EMORY
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Comprehensive Cancer Center

Molecular Testing in Hematologic Malignancies: What Does Every Patient Need at a Minimum?

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Disclosures (Corporate relationships in last 24 months)

Research Support

Geron

Singh Biotechnology

Consultant/ Scientific Advisory Board

Kymera

No information discussed in this presentation overlaps with these relationships

Objectives

- Why is molecular testing for patients with leukemias so important?
- What testing is appropriate?
- Where is this field heading?

Why is molecular testing important?

- Understanding causation
- Providing prognostic information
- Predicting response to specific therapies
- Monitoring response to therapy
- Defining new therapeutic approaches

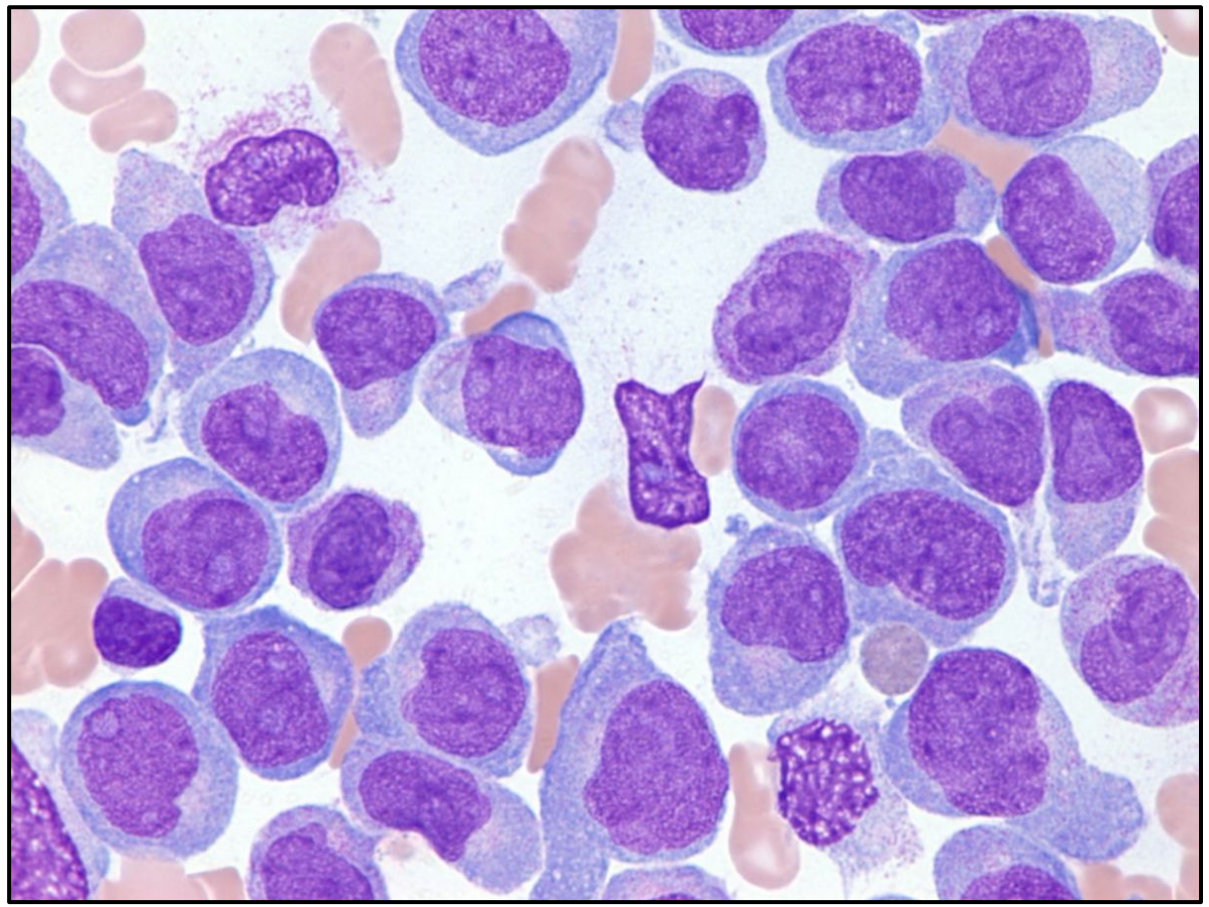
What molecular testing is necessary?

- Morphology
  - Microscopy of blood and bone marrow
- Immunophenotyping
  - Flow cytometry
- Cytogenetics
  - Karyotype
  - FISH
- Next generation sequencing (NGS)
  - Quantitative studies of specific mutations (such as NPM1)

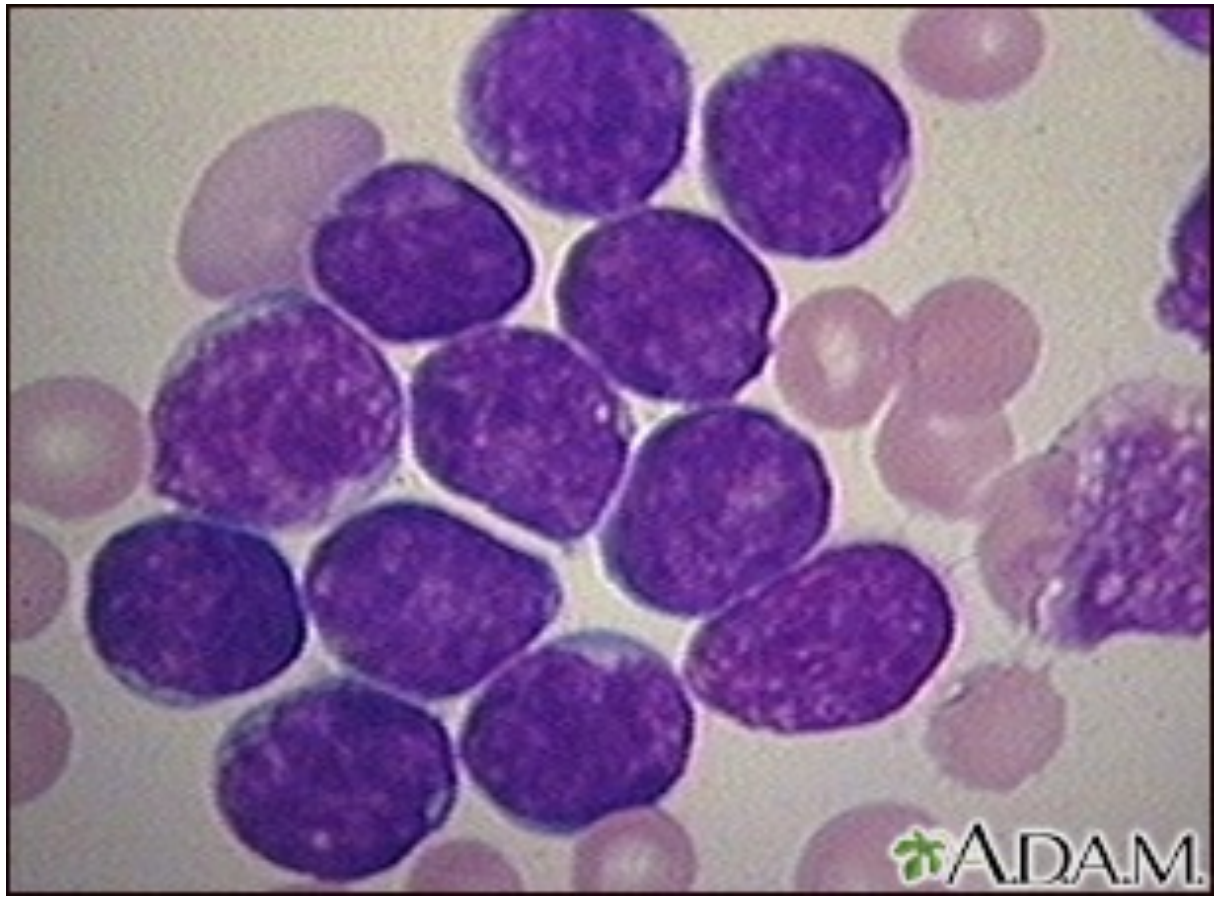
Recommendations by the College of American Pathologists and ASH(CAP/ASH), endorsed by ASCO

