

Considerations for the use of molecular markers to guide therapy in cytogenetically normal (CN) AML in adults under 60 years



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Molecular Biomarkers and Personalized Cancer Therapy

- Cytogenetic abnormalities of the leukemic cell are the most important prognostic factor in AML and routinely used to select therapy

Molecular Biomarkers and Personalized Cancer Therapy

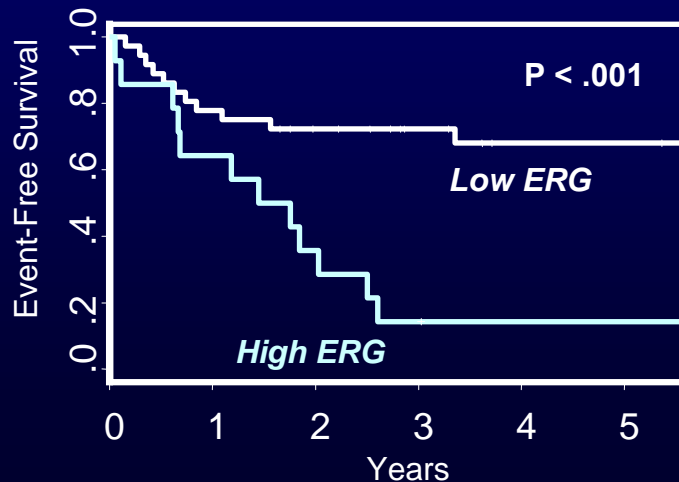
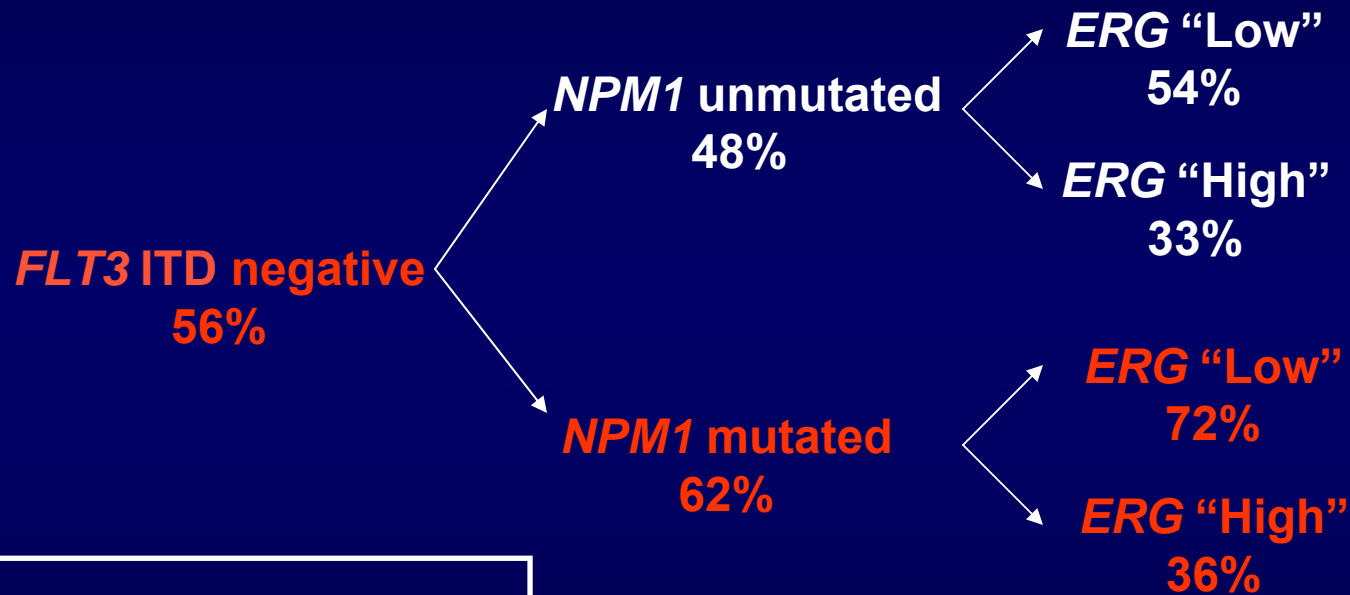
- Cytogenetic abnormalities of the leukemic cell are the most important prognostic factor in AML and routinely used to select therapy
- Approximately 45% of adults with AML under the age of 60 years are cytogenetically normal (CN-AML)
- Approximately 40% of CN-AML are cured with autologous stem cell transplantation (SCT) or 4 cycles of high-dose cytarabine (HiDAC)
- How might we prioritize the use of molecular information to identify the 40% cured with current therapy and develop better treatment for the rest?

