and later has immunophenotyping, genetic testing or JAK2 which confirms a more specific neoplasm and there is no evidence of transformation, change the histology code to the more specific neoplasm and change the diagnostic confirmation to code 3.
- Do not use diagnostic confirmation code 3 for cases diagnosed prior to 1/1/2010.

NEVER ASSIGN DX CONFIRMATION = 9 FOR MYELOID NEOPLASMS – IT IS 1 or 3 - PERIOD

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Diagnostic Confirmation for Myeloid Neoplasms

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Assign code 1 for

1. Tissue from lymph node(s), organ(s) or other tissue specimens from biopsy, frozen section, surgery, or autopsy
2. Bone marrow specimens (aspiration and biopsy)
3. Peripheral blood smear
   a. Can be used as a histological diagnosis for any of the hematopoietic histologies (9590/3-9993/3)
4. **Leukemia** only (9800/3-9948/3): positive histology also includes
   a. Complete blood count (CBC)
   b. White blood count (WBC)
   Note: A registrar may not abstract a hematopoietic neoplasm based on a CBC or WBC with abnormal counts alone. There must be a diagnosis of a reportable Heme neoplasm on the CBC or WBC report or a subsequent physician diagnosis based on the WBC or CBC.
   c. Immunophenotyping, genetic testing, or JAK2 **not** done **OR**
   d. Immunophenotyping, genetic testing, or JAK2 done but **negative** (non-diagnostic) for the neoplasm being abstracted

   Example: Acute myelomonocytic leukemia (9867/3) CD7-. CD7 is listed under Immunophenotyping for this histology and this case is CD7-, so diagnostic confirmation should be 1.
5. IHC studies are done, but the patient has a provisional (NOS) diagnosis or one or more provisional diagnoses.
6. Historical cases not already in the database if information states that there was histologic confirmation

   Example: Patient diagnosed in 2012 with Stage III mantle cell lymphoma, diagnosed by LN biopsy. Mantle cell lymphoma not in the database. Now presents with DLBCL in 2015.

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Diagnostic Confirmation for Myeloid Neoplasms

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Code 3: Positive histology PLUS positive immunophenotyping or genetic testing
Code 3 can be used for cases diagnosed **2010+** with histologic confirmation (see code 1) **AND** immunophenotyping, genetic testing, or JAK2 confirmation

Note 1: While every attempt is made to keep the Hematopoietic database updated, it is impossible to keep the Hematopoietic database updated with all the immunophenotyping or genetics that can be done for a specific histology since clinical medicine continues to evolve. If immunophenotyping or genetics is used by the pathologist/managing physician to identify a **specific** neoplasm that are not included in the Hematopoietic database, and genetic testing and/or immunophenotyping are listed as Definitive Diagnostic methods for that histology, go ahead and use these.

Note 2: The following histologies are diagnosed based on immunophenotyping or genetics and therefore should only be diagnostic confirmation 3: 9806/3, 9807/3, 9808/3, 9809/3, 9812/3, 9813/3, 9814/3, 9815/3, 9816/3, 9817/3, 9818/3, 9819/3, 9865/3, 9866/3, 9867/3, 9871/3, 9872/3, 9873/3, 9875/3, 9876/3, 9879/3, 9896/3, 9897/3, 9911/3, 9912/3, 9965/3, 9966/3, 9967/3, 9968/3, 9986/3.

Note 3: The following histologies should never be assigned diagnostic confirmation 3 since they are non specific codes and neither genetic testing or immunophenotyping are listed as Definitive Diagnostic Methods for these histologies. If there is immunophenotyping or genetics available, then a more specific histology code may be able to be assigned: 9590/3, 9655/3, 9800/3, 9820/3, 9860/3, 9863/3, 9980/3, 9982/3, 9989/3, 9991/3.

