

Methods Used to Classify Cancer Outcomes (specifically lymphohematopoietic cancers)

Bernard D. Goldstein, MD
University of Pittsburgh
Graduate School of Public Health
bdgold@pitt.edu

Overview of Presentation

- Specific issues related to classification of hematological cancers
- Current classification/reclassification
- Broad overview of implications to interpretation of literature

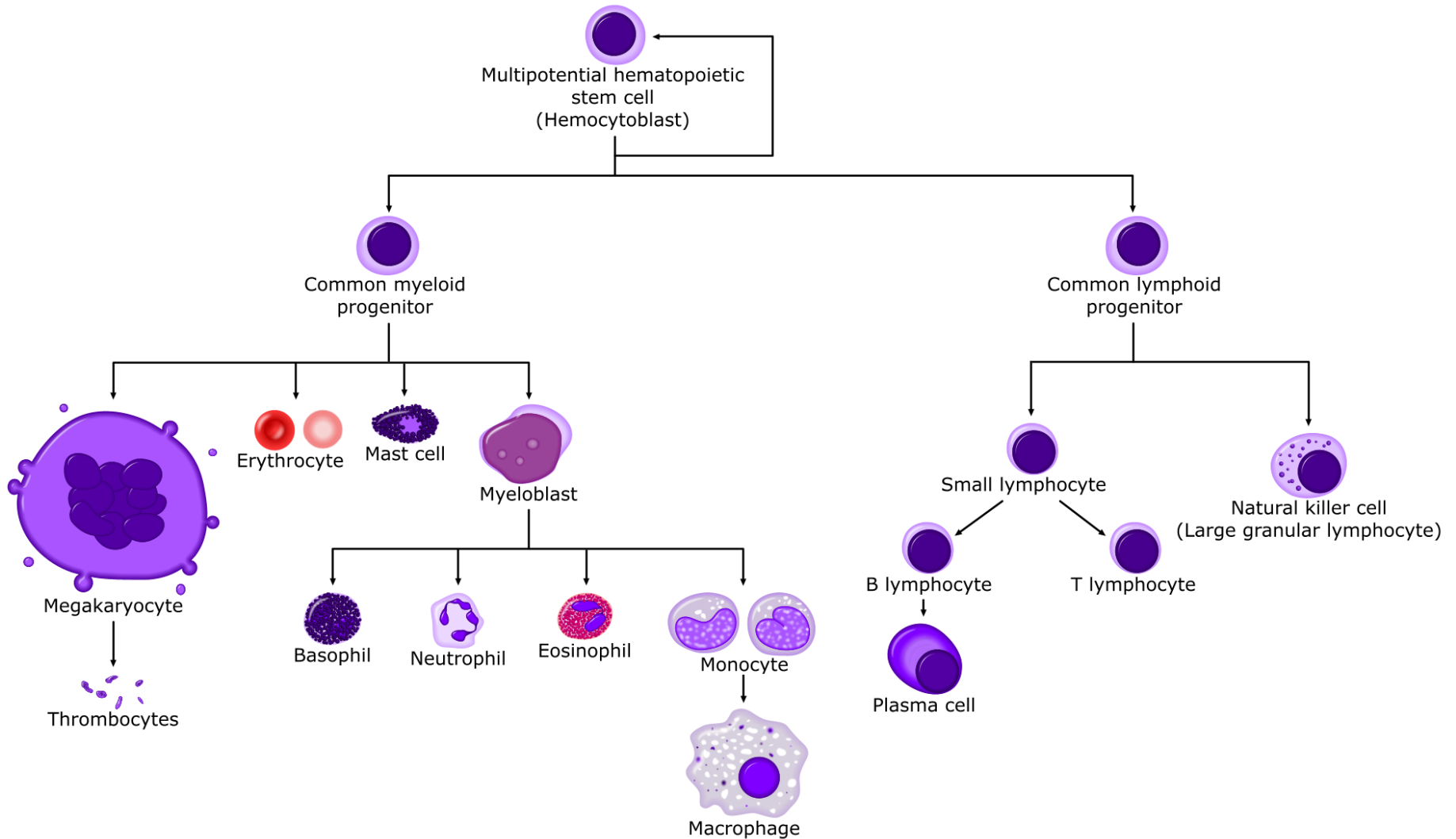
Context Issues

- Hematological cells are relatively easy to obtain during the course of a disease, whether local or circulating in the blood.
- Molecular biology has greatly supplemented microscopic morphology in hematological cancer classification
- Almost all hematological research is focused on medical aspects of diagnosis and treatment
- Response to treatment is considered in disease classification – and there has been marked improvement in hematological cancer response

Public Health Research Reported at the 2009 American Society of Hematology Annual Meeting

- Five of 5515 abstracts focused on the causation of hematological disease
- Abstracts related to prevention were primarily about how to avoid complications of chemotherapy

Hematopoiesis



Why Classify?

