Chronic Myeloid Leukemia

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Objectives

- To discuss the clinical presentation and diagnosis of CML
- To discuss front line treatment options for CML and common side effects
- To discuss milestones for response to treatment

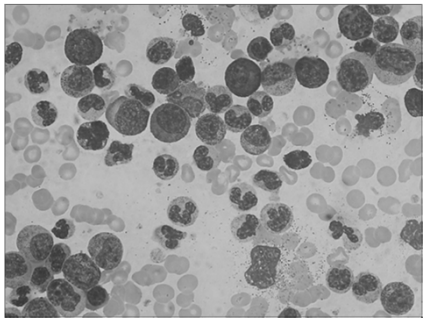
Case Scenario

- 40 year old man presents for routine physical. He reports mild fatigue that he attributes to increased hours at work.
- PMH/PSH: Seasonal allergies
- Meds/Allergies: None
- FH: Significant for CAD
- SH: No smoking or alcohol use
- Physical exam shows a I/VI systolic murmur and a palpable spleen.

Case Scenario

- CBC: WBC 50, Hb 10, platelets 470 with diff:
  - 11% neutrophils
  - 48% bands
  - 7% lymphocytes
  - 3% monocytes
  - 1% eosinophils
  - 3% basophils
  - 10% metamyelocytes
  - 15% myelocytes
  - 1% promyelocytes
  - 1% blasts

Peripheral Blood Film



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https://commons.wikimedia.org/w/index.php?curid=8793165

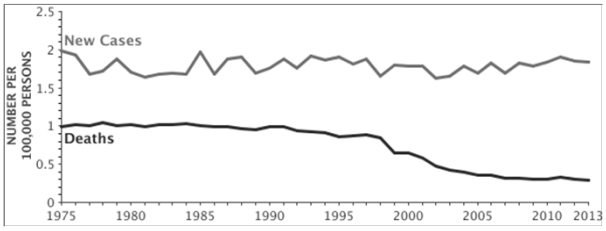
Clinical Presentation

- 50% are asymptomatic:
  - Abnormal labs (usually leukocytosis) detected during routine visit
- 50% are symptomatic:
  - Constitutional symptoms
  - LUQ discomfort
  - Early satiety
- Physical exam findings:
  - Splenomegaly
  - Hepatomegaly
  - Bruising

Epidemiology

- First clinical case described in 1845 by Dr. Bennet who reported a "Case of Hypertrophy of the Spleen and Liver in which Death Took Place from Suppuration of the Blood" in the Edinburgh Medical Journal.
- American Cancer Society 2016 US Estimates:
  - 8229 patients expected to be diagnosed.
  - 1079 patients expected to die from disease.
  - 10-15% of all new leukemia cases
  - 1 person in 555 will be diagnosed with CML

SEER Statistics for CML



Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	17.2%	28.3%	22.8%	32.0%	34.2%	47.2%	54.5%	64.4%

http://seer.cancer.gov/statfacts/html/cmyl.html

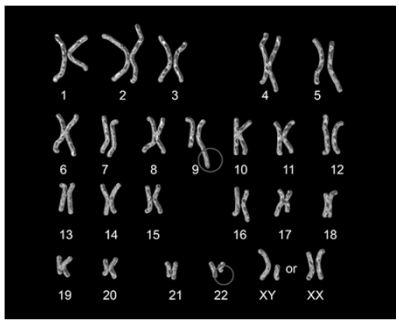
Diagnosis

- Laboratory Testing:
  - CBC with differential
  - Review of peripheral blood smear
  - CMP
  - LDH
  - Uric Acid
- Bone marrow aspirate and biopsy:
  - Required at diagnosis to determine phase of disease
  - Full Karyotype
  - FISH for t(9;22)
  - PCR for BCR-ABL to establish baseline

CML Phase Determined by Blood and Marrow

	Presentation	Criteria (Blood or Bone Marrow)	Prognosis
Chronic Phase	80-85%	<10% blasts	Good
Accelerated Phase (AP)	10%	1) 10-19% blasts OR 2) 20% basophils or more	4-5 years
Blast Crisis (BC)	5%	1) >20% blasts or more in the marrow OR 2) Extramedullary disease with localized blasts	6-12 months