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Diagnostic Confirmation for Myeloid Neoplasms

Assign code 3 for

1. Cases with positive histology for the neoplasm being abstracted (including acceptable ambiguous terminology and provisional diagnosis) **AND** immunophenotyping, genetic testing, or JAK2 is listed in the Definitive Diagnosis in the Heme DB **AND** the testing
   a. Confirms the neoplasm **OR**
   b. Identifies a more specific histology (not preceded by ambiguous terminology)
      Note 1: Do not use code 3 for positive immunophenotyping or genetic testing identifying a more specific histology when preceded by ambiguous terminology.
      Note 2: Do not use code 3 for positive immunophenotyping or genetic testing identifying a more specific histology when the test result is preceded by "patchy weak staining."
   c. Peripheral blood smear followed by flow cytometry (most commonly done with CLL/SLL, 9823/3)
      Note: Flow cytometry studies are normally done based on an abnormal blood smear. If unable to find documentation that a peripheral blood smear was done first, assume that it was and code 3

   Example: Peripheral blood flow cytometry report: Flow cytometry express HLA-DR, CD5, CD19, moderate CD20, CD22, bright CD45, bright CD200 and exhibit lambda immunoglobin light chain restriction by intracellular staging. These cells lack expression of CD38. Taken together, these results demonstrate the presence of a clonal population of B-cell, immonphenotypically diagnostic of CLL/SLL

2. NOS histology diagnosed and not a provisional diagnosis and genetics/immunophenotyping was performed.

Example 1 (Identifying a more specific histology): Bone marrow biopsy positive for acute myeloid leukemia (9861/3). Genetic testing positive for AML with inv (16) (p13.1q22) (9871/3). Code Diagnostic Confirmation code 3, positive histology and positive genetic testing, which identified a more specific histology.

Example 2 (Identifying a more specific histology): Peripheral blood smear with lymphoblastic lymphoma (9671/3). Bone marrow biopsy with immunophenotyping showing CD5 negative and IgM positive, diagnosis Waldenstrom Macroglobulinemia (9761/3). Code Diagnostic Confirmation code 3, positive histology and positive immunophenotyping testing which identified a more specific histology.

Example 3 (Confirming the histologic diagnosis): Bone marrow biopsy diagnosis is plasma cell dyscrasia. Peripheral blood smear is compatible with plasma cell leukemia. FISH and chromosome analysis revealed plasma cell myeloma. Both plasma cell leukemia and plasma cell myeloma are coded to the same ICD-O code, 9732/3, so there is only one disease process. The peripheral blood smear is histologic diagnosis for the plasma cell leukemia and FISH confirmed the diagnosis of multiple myeloma/plasma cell myeloma. Code Diagnostic Confirmation 3, positive histology and positive genetic testing.

Example 4 (Histologic confirmation plus genetic and immunophenotyping confirmation): Patient diagnosed with CLL by CBC and flow cytometry that was positive for both the genetic and CD antigens (immunophenotyping) for CLL. A bone marrow biopsy not performed. Since this is leukemia, the CBC is histologic confirmation, so this patient had histologic confirmation, genetic, and immunophenotyping positive for CLL. Code Diagnostic Confirmation 3, positive histology and positive genetic testing/immunophenotyping.

Example 5 (Ambiguous terminology used with immunophenotyping): Bone marrow biopsy shows B lymphoblastic leukemia. Abnormal FISH results most likely represent a hyperdiploid clone. Code the histology to 9811 (B-ALL, NOS) and assign a diagnostic confirmation code of 1. Neither Diagnostic confirmation code 3 nor the more specific hyperdiploidy histology is coded because the associated FISH result is preceded by ambiguous terminology.

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Diagnostic Confirmation for Myeloid Neoplasms

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Code 5: Positive laboratory test/marker study

Assign code 5 when the diagnosis of cancer is based on laboratory tests, tumor marker studies, genetics or immunophenotyping that are diagnostic for that specific cancer. Laboratory tests are listed under Definitive Diagnostic Methods in the Hematopoietic Database. Do not assign code 5 when there is histologic confirmation (See code 1).

Example 1: CT scan consistent with plasma cell myeloma (9732/3). Twenty-four-hour urine protein elevated with the presence of Bence-Jones kappa. Assign code 5 because the diagnosis is based on the positive Bence-Jones and there is no histologic confirmation in this case. Bence-Jones protein is a lab test listed in the Heme DB as one of the definitive diagnostic methods for plasma cell myeloma.