“Classification is the language of medicine: diseases must be described, defined, and named before they can be diagnosed, treated, and studied. A consensus on definitions and terminology is essential for both clinical practice and investigation.”

N.L. Harris, et al. (2008) Introduction to the WHO classification of tumours of haematopoietic and lymphoid tissues. Swerdlow Sh, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman, JW (Eds), IARC Lyon

Principles of the WHO Classification:

1. It utilizes all available information- clinical findings, morphology, immunophenotype, and genetic features- in an attempt to define disease entities of clinical significance
2. It has a “consensus” classification in which a majority of experts in various areas have agreed to the definition, criteria for diagnosis and the classification of specific disease entities
3. It is a classification that is amenable to regular updates to allow new information to be incorporated into the scheme

The 4th Edition of the WHO classification has a number of changes, including:

- New names for old diseases
- Movement of some diseases from one category to another
- Clarification, corrections and/or other changes in the definition and in diagnostic criteria for previously described diseases
- Increasing number of genetic abnormalities as major defining criteria, particularly in the myeloid neoplasms
- Acknowledgement of areas of uncertainty (“gray zones”)
- Inclusion of a number of “provisional entities” – disorders for which current evidence is insufficient to recognize them as “full” entities but which merit further study.

NCI ICD-0-3 Code Lists: Hematopoietic and Lymphoid Neoplasm Database.

- **Designed specifically for cancer registries**
 - 161 diagnoses of which 31 are listed as “obsolete”
 - Lymphomas make up about 70% of total diagnoses

“This manual and the corresponding database are to be used for coding cases diagnosed January 1, 2010 and forward. **The changes made do not require registrars to recode old cases.**”

- <http://seer.cancer.gov/tools/heme/>

WHO Classification of Myeloid Neoplasms

- I. Myeloproliferative Neoplasms*
- II. Myeloid/Lymphoid Neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1**
- III. Myelodysplastic / Myeloproliferative Neoplasms*
- IV. Myelodysplastic Syndromes
- V. Acute Myeloid Leukemia

* Name change

** New category

Your Grandparents' Leukemia Classification

	MYELOCYTIC	LYMPHOCYTIC
ACUTE	AML	ALL
CHRONIC	CML	CLL

Your Grandparents' Lymphoma Classification

- Hodgkin's Lymphoma
- Non-Hodgkin's Lymphoma (NHL)
 - (reticulum cell sarcoma)
 - B cell subtypes
 - T cell subtypes
- Lymphocytic leukemias
 - Acute
 - Chronic
- Multiple Myeloma

WHO Classification of Lymphoid Neoplasms

- Hodgkin Lymphoma
 - Nodular lymphocyte predominant Hodgkin lymphoma
 - Classic Hodgkin lymphoma
 - Nodular sclerosis Hodgkin lymphoma
 - Mixed cellularity Hodgkin lymphoma
 - Lymphocyte-rich classic Hodgkin lymphoma
 - Lymphocyte-depleted Hodgkin lymphoma