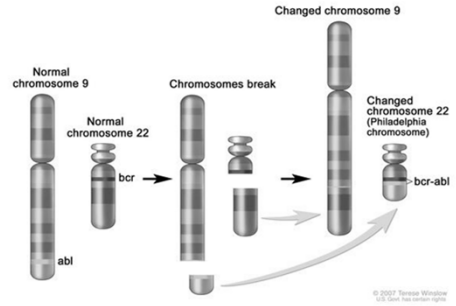
Full Karyotype



Red circles indicate the chromosomes changed by the translocation between 9 and 22

Artist: Kateryna Kon, included with permission from shutterstock

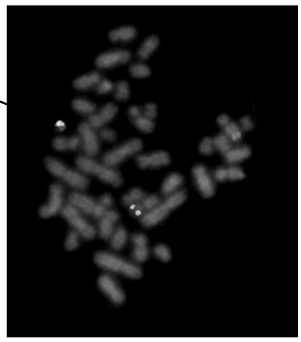
Cytogenetic Criteria: Philadelphia Chromosome



Author: National Cancer Institute (https://www.cancer.gov/)

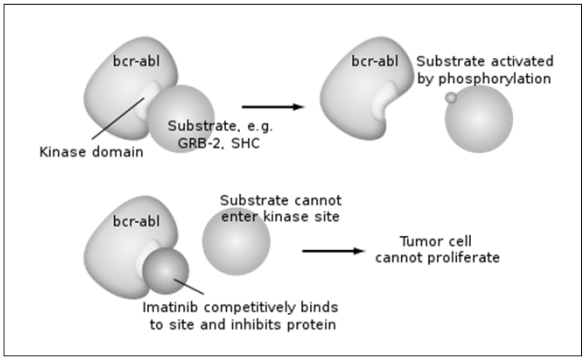
FISH for t(9;22)

Detection of BCR/ABL fusion



https://en.wikipedia.org/wiki/Chronic_myelogenous_leukemia

CML Pathogenesis



By Author of original image was Sodium at en.wikipedia., CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=3221233

Prognosis dramatically improved with TKI therapy

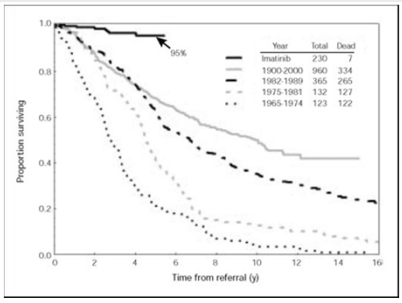


FIGURE 2. Survival of patients with early chronic phase chronic myeloid leukemia treated at M. D. Anderson Cancer Center in different eras compared with those treated with imatinib.

Quintás-Cardama and Cortes. Chronic Myeloid Leukemia: Diagnosis and Treatment. Mayo Clinic Proceedings, Volume 81, Issue 7, 2006, 973–988. http://dx.doi.org/10.4065/81.7.973.
Figure included with permission from Elsevier

Case Continued

- **The diagnosis of chronic phase CML is confirmed:**
  - **FISH sent from peripheral blood returns the next day as positive for BCR/ABL fusion**
  - **Bone marrow biopsy report returns consistent with chronic phase CML.**
- **Our next step is considering treatment options.**

Treatment Goals (Milestones)

- Complete Hematologic Response (CHR)
  - Normal CBC by 3 months
- Complete Cytogenetic Response (CCyR)
  - Negative FISH for t(9;22) by 12 months
- Major Molecular Response (MMR)
  - PCR for BCR/ABL <0.1% at about 18 months
  - Faster time to MMR with second generation TKI

What should we recommend?

- A. Allogeneic stem cell transplant
- B. Imatinib
- C. IFN-α
- D. Bosutinib
- E. Omacetaxine
- F. Observation

CML Treatment Options

- First Line:
  - Imatinib (first generation)
  - Nilotinib (second generation)
  - Dasatinib (second generation)
  - Same overall survival for all three
- Second Line:
  - Bosutinib
  - Ponatinib
- Agent selected takes in to account side effect profiles and time to MMR.