Note: Do not use this code when a peripheral blood smear is done (which qualifies for a code 1) or a peripheral blood smear followed by flow cytometry (which qualifies for a code 3). Flow cytometry studies are normally done based on an abnormal peripheral blood smear. If unable to find documentation that a peripheral blood smear was done first, assume that it was and code 3

DX CONFIRMATION = 5 CAN ONLY BE USED IN PLASMA CELL MYELOMA (9732/3)

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"Transformations"

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Transformations: Chronic Neoplasms and Acute Neoplasms

Transformations to

If a chronic neoplasm can transform to an acute/more severe neoplasm, the Heme DB will show the acute neoplasm in the "Transformations to" section. For example, if you search the Heme DB for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (9823/3), the "Transformations to" section shows that CLL/SLL transforms to diffuse large B-cell lymphoma (9680/3). That indicates CLL/SLL is a chronic neoplasm and diffuse large B-cell lymphoma is an acute neoplasm.

Transformations from

Information in this field is intendedoi to help registrars determine which histologies are chronic and which are acute. Acute neoplasms may have multiple histologies listed in the "Transformations from" field. Histologies listed in the "Transformations from" field are chronic. For example, in the Heme DB under plasma cell myeloma (9732/3), the "Transformations from" field lists solitary plasmacytoma of bone (9731/3) and extraosseous plasmacytoma (9734/3). That means that plasma cell myeloma (9732/3) is an acute neoplasm which could have transformed from the two listed plasmacytomas (9731/3 and 9734/3) which are chronic neoplasms.

See Rules M8-M13 for determination of single or multiple primaries involving cases noting both chronic and acute diagnoses.
The most common form of transformation is when a neoplasm progresses from chronic to acute; however, neoplasms may be diagnosed in an acute phase and transform to a less aggressive chronic phase after treatment. In these cases, it is important to determine if the patient received treatment for the acute neoplasm. If the patient was treated, abstract the chronic neoplasm as a second primary (see Rule M13). If the patient was not treated for the acute neoplasm, code only the acute neoplasm (see Rule M12). Follow back is definitely recommended to determine whether there was any further diagnostic workup that proved the acute diagnosis was incorrect or documentation that the acute diagnosis was provisional.

The inclusion of the terms "chronic" or "acute" in a neoplasm do not mean the neoplasm may transform. The terms "chronic" and "acute" refer to the indolent or aggressive nature of the neoplasm, respectively. The key to determining if the chronic/acute rules apply is following the information in the Heme database. If a neoplasm has transformations listed (either in "transformation to" or "transformation from"), then usually the chronic/acute rules apply. If no transformations are listed, then the chronic acute rules do not apply.

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"Transformations"

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- Patients with myeloproliferative neoplasms (MPNs), including polycythemia vera, essential thrombocythemia, and primary myelofibrosis, have a propensity to develop acute myeloid leukemia (AML) and myelodysplastic syndromes (MDSs).
- Blastic Transformation represents a transformation of disease from an indolent or chronic condition to an acute and immediately life threatening disease.
- Many patients now diagnosed and treated at early phase of disease
- FCDS captures these cases from hematology/oncology claims records
- FCDS usually does not capture these cases from epath because most do not get biopsy, many are diagnosed from other non-bone marrow or tissue biopsy testing
- Patients used to just be followed for MPN/MDS – today many are treated early
- We seldom see intermediate/accelerated phase – usually chronic or acute phase
- Acute Phase is immediately life-threatening

A Myeloid disease process will not transform to lymphoid or vice versa

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Transformation or Progression

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When a Myeloid Disease (MPN, MDS, Chronic Myeloid Leukemia) Transforms to Acute Myeloid Leukemia – See Heme DB for Transformations

Acute Leukemia
The phase of leukemia in which 20% or more of the cells in the blood or bone marrow are blast cells. Lymphoblasts or Leukemic Blasts.

Lymphoma does not have Transformation

Some lymphoma progresses to Stage IV lymphoma that involves bone marrow

Other lymphomas begin in bone marrow as lymphoid leukemia

Leukemia/Lymphoma is always Distant Stage/Systemic Disease

Chronic Leukemia is always Distant Stage/Systemic Disease

Acute Leukemia is always Distant Stage/Systemic Disease

Plasma Cell Myeloma is always Distant Stage/Systemic Disease

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Use the Hematopoietic DB

Diagnostic Confirmation

This AML is part of the "AML with recurrent genetic abnormalities" group. Since this AML is diagnosed based on genetics, diagnostic confirmation will always be 3.