Morphology

Still the best way to rapidly assess “atypical cells”…



AML

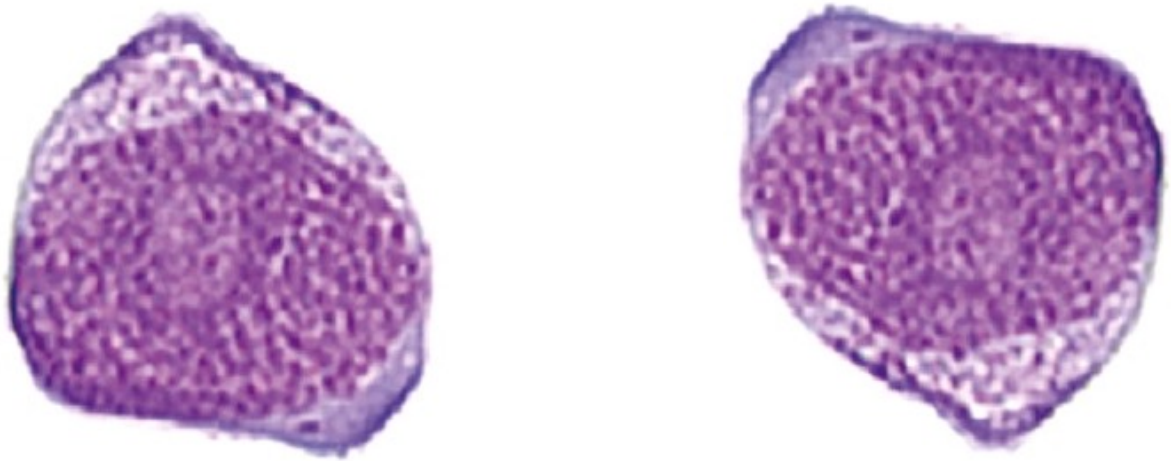


ALL

ASH Image Bank

Morphology

…and to assess for promyelocytes (APL)



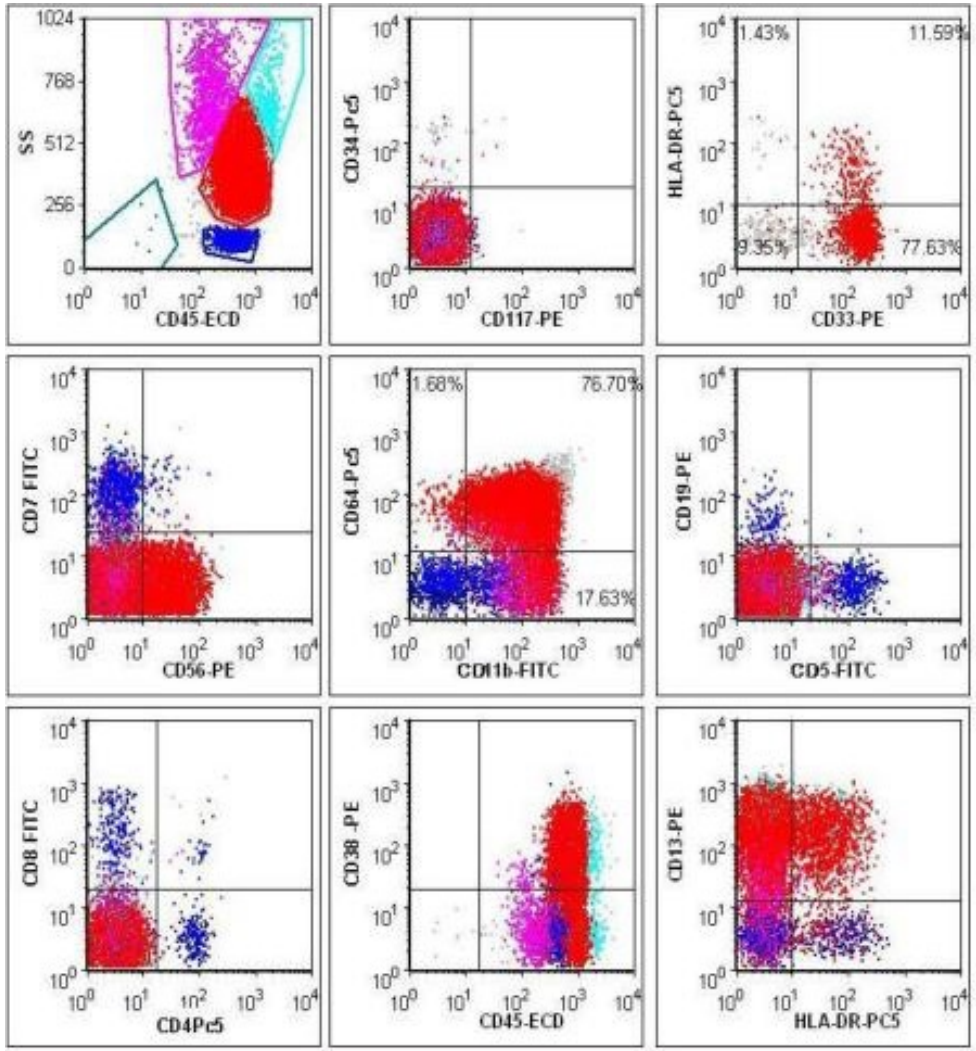
"Don't miss diagnosis"