Adverse Events with TKIs

AE	Imatinib	Nilotinib	Dasatinib
Fluid Retention	+++ (low grade)	(+)	(+)
GI (N/V/D)	++	(+) requires fasting	(+)
Pleural Effusion	-	-	++ significant
Myalgia	+++ significant	(+)	(+)
LFT increases	+	++ significant	+
Myelosuppression	++ (neutropenia)	+	++ (thrombocytopenia)
QTc prolongation	+	+, additional cardiac concerns	+

Case Continued

- The patient chooses imatinib because he wants to take a drug with longer term follow up.
  - 3 months: CHR achieved and PCR <10%
  - 12 months: CCyR achieved and PCR improved to 0.2%
  - 15 months: CCyR lost and PCR increased to 8%
- What actions should be taken for these results?

Indications for BCR-ABL Kinase Domain Mutation Analysis

- Chronic Phase
  - Inadequate initial response:
    - PCR > 10% at 3 months
    - Failure to achieve CCyR at 12 months
  - Any sign of loss of response:
    - Hematologic Relapse
    - Cytogenetic Relapse
    - Loss of MMR
- If T3151 mutation is identified, the only TKI with activity against this is ponatinib

Adapted from Table 2 of the NCCN Guidelines Version 3.2013

Case Conclusion

- Our patient's mutation analysis indicates resistance to imatinib but sensitivity to nilotinib.
- After switching therapy to nilotinib, he regains CCyR and achieve MMR.

Future Research

- Active area of research is if TKI therapy can be safely stopped in patients who have achieved MMR for 2 years or more.
- With 5 years of clinical trial data:
  - Roughly 50% of patients are able to stop TKI and maintain MMR (PCR <0.1%)
  - Roughly 50% of patients have to restart TKI within 6 months due to loss of MMR

Summary

- Consider CML as a diagnosis for patients who present with leukocytosis and splenomegaly.
- Front line treatment options for CML are imatinib, dasatinib, and nilotinib
  - Agent select depends on side effect profiles of the TKIs and time to MMR
- Milestones goals are 1) normal CBC by 3 months, 2) negative FISH by 12 months, and 3) PCR <0.1% at 18 months.

Improving Outcomes in Acute Myeloid Leukemia

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AML: Definition and diagnosis

A heterogeneous hematologic malignancy characterized by clonal expansion of myeloblasts in the peripheral blood, bone marrow and other tissues.

AML: Definition and diagnosis

A heterogeneous hematologic malignancy characterized by clonal expansion of myeloblasts in the peripheral blood, bone marrow and other tissues.

Diagnosed based on ≥ 20% myeloblasts in the peripheral blood and bone marrow, with some important exceptions…

*Patients with t(8;21), inv(16) and t(15;17) do not need to meet to 20% blast cut-off to be formally diagnosed with AML

AML STILL ASSOCIATED WITH POOR OVERALL SURVIVAL

- AML historically portends a dismal prognosis
  - 20,830 new U.S. cases and 10,460 deaths estimated in 2015
  - 5 year survival for ≥60 y/o is approximately 20% or less
  - Average age of patient with AML is 67 y/o
- Cytotoxic standard of care has not changed since the 1960s
- Chemotherapy followed by allogeneic (donor) stem cell transplantation can be curative
- Even with intensive induction chemotherapy/transplantation most patients die of their disease
- New insights are needed
  - Directing specific therapies toward a specific molecular aberration

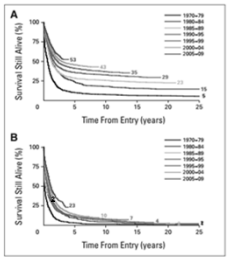

Fig 1. Change in overall survival with time. (A) Age 15 to 59 years; (B) 60 or more years.

1) Cancer Facts and Figures, 2015, ACS
2) Burnett , Wetzler and Lowenberg. JCO 2011. 29: 487

LITTLE CHANGE IN THE TREATMENT OF AML IN DECADES…

- Lack of change in treatment options is not due to a lack of resources or interest
- Heterogeneous disease with a growing number of mutations makes it difficult to develop treatments which work for all AML patients
- AML leads sequencing efforts, although clinical translation is still needed, our knowledge of AML pathogenesis is rapidly advancing
- Majority of patients relapse due to the heterogeneity of the disease and require further therapy
- Few transformational agents with durable responses in relapsed disease, particularly when given as monotherapy