Grade

Not Applicable

Module Rule

None

Alternate Names

None

Definition

Acute myeloid leukemia (AML) with mutated RUNX1 is a de novo leukemia with greater than or equal to 20% bone marrow or peripheral blood blasts cells that may have morphological features of most AML, NOS categories and has a higher frequency among cases with minimal differentiation.

Definitive Diagnostic Methods

Bone marrow biopsy
Genetic testing
Immunophenotyping
Karyotyping

Genetics Data

ASXL1
FLT3-ITD
IDH1R132
Karyotypic abnormalities, most commonly trisomies 8 and 13
KMT2A
Mutated RUNX1

Immunophenotyping

CD13 expression
CD33 expression
CD34 expression
HLA-DR expression
MPO expression

Transformations to

None

Transformations from

9875/3 Chronic myeloid leukemia, BCR-ABL1-positive
9920/3 Therapy-related myeloid neoplasms
9945/3 Chronic myelomonocytic leukemia
9950/3 Polycythemia vera
9960/3 Myeloproliferative neoplasm, NOS
9961/3 Primary myelofibrosis
9962/3 Essential thrombocythemia
9963/3 Chronic neutrophilic leukemia
9964/3 Chronic eosinophilic leukemia, NOS
9965/3 Myeloid/lymphoid neoplasms with PDGFRA rearrangement
9967/3 Myeloid/lymphoid neoplasms with FGFR1 rearrangement
9975/3 Myelodysplastic/myeloproliferative neoplasm, unclassifiable
9980/3 Myelodysplastic syndrome with single lineage dysplasia
9982/3 Myelodysplastic syndrome with ring sideroblasts and single lineage dysplasia
9983/3 Myelodysplastic syndrome with excess blasts
9984/3 Refractory anemia with excess blasts in transformation
9985/3 Myelodysplastic syndrome with multilineage dysplasia
9986/3 Myelodysplastic syndrome with isolated del(5q)
9987/3 Therapy-related myelodysplastic syndrome, NOS
9989/3 Myelodysplastic syndrome, unclassifiable
9991/3 Refractory neutropenia
9992/3 Refractory thrombocytopenia
9993/3 Myelodysplastic syndrome with ring sideroblasts and multilineage dysplasia

Same Primaries

9800/3 Leukemia, NOS
9801/3 Acute undifferentiated leukemia
9860/3 Myeloid leukemia, NOS
9861/3 Acute myeloid leukemia, NOS

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Workup and Staging Myeloid Neoplasms

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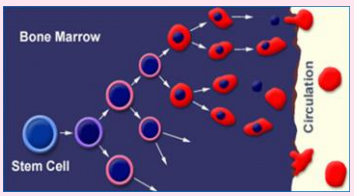
- CBC - Histology
- Peripheral Blood Smear - Histology
- Bone Marrow Biopsy - Histology
- Lumbar Puncture - Histology
- Flow Cytometry – Immuno/Genetic
- Immunophenotype – Immuno/Genetic
- Cytogenetic Analysis – Immuno/Genetic
- Imaging – Exceedingly Rare Dx Confirmation
- RT-PCR – Immuno/Genetic
- FISH – Immuno/Genetic
- DNA Microarray – Immuno/Genetic

ALL Myeloid Neoplasms are Systemic Disease
ALL Bone Marrow Primaries are Systemic
You Cannot Assign AJCC TNM Stage
But, you DO assign Distant Stage
Stage is NEVER Unknown or NA



Exception
There is a localized myeloid neoplasm called a Myeloid Sarcoma – check if patient has AML