ASH Image Bank

Multiparameter flow cytometry

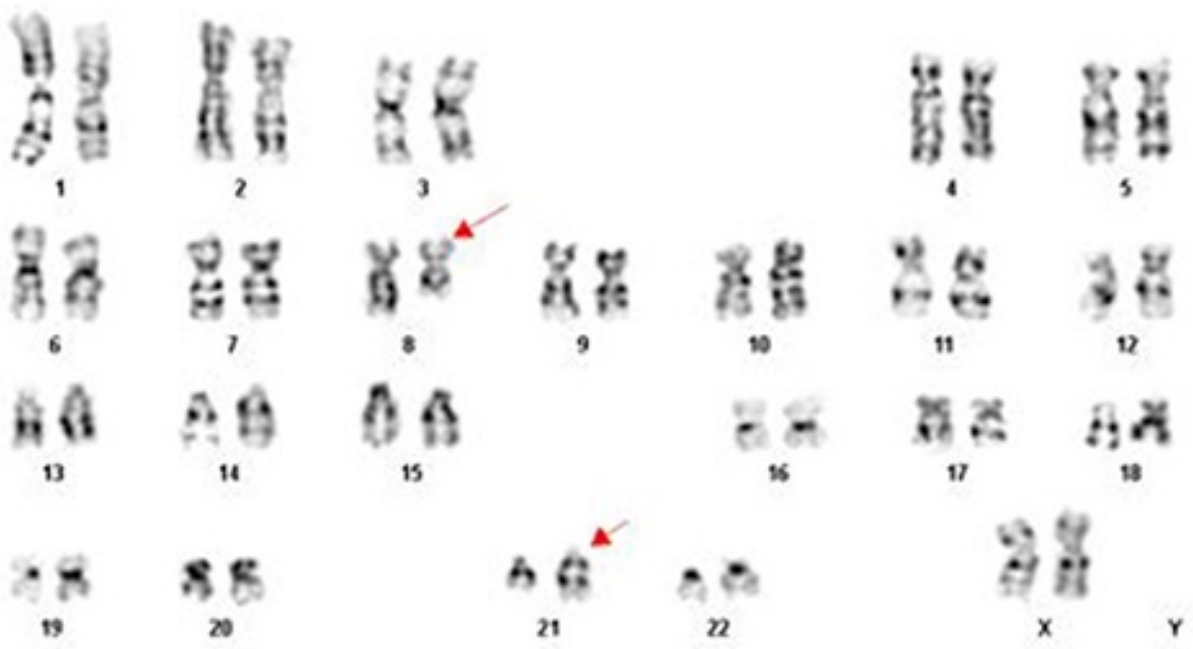
Provides qualitative and quantitative information about cellular differentiation states