French-American British (FAB) Classification for AML

FAB subtype	Name	% of adult AML patients	Prognosis compared to average for AML
M0	Undifferentiated acute myeloblastic leukemia	5%	Worse
M1	Acute myeloblastic leukemia with minimal maturation	15%	Average
M2	Acute myeloblastic leukemia with maturation	25%	Better
M3	Acute promyelocytic leukemia	10%	Best
M4	Acute myelomonocytic leukemia	20%	Average
M4 eos	Acute myelomonocytic leukemia with eosinophilia	5%	Better
M5	Acute monocytic leukemia	10%	Average
M6	Acute erythroid leukemia	5%	Worse
M7	Acute megakaryoblastic leukemia	5%	Worse

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M7	Acute megakaryoblastic leukemia	5%	Worse

Morphology does not tell which patients will be cured

AML Risk Stratification

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

Hartmut Döhner et al. Blood 2010;115:453-474
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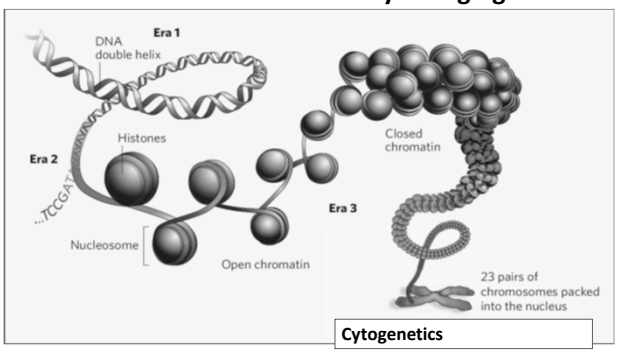
blood

How we understand risk in is finally changing…

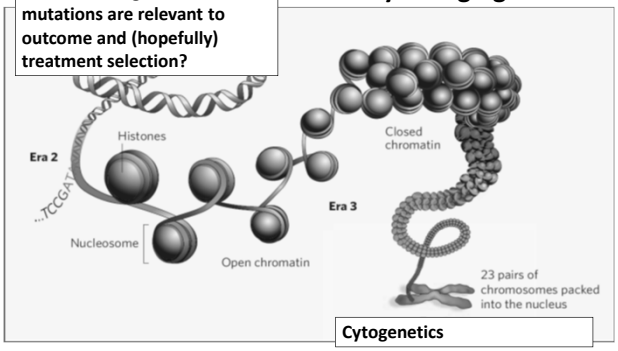


Cytogenetics

Figure from Baylin and Schuebel, Nature 2007

How we understand risk in is finally changing…

Molecular diagnostics—what mutations are relevant to outcome and (hopefully) treatment selection?



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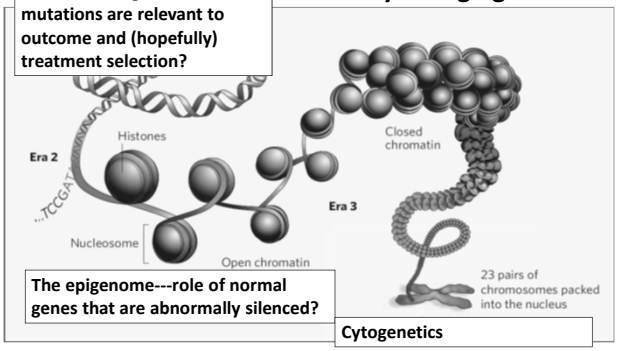

The epigenome---role of normal genes that are abnormally silenced?

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Figure from Baylin and Schuebel, Nature 2007

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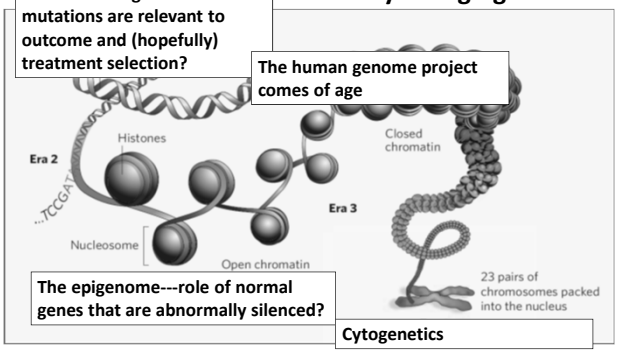
Molecular diagnostics—what mutations are relevant to outcome and (hopefully) treatment selection?