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- **Histology** – Microscopy examines the microanatomy of cells, tissues, and organs as seen through a microscope – physical characteristics. It examines the correlation between structure and function.
- **Biologic Tumor Marker** – Immunoassay can be used to identify anything present in or produced by cancer cells or other cells from blood, urine and body fluids. Tumor Markers provide information about a cancer, aggressiveness, what kind of treatment it may respond to, or whether it is responding to treatment. Tumor markers can be proteins, conjugated proteins, peptides and carbohydrates.
- **Immunohistochemistry** – a microscopy-based technique that allows selective identification and localization of antigens in cells. IHC selectively identifies antigens (proteins) in cells from tissue by exploiting the principle of antibodies binding specifically to antigens in biological tissues. IHC uses light or fluorescent microscopy to analyze results. IHC is less expensive than flow cytometry.
- **Flow Cytometry** – a laser-based technique that detects and measures the physical and chemical characteristics of a cell population. Flow cytometry can be used to count and sort cells (identify proliferation of cells and type), determine cell characteristics, identify biomarkers and to diagnose/classify certain cancers. It is more precise metric for antigens than histology or IHC testing.
- **Cluster of Differentiation (CD) Molecules** – cell surface molecules used to classify white blood cells that are especially important for diagnosis of lymphomas and leukemias. CD marker antibodies have been widely used for cell sorting, phenotyping, and blood cancer diagnosis and for treatment.
- **Immunophenotype** – uses the CD system to define markers associated with specific cells or conditions
- **Proteomics** – provide valuable information on the identity, expression levels, and modification of proteins. For example, cancer proteomics unraveled key information in mechanistic studies on tumor growth and metastasis, which has contributed to the identification of clinically applicable biomarkers as well as therapeutic targets. Proteomics-based technologies have enabled the identification of potential biomarkers and protein expression patterns that can be used to assess tumor prognosis, prediction, tumor classification, and to identify potential responders for specific therapies
- **Cytogenetics** - involves testing samples of tissue, blood, or bone marrow in a laboratory to look for changes in chromosomes, including broken, missing, rearranged, or extra chromosomes. Changes in certain chromosomes may be a sign of a genetic disease or condition or some types of cancer. FISH is common cytogenetics test.
- **DNA Microarray** – used to study the extent to which certain genes are turned on or off in cells and tissues. It is used to identify the changes in gene sequences that are most often associated with a particular disease.
- **Next Generation Sequencing** – a large-scale DNA and RNA sequencing technology to determine the order of nucleotides in entire genomes or targeted regions of DNA or RNA in cells and tissues.

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Treatment Guidelines for Myeloid Neoplasms

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- NCCN Treatment Guidelines:
  - Myeloproliferative Neoplasms
  - Myelodysplastic Syndromes
  - Chronic Myeloid Leukemia
  - Histiocytic Neoplasms, NOS
  - Mastocytosis
  - Acute Myeloid Leukemia

RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

Risk Category*	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Biallelic mutated *CEBPA* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

- NCCN Guidelines Include:
  - Detailed Description of Diseases
  - Descriptions of Genetic Mutations
  - Evaluation of Disease at Diagnosis
  - Risk Stratification by Genetics
    - Criteria for Low Risk
    - Criteria for Intermediate Risk
    - Criteria for High Risk
  - Non-Genetic Risk Stratification Factors
  - Treatment Strategies by Risk Group
    - Induction Therapy
    - Post-Induction Therapy
    - Consolidation Therapy
    - Post-Remission Maintenance Therapy
    - BMT/SCT Transplant Criteria
    - Monitoring Post-Treatment
    - Relapsed/Refractory Disease
  - Response Criteria

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Blood & Marrow Stem Cell Transplant Procedures

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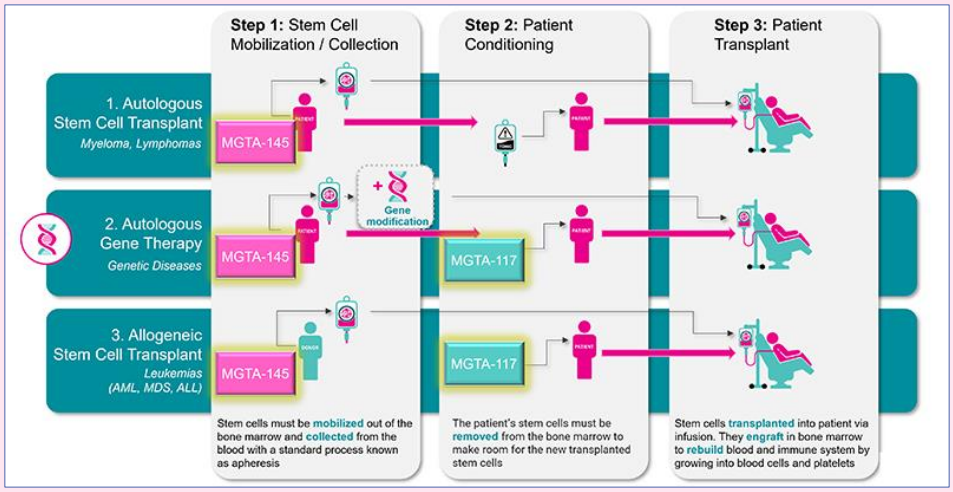

https://www.magentatx.com/revolutionizing-medicine/programs/

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Documentation Needed for Myeloid Neoplasms