Has largely replaced cytochemical staining, such as for myeloperoxidase



Karyotype

8;21 translocation

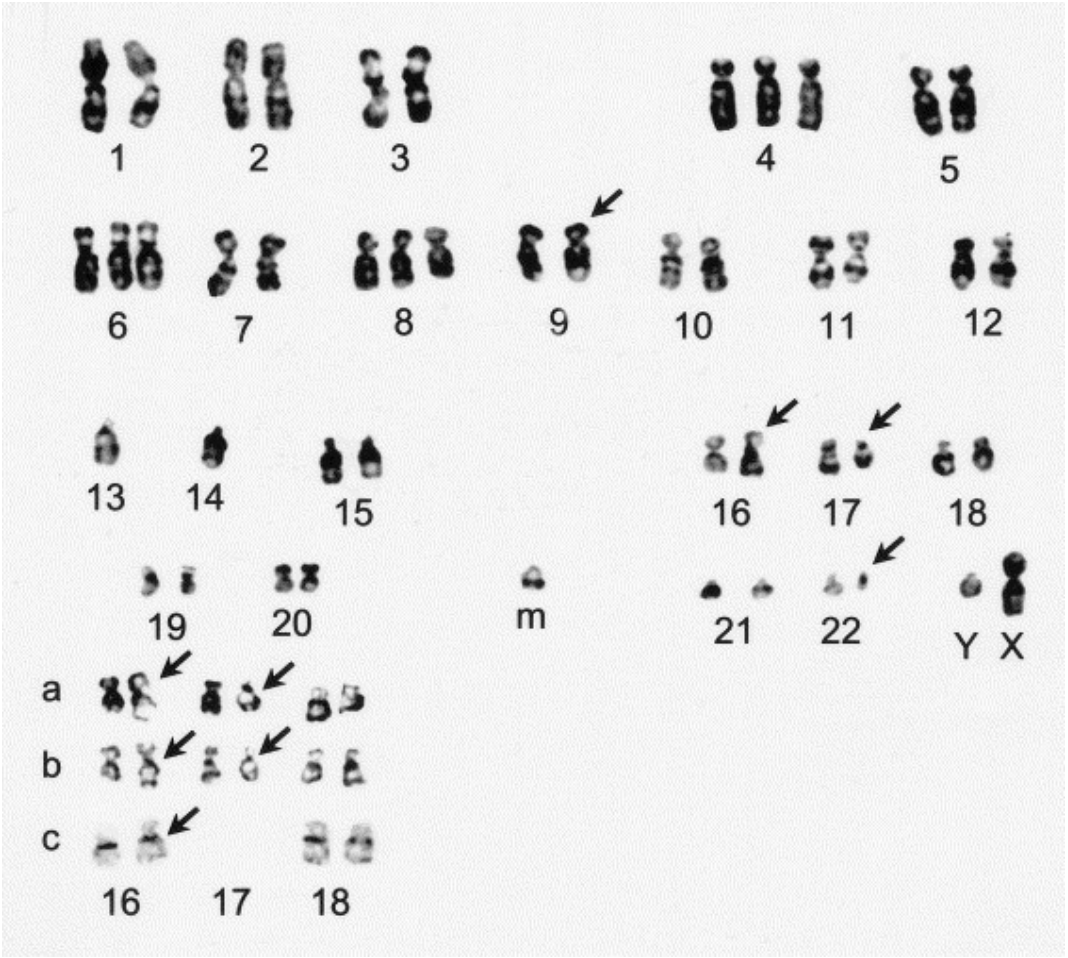


Provides comprehensive information about large scale chromosome structure…

…but requires the need (and time) to generate metaphases and expert analysis

Karyotype

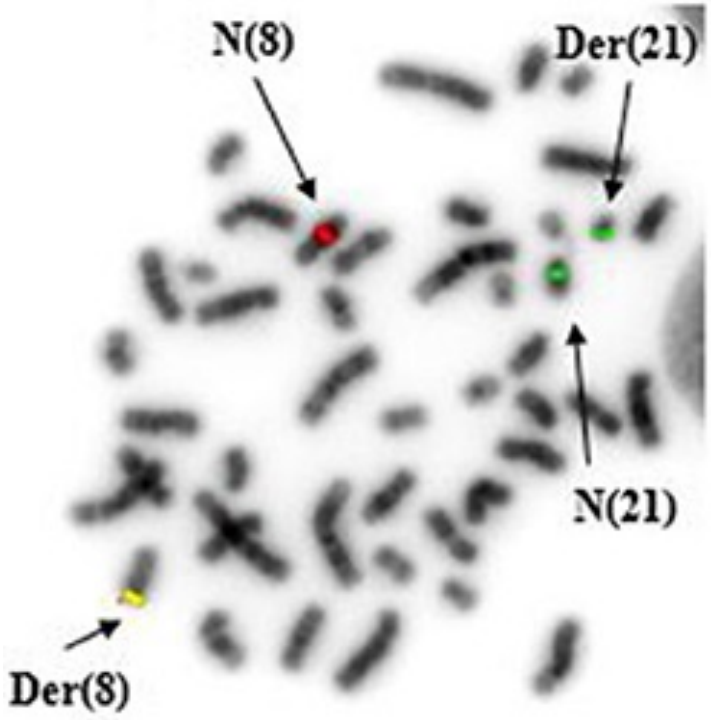
Complex karyotype



- Associated with prior exposure to mutagens (radiation, cytotoxic chemotherapy)
- Associated with defects in DNA repair (including heritable syndromes)
- Associated with poor prognosis

FISH

Fluorescence in situ hybridization (8;21 translocation)



Rapid and highly sensitive…

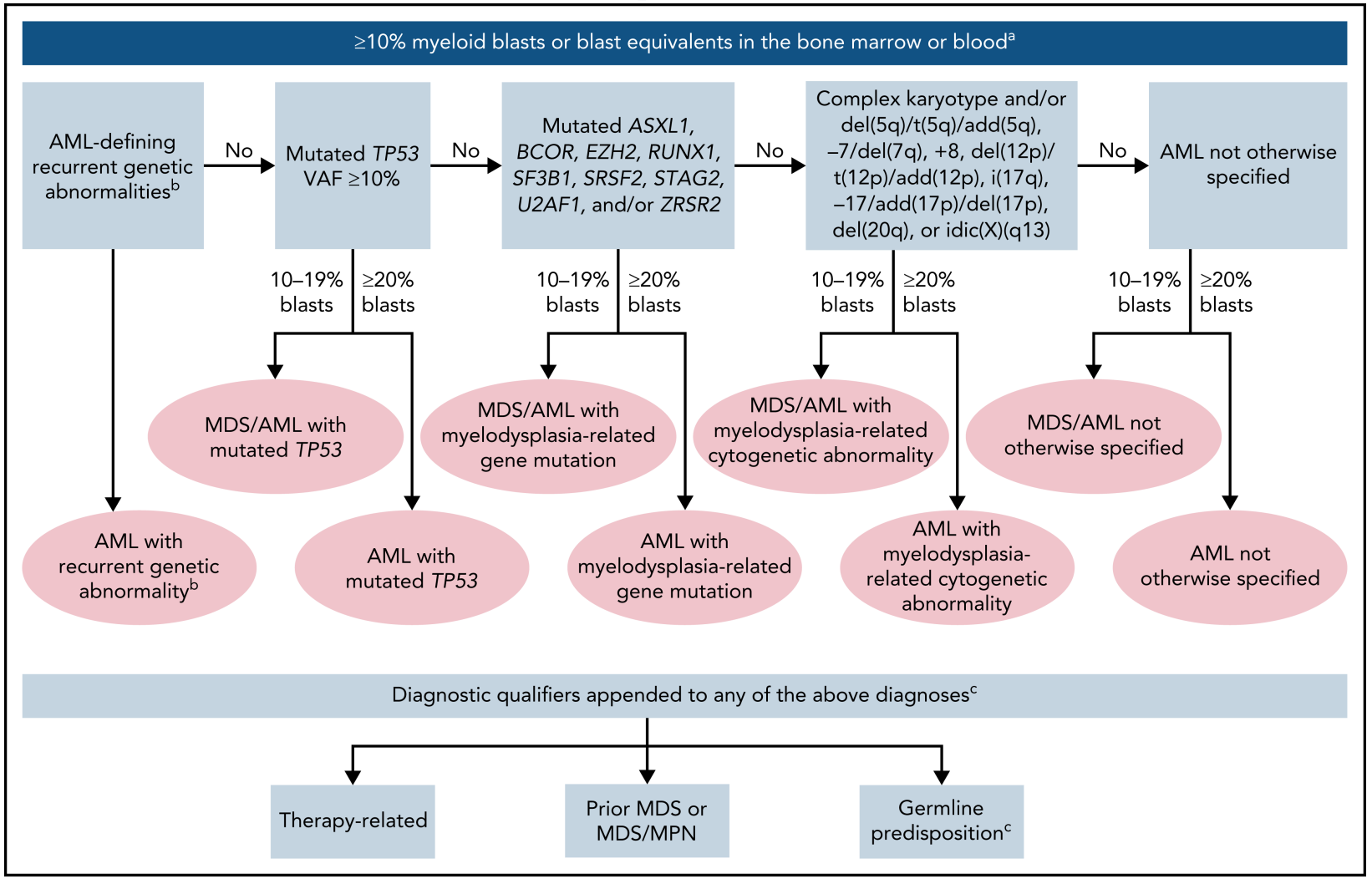
…but only generates data on specific translocations being interrogated

NGS: Next Generation Sequencing

- TP53
- Myelodysplasia-related gene mutations
  - ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2
- Targetable mutations
  - FLT3, IDH1, IDH2
- Mutations that can be analyzed with high sensitivity for disease monitoring (NPM1)
- Copy number variations (CNVs)
- Therapeutic dependencies

Actionable gene panel is continuing to expand

Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN (European LeukemiaNet)