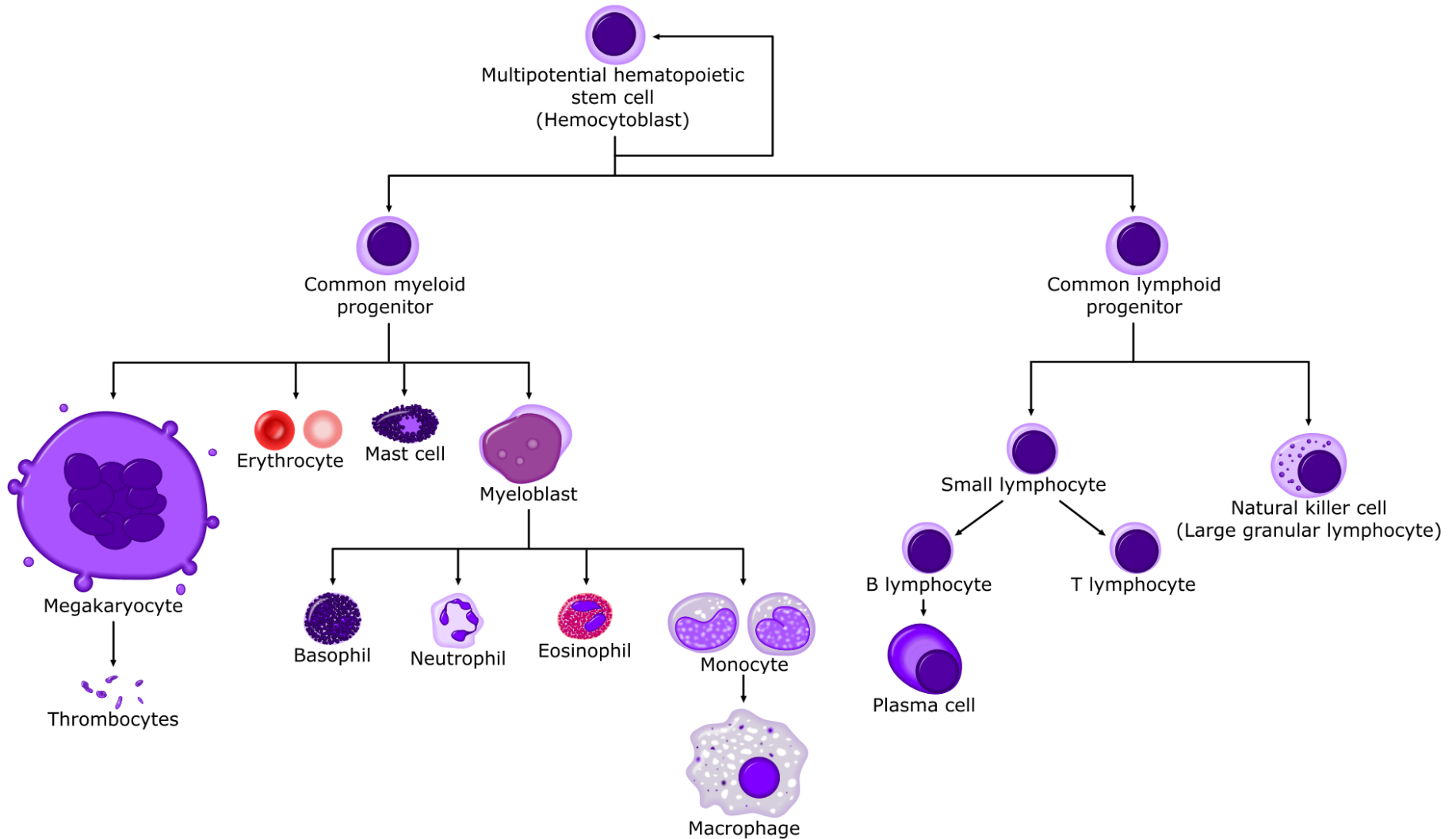
WHO Classification of Lymphoid Neoplasms

- B Cell Neoplasms
 - Precursor B cell neoplasm
 - Precursor B lymphoblastic leukemia/lymphoma

WHO Classification of Lymphoid Neoplasms

- B Cell Neoplasms
 - Mature B cell neoplasms
 - Predominantly disseminated/leukemic neoplasms
 - Chronic lymphocytic leukemia/small lymphocytic lymphoma
 - B cell prolymphocytic leukemia
 - Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
 - Splenic marginal zone lymphoma
 - Hairy cell leukemia
 - Plasma cell neoplasms
 - » Plasma cell myeloma
 - » Plasmacytoma
 - » Monoclonal immunoglobulin deposition disease
 - » Heavy chain disease

Hematopoiesis



WHO Classification of Lymphoid Neoplasms

- B Cell Neoplasms
 - Mature B cell neoplasms
 - Primarily extranodal neoplasm
 - Extranodal marginal zone B cell lymphoma ((Mucosa-associated lymphoid tissue [MALT] lymphoma)
 - Mediastinal (thymic) large B cell lymphoma
 - Intravascular large B cell lymphoma
 - Primary effusion lymphoma
 - Lymphomatoid granulomatosis