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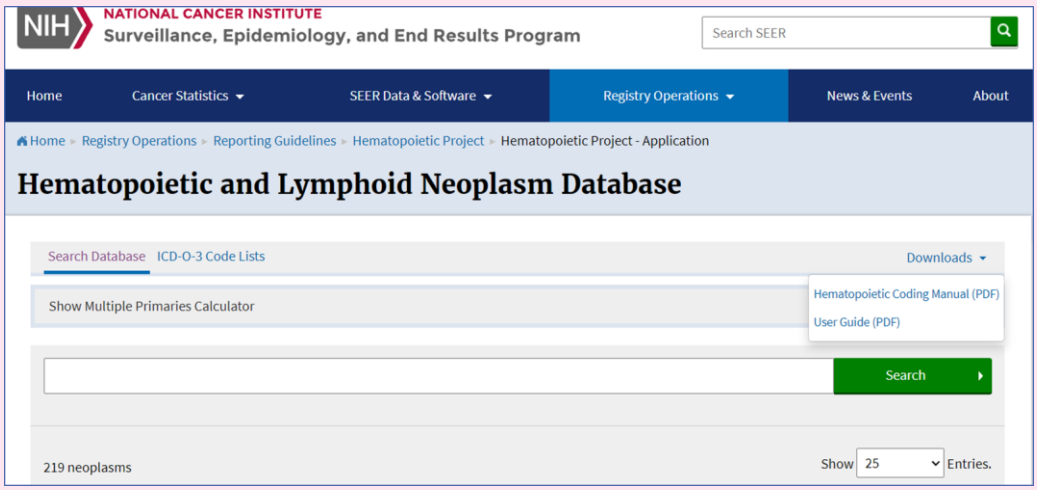

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Use the Hematopoietic DB

Diagnostic Confirmation

This AML is part of the "AML with recurrent genetic abnormalities" group. Since this AML is diagnosed based on genetics, diagnostic confirmation will always be 3.

Grade

Not Applicable

Module Rule

None

Alternate Names

None

Definition

Acute myeloid leukemia (AML) with mutated RUNX1 is a de novo leukemia with greater than or equal to 20% bone marrow or peripheral blood blasts cells that may have morphological features of most AML, NOS categories and has a higher frequency among cases with minimal differentiation.

Definitive Diagnostic Methods

Bone marrow biopsy
Genetic testing
Immunophenotyping
Karyotyping

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FLT3-ITD
IDH1R132
Karyotypic abnormalities, most commonly trisomies 8 and 13
KMT2A
Mutated RUNX1

Immunophenotyping

CD13 expression
CD33 expression
CD34 expression
HLA-DR expression
MPO expression

Transformations to

None

Transformations from

9875/3 Chronic myeloid leukemia, BCR-ABL1-positive
9920/3 Therapy-related myeloid neoplasms
9945/3 Chronic myelomonocytic leukemia
9950/3 Polycythemia vera
9960/3 Myeloproliferative neoplasm, NOS
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Same Primaries

9800/3 Leukemia, NOS
9801/3 Acute undifferentiated leukemia
9860/3 Myeloid leukemia, NOS
9861/3 Acute myeloid leukemia, NOS

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2022 FCDS Audit of Lymphoid and Myeloid Neoplasms

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FCDS DATA VALIDATION AUDIT with E-PATH VERIFICATION

Diagnosis Year: 2020

Cancer Site: Adult & Pediatric Lymphoid and Myeloid Neoplasms

Includes;

Any Lymphoma (Nodal/Extra-Nodal), Any Plasma Cell Neoplasm,

Myelodysplastic Syndrome (MDS), Myeloproliferative Neoplasm (MPN),

Acute Leukemia (myeloid/lymphoid), Chronic Leukemia (myeloid/lymphoid)