Blood, 2022, 140:1345-1377

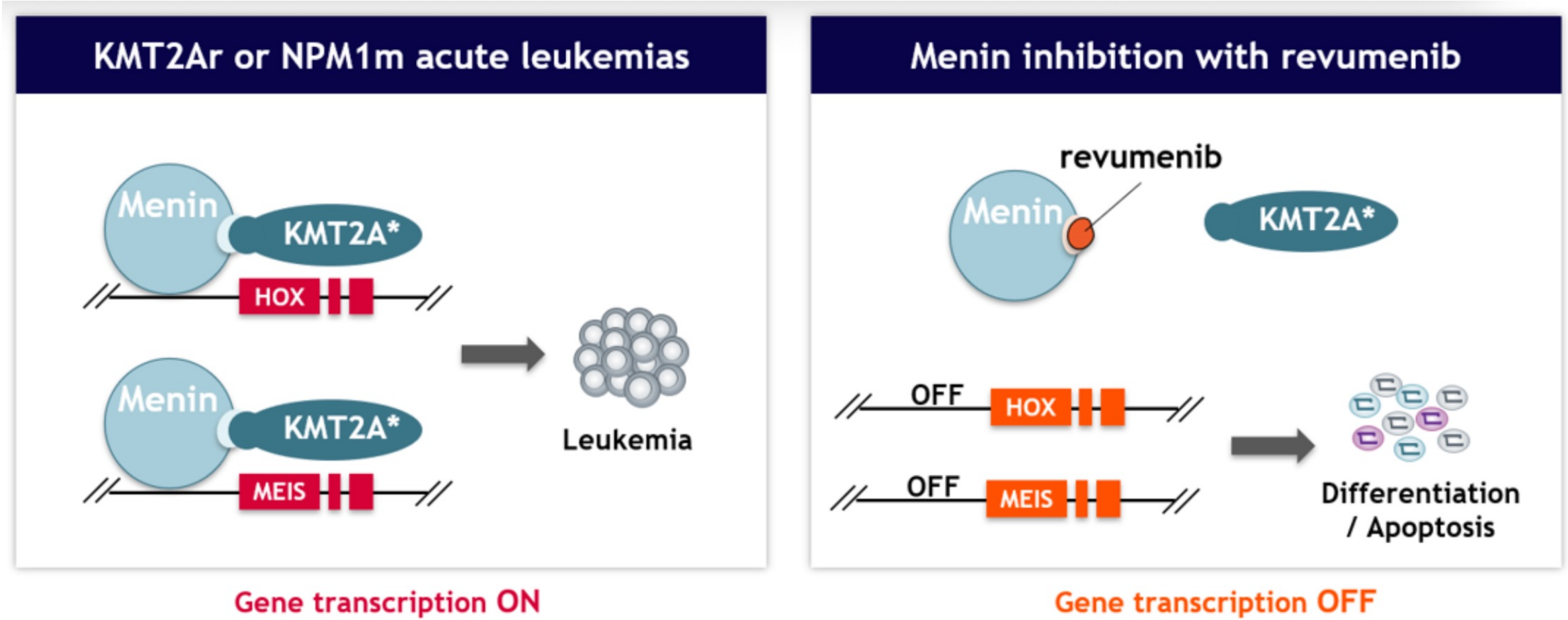
What is the future of molecular testing?

- Defining targetable dependencies
- Using machine learning to derive novel molecular information

What are “Dependencies”?

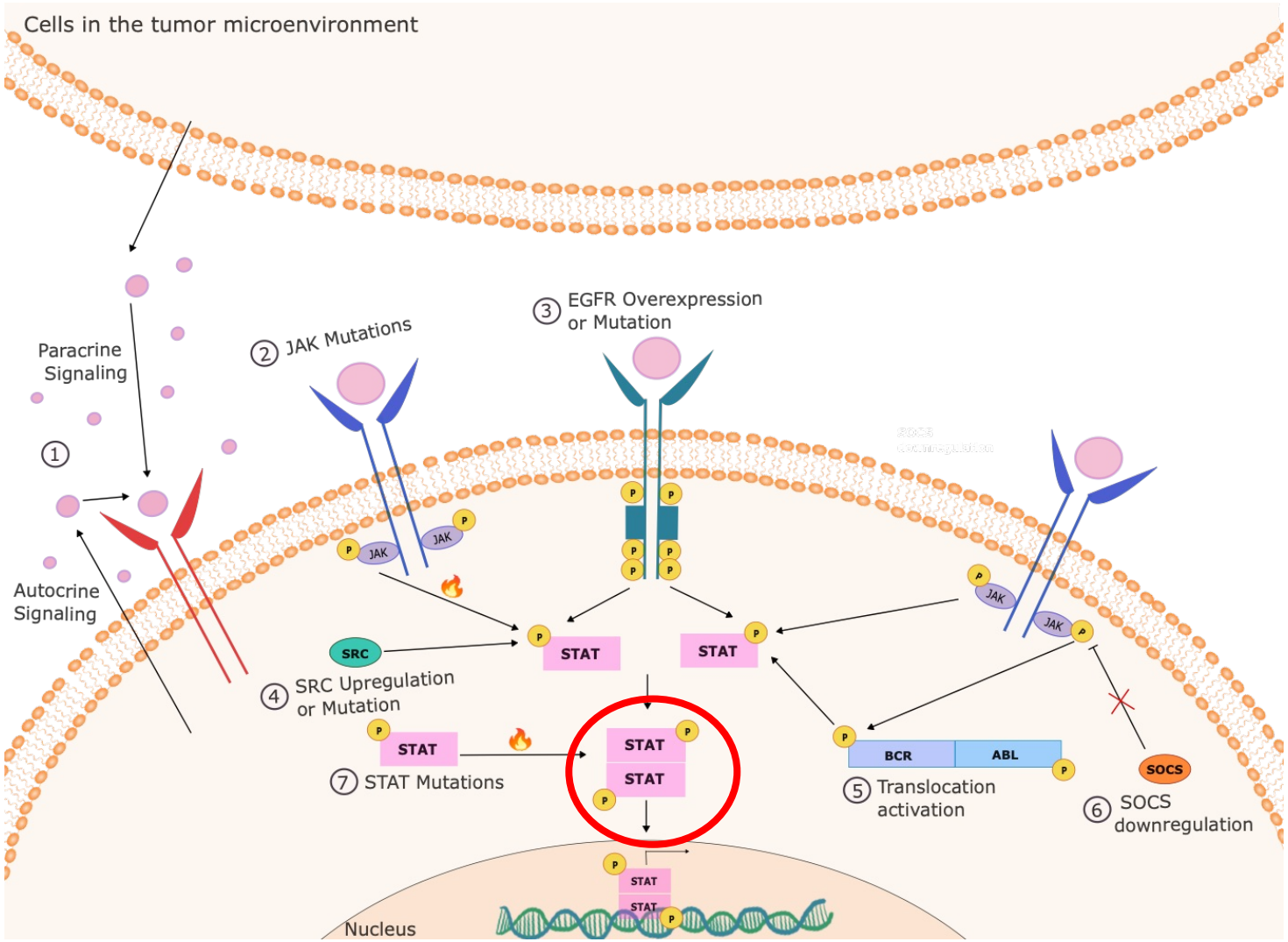
- Molecular changes in a cancer cell that render that cell susceptible to targeting a different pathway
- A form of “synthetic lethality”

A targetable dependency in AML:
Menin inhibitors with KMT2A rearrangements or NPM1 mutations