Prognostic Single-gene Markers in CN-AML

Gene Symbol	Location	Prognostic Impact
<i>NPM1</i> mutations	5q35	Favorable
<i>CEBPA</i> mutations	19q13.1	Favorable
<i>FLT3</i> ITD	13q12	Adverse
<i>FLT3</i> TKD	13q12	? adverse
<i>MLL</i> PTD	11q23	Adverse→Neutral
<i>WT1</i> mutations	11p13	Adverse

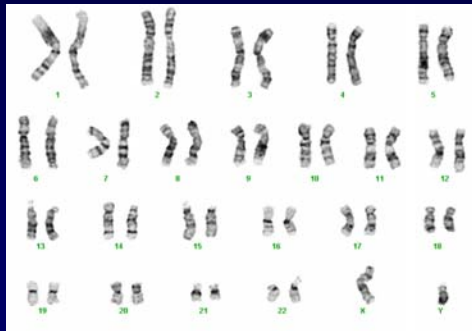
<i>ERG</i> overexpression	21q22.3	Adverse
<i>BAALC</i> overexpression	8q22.3	Adverse

2 year EFS in CN-AML: Impact of *ERG* Expression Levels in Molecular Low Risk Group (*FLT3* ITD-/*NPM1*+)

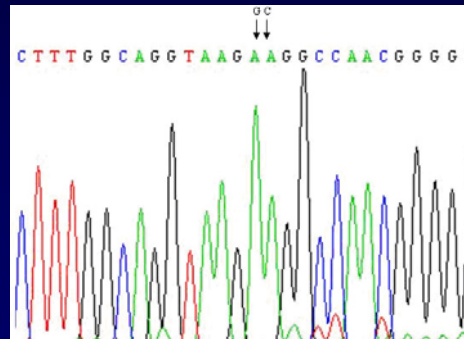


Can we use genome wide analyses to guide treatment in addition to cytogenetics and single-gene markers?