The human genome project comes of age

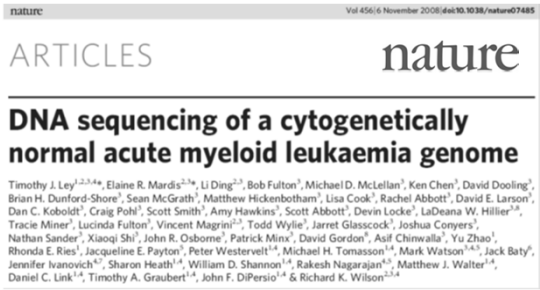


The epigenome---role of normal genes that are abnormally silenced?

Cytogenetics

Figure from Baylin and Schuebel, Nature 2007

Unfortunately, the problem of assigning risk in AML is getting more and more complex…


nature Vol 456|6 November 2008|doi:10.1038/nature07485

ARTICLES nature

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Timothy J. Ley[1,2,3,4*], Elaine R. Mardis[2,3*], Li Ding[2,3], Bob Fulton[3], Michael D. McLellan[3], Ken Chen[3], David Dooling[3], Brian H. Dunford-Shore[3], Sean McGrath[3], Matthew Hickenbotham[3], Lisa Cook[3], Rachel Abbott[3], David E. Larson[3], Dan C. Koboldt[3], Craig Pohl[3], Scott Smith[3], Amy Hawkins[3], Scott Abbott[3], Devin Locke[3], LaDeana W. Hillier[3,8], Tracie Miner[3], Lucinda Fulton[3], Vincent Magrini[2,3], Todd Wylie[3], Jarret Glasscock[3], Joshua Conyers[3], Nathan Sander[3], Xiaoqi Shi[3], John R. Osborne[3], Patrick Minx[3], David Gordon[3], Asif Chinwalla[3], Yu Zhao[1], Rhonda E. Ries[1], Jacqueline E. Payton[5], Peter Westervelt[1,4], Michael H. Tomasson[1,4], Mark Watson[1,4,5], Jack Baty[6], Jennifer Ivanovich[6,7], Sharon Heath[1,4], William D. Shannon[1,4], Rakesh Nagarajan[4,5], Matthew J. Walter[1,4], Daniel C. Link[1,4], Timothy A. Graubert[1,4], John F. DiPersio[1,4] & Richard K. Wilson[2,3,4]

Sequencing the AML genome

- Using next generation technology and the apparatus previously harnessed for the Human Genome Project, the authors sequenced the entire genome in two ways from the same AML patient, examining both

  1) leukemia cells
  2) normal germline cells (skin)

- By comparing the two results, they found 10 genes that were mutated in the leukemia cells and <u>normal</u> in the skin cells. 8 of these genes had never before been found to be associated with leukemia.

10 genes were mutated in the patient's AML cells but were normal in skin

Gene	Type of mutation	Mutations in other AML cases
** CDH24*	Nonsense	**0/187**
** SLC15A1*	Nonsense	0/187
**KNDC1*	Missense	0/187
**PTPRT*	Missense	0/187
**GRINL1B*	Missense	0/187
**GPR123*	Missense	0/187
**EB12*	Missense	0/187
** PCLKC*	Missense	0/187
FLT3	Indel	51/185
NPM1	Indel	43/180

* in pathway known to be associated with cancer pathogenesis
* in pathway that suggests potential mechanism in cancer pathogenesis

What does it mean?

- Is it practical? How long did it take? How much did it cost?
  - First case took 8 months, second case 8 weeks?
  - As of 2010, 50+ AML patients sequenced by this group
    - Week to month for results, costs $ 35K
  - As of 2016, thousands of patients sequenced, multiple "tailor made" methods to look at 90+ genes of interest
    - About a week for results, $ 1K to 5K

BIOLOGY OF AML – COMPLEX AND HETEROGENOUS

Growing number of gene mutations
- Relatively small number per case
- Significant differences between cases including in co-mutational patterns
- However some groups of mutations converge on common mechanisms of transformation (TET/IDH/WT1)

Relapse represents more complex mixture of disease
- Presence of pre-existence and/or evolution of resistant subsets within single AML cases