WHO Classification of Lymphoid Neoplasms

- B Cell Neoplasms
 - Mature B cell neoplasms
 - Predominantly nodal neoplasms
 - Nodal marginal zone B cell lymphoma
 - Follicular lymphoma
 - Mantle cell lymphoma
 - Diffuse large B cell lymphoma
 - Burkitt lymphoma/leukemia

WHO Classification of Lymphoid Neoplasms

- T Cell Neoplasms
 - Precursor T cell neoplasm
 - Precursor T lymphoblastic leukemia/lymphoma
 - Mature T cell neoplasms
 - Predominantly disseminated/leukemic neoplasms
 - T cell prolymphocytic leukemia
 - T cell large granular lymphocytic leukemia
 - Aggressive NK cell leukemia
 - Adult T cell leukemia/lymphoma

WHO Classification of Lymphoid Neoplasms

- T Cell Neoplasms
 - Mature T cell neoplasms
 - Primary extranodal neoplasms
 - Extranodal NK/T cell lymphoma, nasal type
 - Enteropathy-type T cell lymphoma
 - Subcutaneous panniculitis-like T cell lymphoma
 - Blastic NK cell lymphoma
 - Mycosis fungoides/Sézary syndrome
 - Primary cutaneous CD-30 positive T cell lymphoproliferative disorders
 - Predominantly nodal neoplasms
 - Angioimmunoblastic T cell lymphoma
 - Peripheral T cell lymphoma, unspecified
 - Anaplastic large cell lymphoma

Challenges to Epidemiology due to Changing Classification of Lymphoid Neoplasms

- **Changes in diagnostic criteria and usage during period of study**
- **Use of different diagnostic criteria in different studies**
- **Different rates of adoption of nomenclature by nosologists and by medical practitioners**
- **Potential for ascertainment bias in incidence studies**
- **Using mechanism/mode of action to avoid improper diagnostic fragmentation (corpuscularization)**

Clonal Architecture of Secondary AML

Walter et al, NEJM 366:1090-1098, 2012

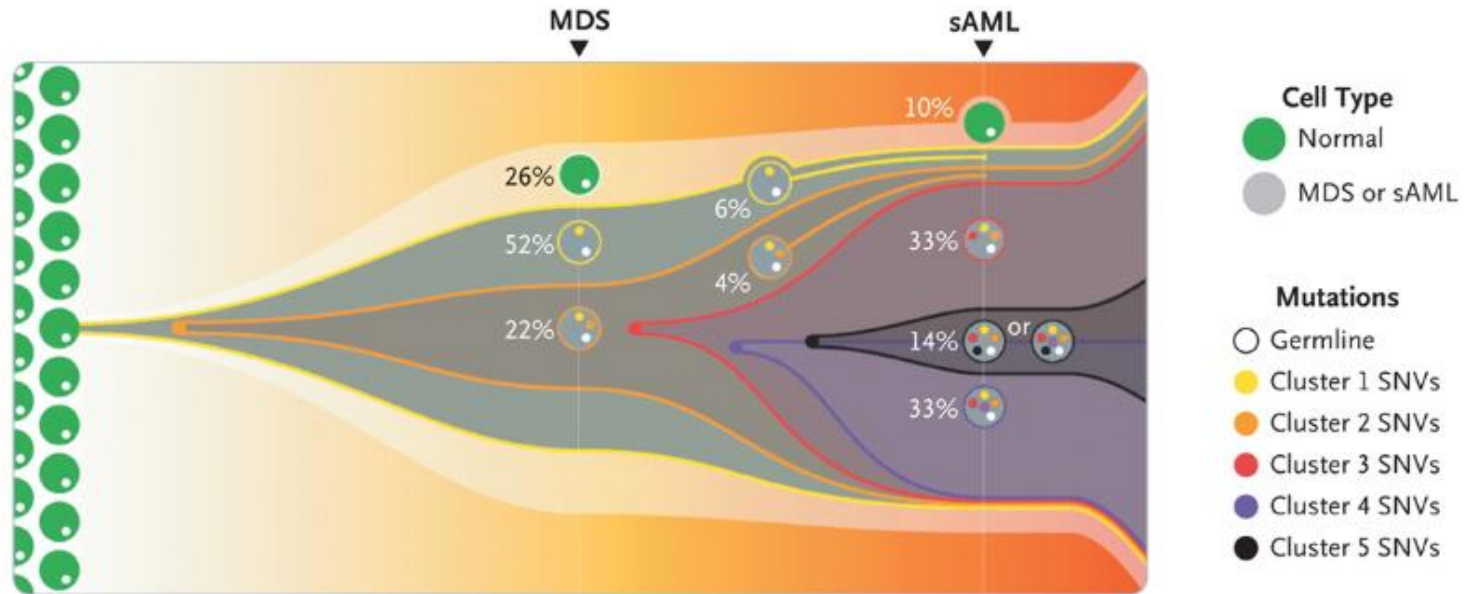
- Whole genome sequencing of paired samples of skin and bone marrow from 7 patients with secondary AML
- Compared with genotype evaluation of bone marrow samples from preceding MDS phase
- 10 of 13 mutations in AML present in MDS