Any ICD-O-3 Histology Code 9590-9993

Hospital Analytic Cases Only

- ALL Option 2-5 Facilities will be included in this audit. The audit will include both adult and pediatric lymphoid and myeloid neoplasms of any type. The number of cases will be stratified by 2020 reporting year caseload for any primary site with histology 9590-9992 – analytic cases only (see below Class of Case).
- A facility may be selected for more than 1 audit during the 5-year cycle using the enhanced facility select criteria.
- A facility may have more than 1 reported cancer selected for this audit.
- Case Selection will be based upon the following criteria:
  - Date of Diagnosis 01/01/2020-12/31/2020
  - Primary Site(s) = Any

Histology-Driven Case Selection	# Cases
Histology Codes 9590-9992	1000
TOTAL	**1000**

  - Behavior = 3 (malignant)
  - Central Sequence = 00 (only 1 cancer ever reported)
  - ICD-O-3 Histology – 9590-9992
  - Class of Case = 10, 11, 12, 13, 14, 20, 21, 22 (hospital analytic – diagnosed and/or treated at facility)
- Case Selection will be stratified by 2020 reporting year caseload for combined lymphoid/myeloid neoplasms.
- Pathology Selection will be based on any e-pathology report(s) with Date of Specimen within 30 days of the original Date of Diagnosis (plus or minus 30 days) as documented/coded on the original case abstract.

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2022 FCDS Audit of Lymphoid and Myeloid Neoplasms

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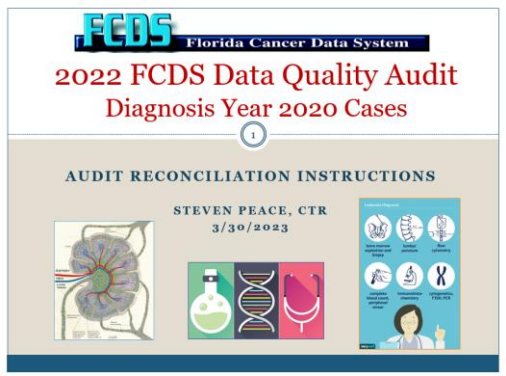

176 Hospitals – 1500 cases/750 e-path

12/2022	1/2023	1/2023	2/2023	3/2023	4/2023	5/2023	6/2023
Final Protocol							
	Software Updates						
	Identify Audit Team	Auditor Orientation Webcast					
		Audit	Audit	Audit			
				Audit Reconciliation Webcast			
					Reconciliation		
						Final Review	Final Review
							Final Audit Report
							Update FCDS Record

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References and Resources

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- A Summary of the Inaugural WHO Classification of Pediatric Tumors: Transitioning from the Optical into the Molecular Era; AACR: Cancer Discover, February 2022
- WHO Classification of Tumours – Online – Haematolymphoid -5th ed. https://whobluebooks.iarc.fr/structures/haematolymphoid/
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- SEER Hematopoietic and Lymphoid Neoplasm Database – https://seer.cancer.gov/seertools/hemelymph/
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- Analysis of genetic variants in myeloproliferative neoplasms using a 22-gene next-generation sequencing panel; Tan et al. BMC Medical Genomics (2022) 15:10 https://doi.org/10.1186/s12920-021-01145-0
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- Classification of acute myeloid leukemia; p-ISSN 2287-979X / e-ISSN 2288-0011, Blood Res 2020;55:S1-S4. https://doi.org/10.5045/br.2020.S001
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- The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia; Blood First Edition paper, April 11, 2016; DOI 10.1182/blood-2016-03-643544.
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) – AML, CML, MDS, MPN, Mastocytosis, Histiocytic Neoplasms – http://nccn/org
- NCI Physician Data Query – AML, CML, MPN, MDS, MDS/MPN – http://cancer.gov
- American Cancer Society – About Cancer – AML, CML, CMML, MDS – http://cancer.org

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Questions

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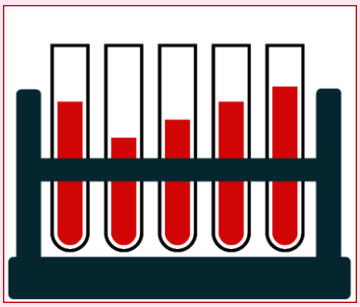

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