Targeting early, untreated disease – potential therapeutic opportunity

Heterogeneity of Cytogenetically Normal AML

Hartmut Döhner et al. Blood 2010;115:453-474
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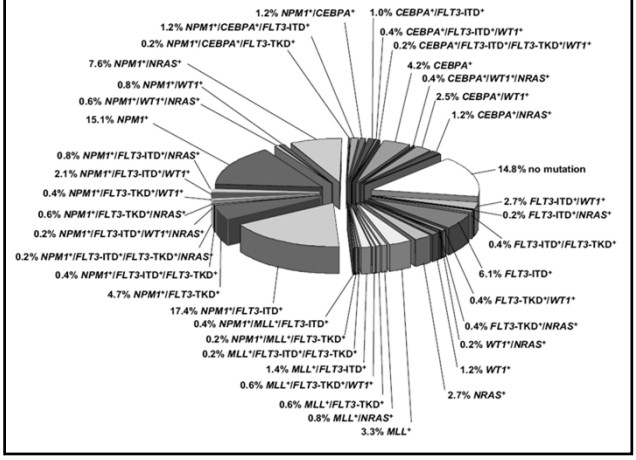
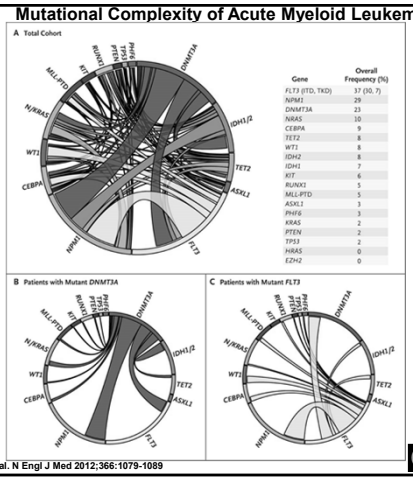
blood



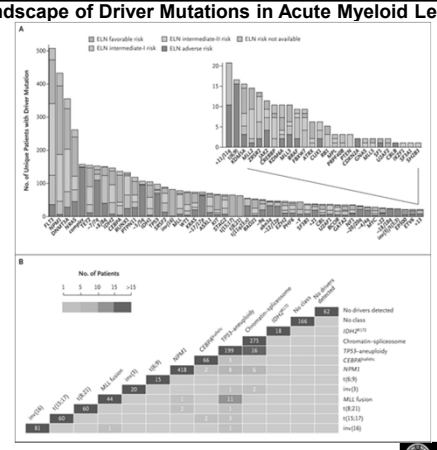
Mutational Complexity of Acute Myeloid Leukemia (AML).



Patel JP et al. N Engl J Med 2012;366:1079-1089

The NEW ENGLAND JOURNAL of MEDICINE

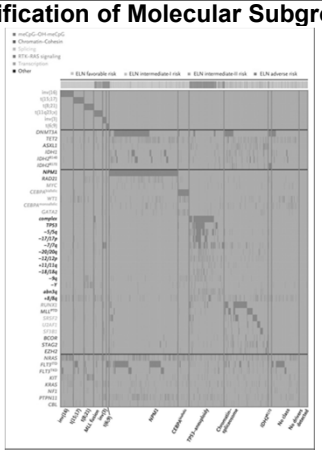
Landscape of Driver Mutations in Acute Myeloid Leukemia (AML).



Papaemmanuil E et al. N Engl J Med 2016;374:2209-2221

The NEW ENGLAND JOURNAL of MEDICINE

Identification of Molecular Subgroups in AML.



Papaemmanuil E et al. N Engl J Med 2016;374:2209-2221

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We have to understand the biology

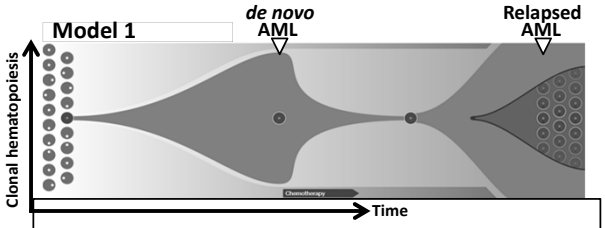
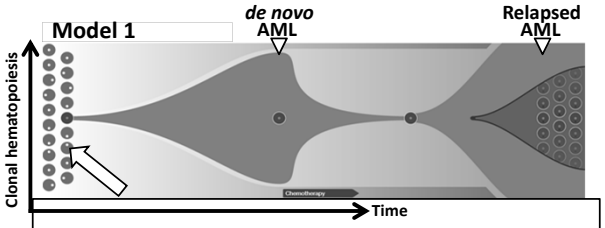