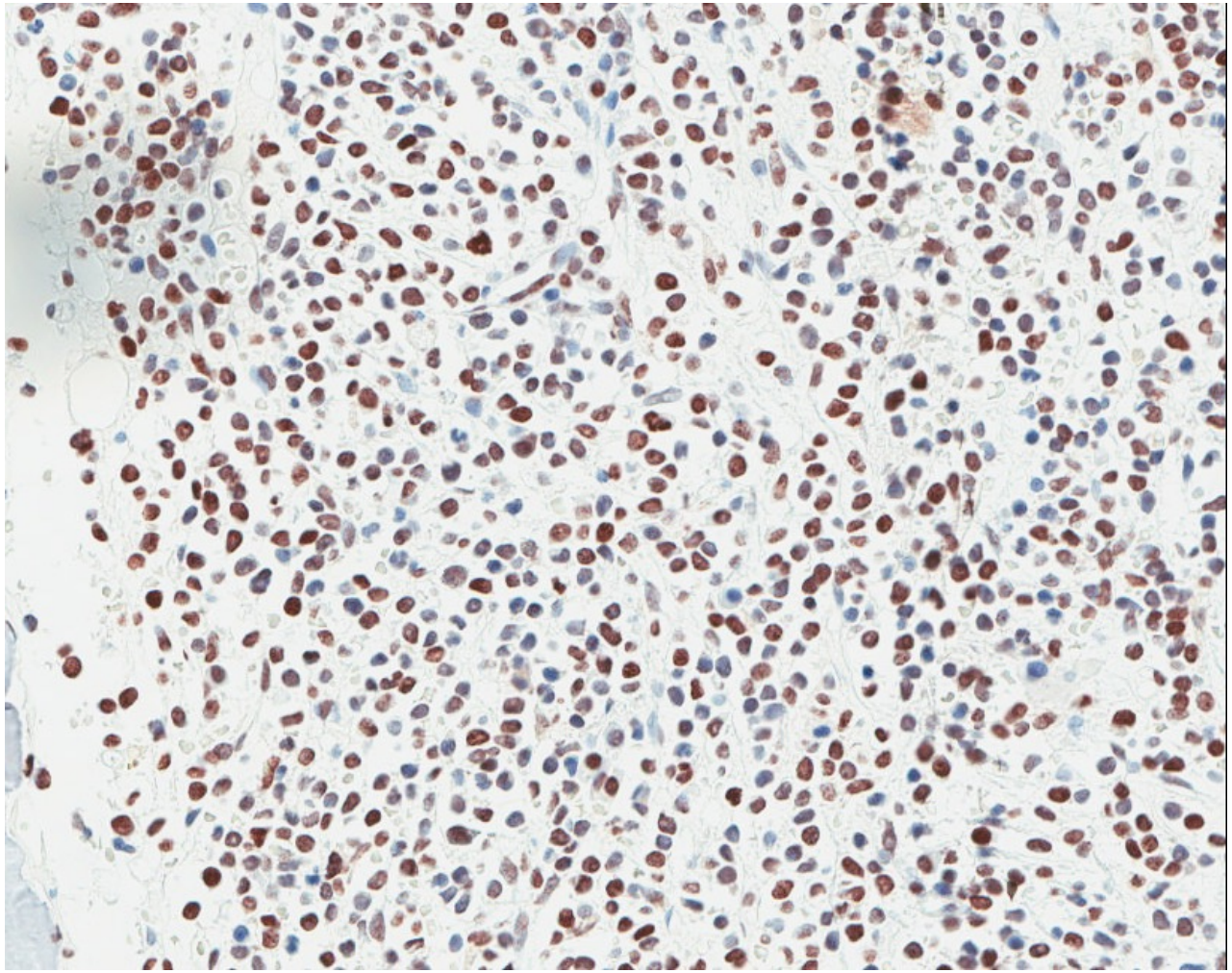
https://syndax.com/treatment/revumenib-sndx-5613/

A targetable dependency in AML: Multiple pathways lead to activation of the transcription factor STAT3



Immunostaining can detect activated STATs in AML

Anti-P-STAT3 immunohistochemistry



Scott Rodig, Brigham and Women's Hospital

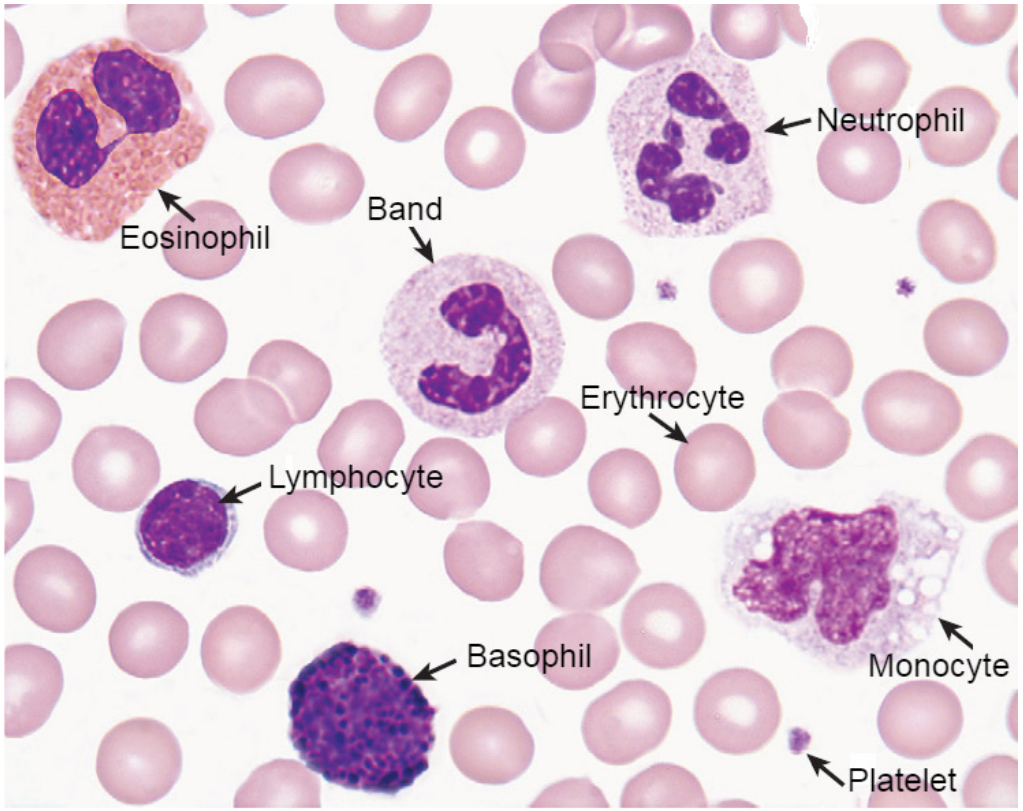
Novel approaches to targeting activated STATs in AML

- Antisense oligonucleotides
- Targeted degraders of STATs
- Small molecule STAT inhibitors (Winship trials in development)

Histologic stains of bone marrow and blood contain a huge amount of information content