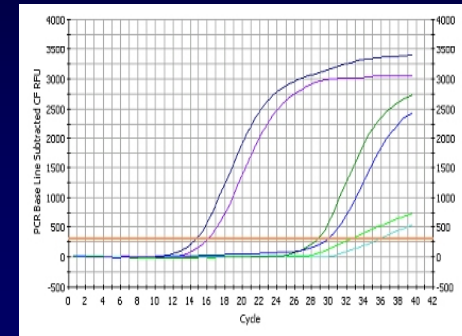
Cytogenetics



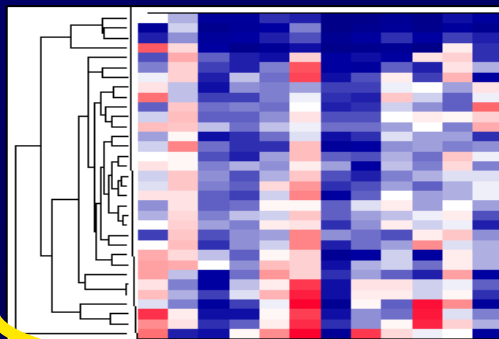
Gene Mutations



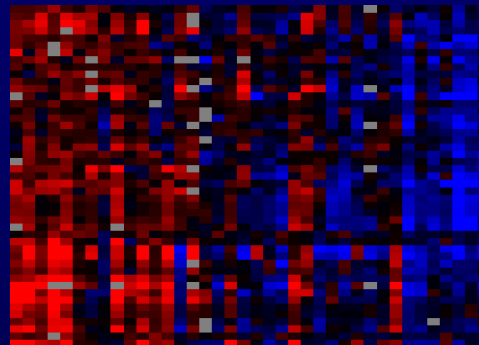
Gene Expression



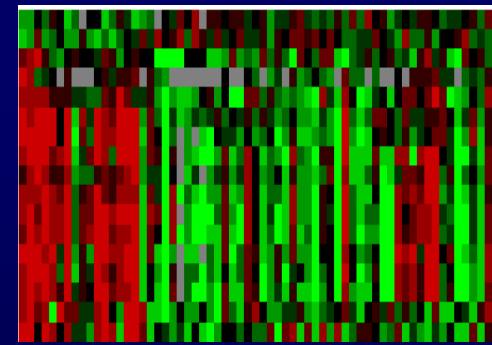
SNP Profiling



Gene profiling



miR Profiling



Integrated Predictors



Risk-adapted stratification to targeted treatments

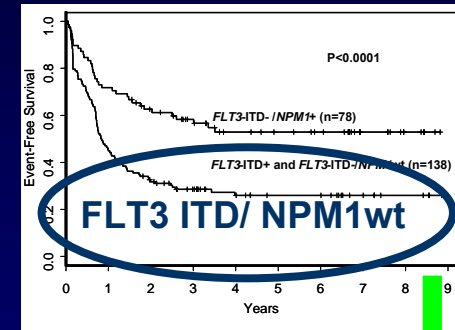
microRNAs in Cytogenetically Normal AML

- MicroRNAs (miRNAs) are 19- to 25-nucleotide long RNA transcripts that inhibit translation of the corresponding proteins
- Involved in different human cancers including leukemia
- Differential miRNA expression has prognostic significance and adds to further prognostic dissection of CN-AML

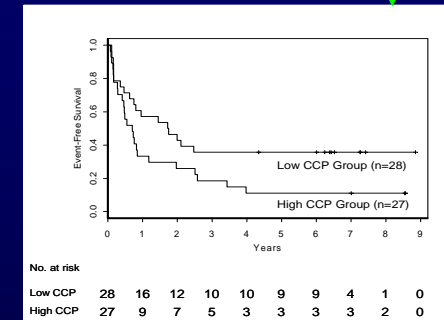
Integration of cytogenetics, gene mutations and genome-wide microRNA & gene expression profiles in high risk CN-AML



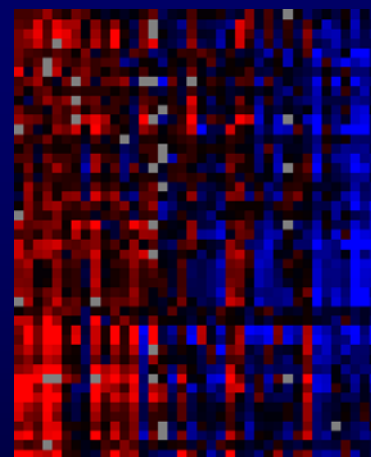
Cytogenetics



Gene mutations



miRNA signature



miRNA-associated gene expression signature

**Function by Gene Ontology:
Activation of genes involved in innate immunity (e.g., *IL1B*)**

Hypothetical treatment

**IL1 β antagonist/
Chemotherapy**

Conclusions

- One can devise predictors that stratify CN-AML patients to risk-adapted treatment using molecular information from different platforms
- The tools to apply some of these predictors to individual patients need to be further developed technically
- These predictors need to be validated
- These predictors need to be incorporated into therapeutic trials

Some further considerations

- Prognostic information is dependent upon the therapy used
 - Thus different groups will come up with different approaches and should test them
- However we have sufficient information to be doing a much better job in testing different therapies in different subgroups of CN-AML
 - **We are much too conservative**
- Personalized therapy for CN-AML will be widely used within the next 10 years and probably double the cure rate to 80%