Clonal Architecture of Secondary AML

Walter et al, NEJM 366:1090-1098, 2012

- Progression to sAML defined by the persistence of an antecedent founding clone containing 182 to 660 somatic mutations and the outgrowth or emergence of at least one subclone, harboring dozens to hundreds of new mutations.
- 86% of MDS and AML cells were clonal

A Clonal Evolution from MDS to sAML



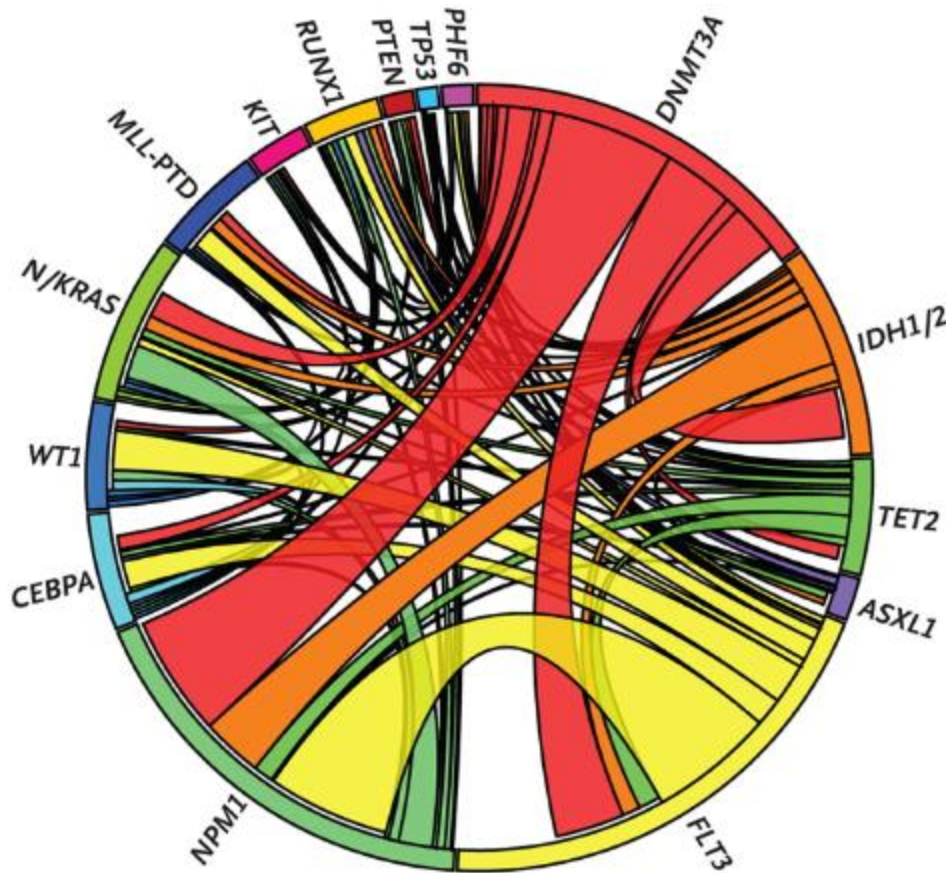
Walter et al: N Engl J Med 2012;366:1090-1098.

Prognostic Relevance of Integrated Genetic Profiling in AML

- Patel et al found that 97% of 502 patients with AML had mutations in one or more of 18 genes selected for study
- Described mutational complexity of AML

Patel, JP et al: NEJM 366:1079-89, 2012

A Total Cohort



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

Patel et al, N Engl J Med 2012;366:1079-89

Questions to consider

- Is it appropriate to combine cancer incidence of different lymphoid tumors in an epidemiological study or meta-analysis?
- What is the role of mechanistic information in answering this question?