Wright Stain: Developed by James Homer Wright in 1902


James Homer Wright

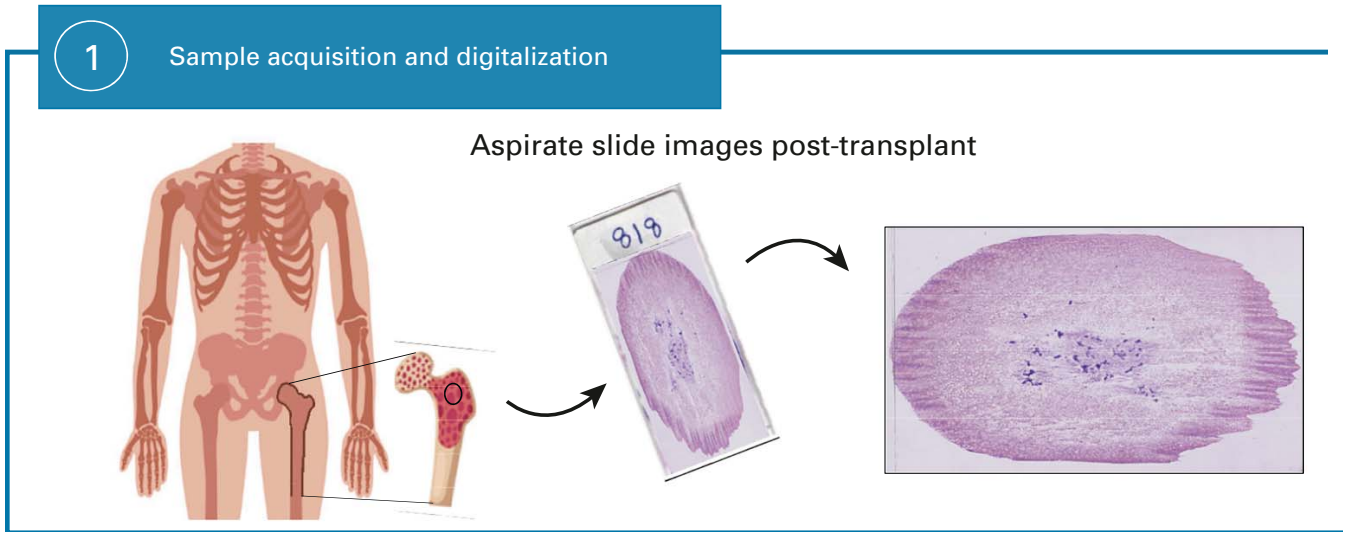


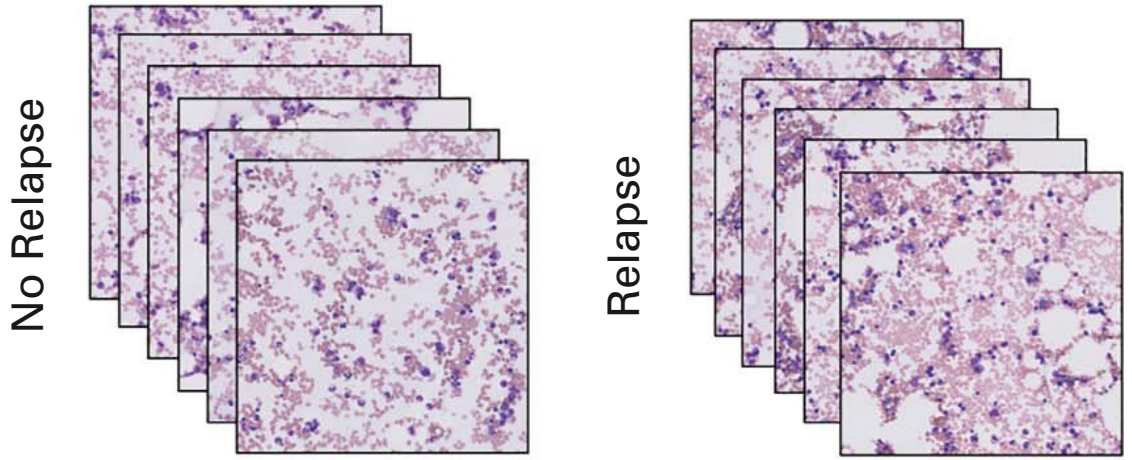

Gustav Giemsa

LaboratoryTests.org
LaboratoryIntern.com

Back to the Future:
Machine learning and AML prediction

Predicting risk of relapse post-transplant:



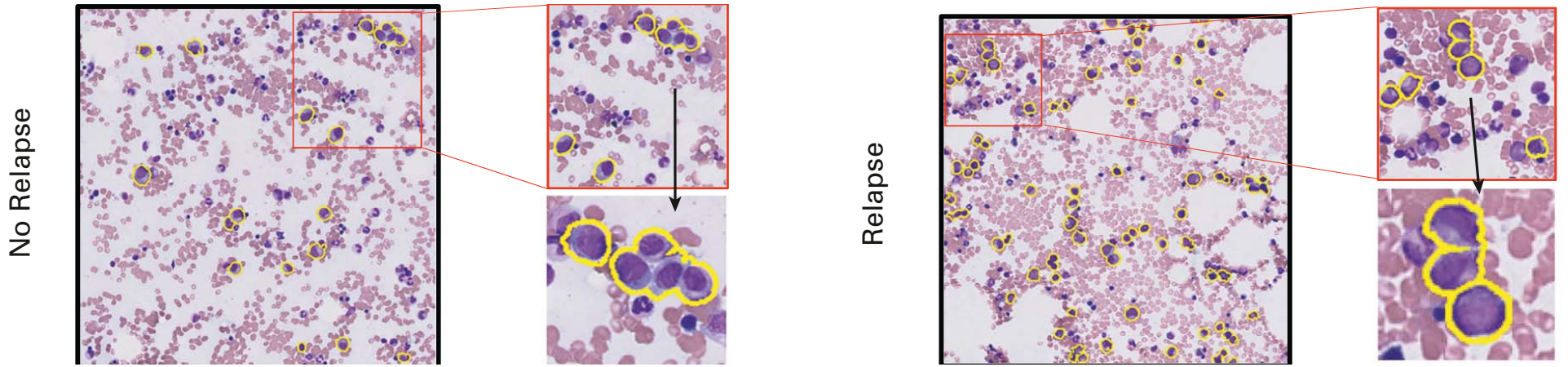


Training set: 40 patients, half of whom relapsed

Anant Madabhushi, et al.
JCO Clin Cancer Informatics, 2022; 6:e2100156

Machine learning and AML prediction

Identifying
Early myeloid cells



Anant Madabhushi, et al.
JCO Clin Cancer Informatics, 2022; 6:e2100156

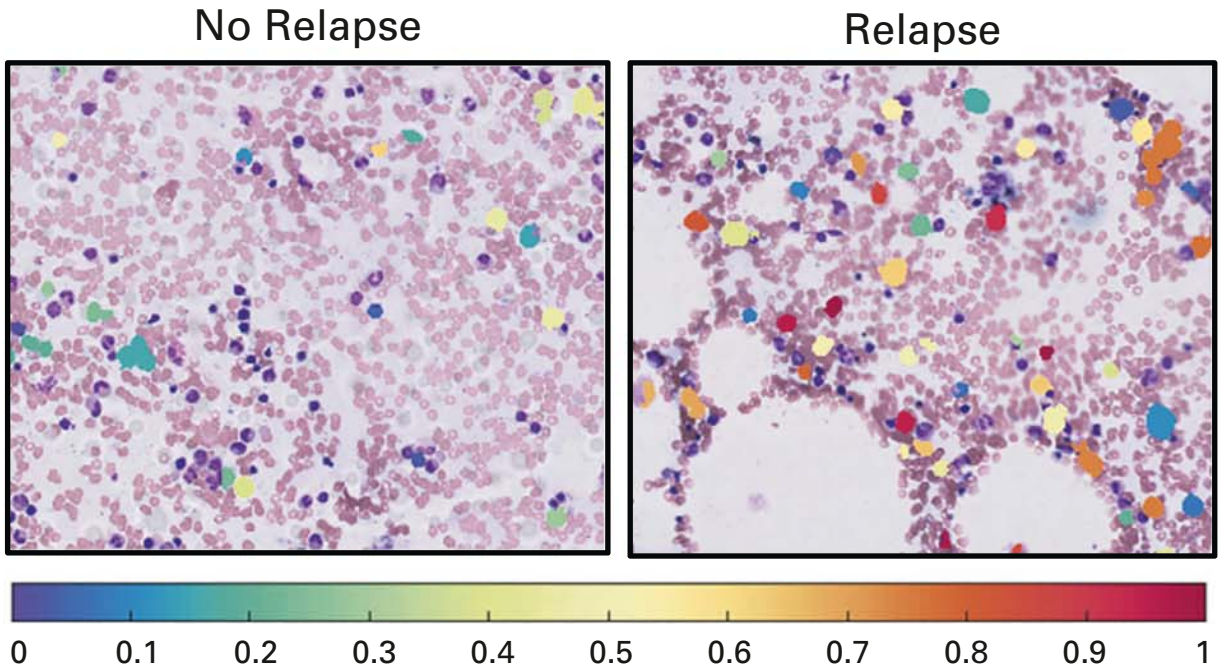
Machine learning and AML prediction

Four types of features quantitated:

- Early myeloid cell statistics
  - Percentage and area ratio
- Haralick texture
  - 52 features related to chromatin pattern
- Fractal dimension
  - 64 features related to complexity and irregularity of structures
- Shape features
  - 96 measurements related to shape irregularity and distortion

JCO Clin Cancer Informatics, 2022; 6:e2100156

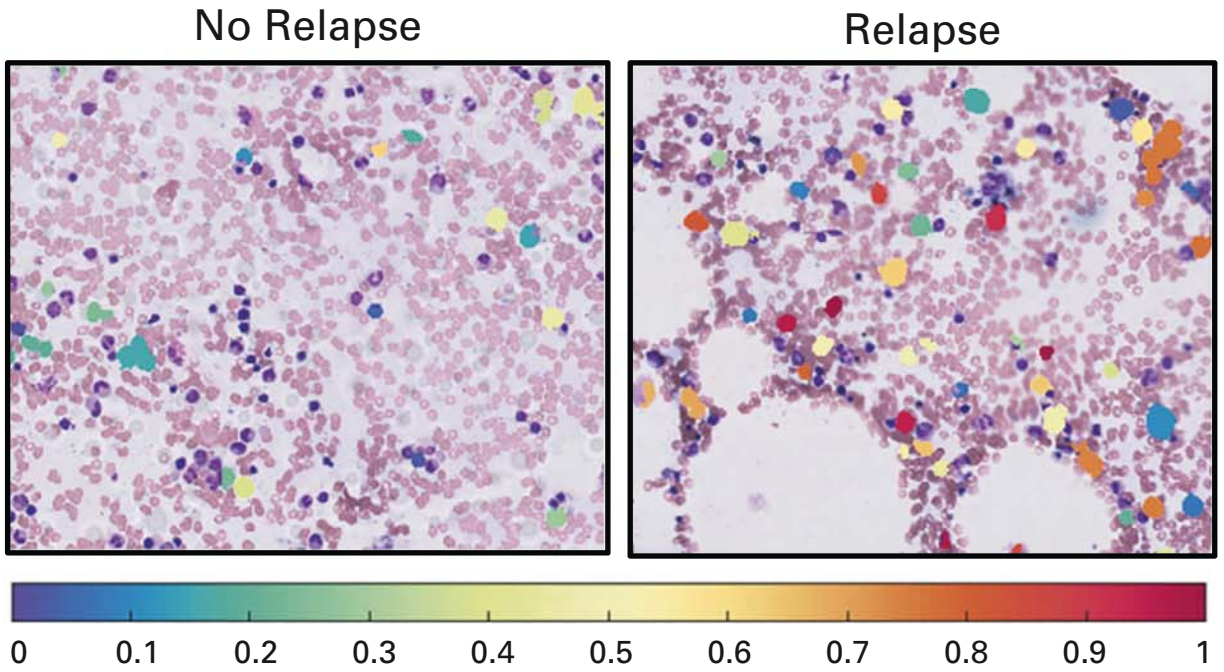
Machine learning and AML prediction



Generation of a pathologic risk score (PRS)

JCO Clin Cancer Informatics, 2022; 6:e2100156

Machine learning and AML prediction



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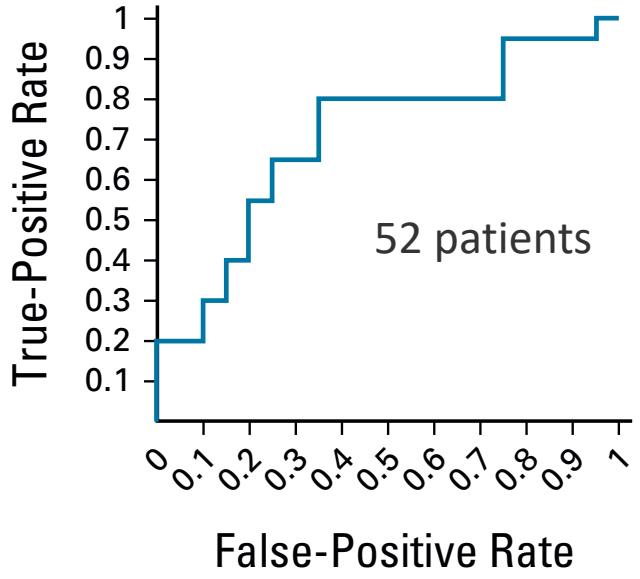

JCO Clin Cancer Informatics, 2022; 6:e2100156

Conclusions

What molecular tests does every patient need:

- Morphology of blood and bone marrow
- Flow cytometry
- Cytogenetics
  - Karyotype
  - FISH
- Next generation sequencing (NGS)

Future Directions

- New molecular targets are being identified
- Targetable molecular dependencies will continue to be identified
- Machine learning is likely to have a major impact on diagnosis and therapeutic selection