Figure from Ding, et al, Nature 2012

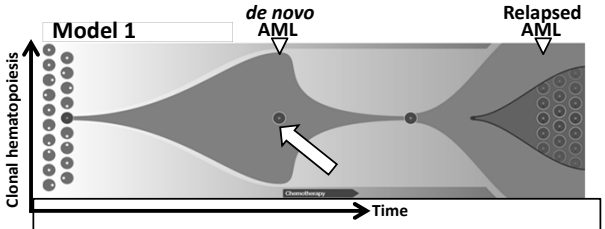
We have to understand the biology



- Majority of mutations preexist (passenger)

Figure from Ding, et al, Nature 2012

We have to understand the biology



- Majority of mutations preexist (passenger)
- Founding clone in each sample (grey) contains at least 1 driver mutation

Figure from Ding, et al, Nature 2012

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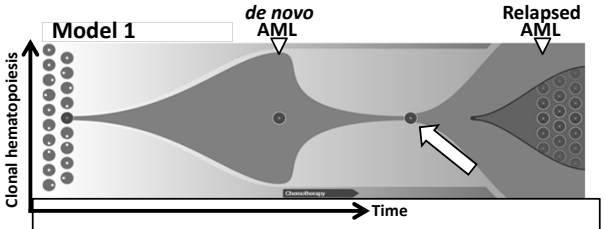

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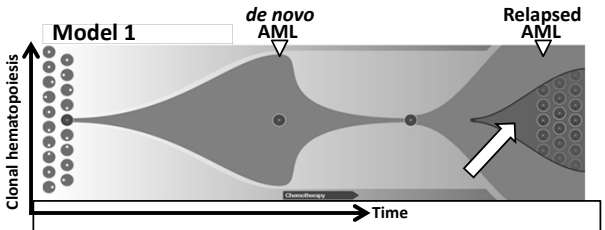
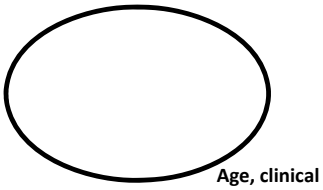


- Majority of mutations preexist (passenger)
- Founding clone in each sample (grey) contains at least 1 driver mutation
- Subclone emerges at relapse (red)

Figure from Ding, et al, Nature 2012

How do we go forward? How can we design the best trial?



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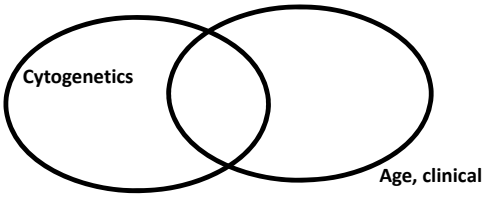

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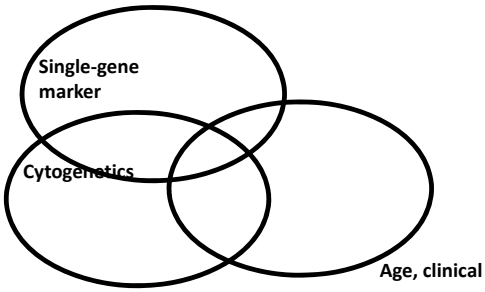

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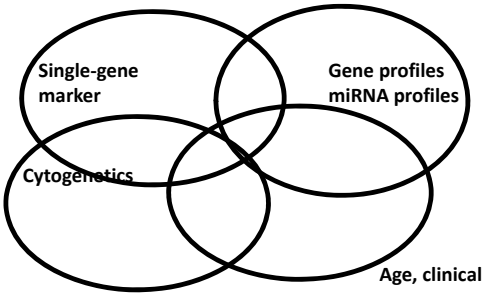

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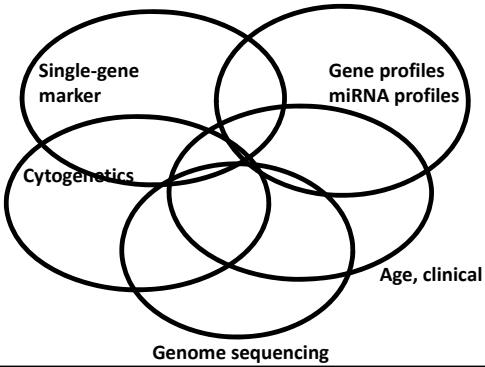

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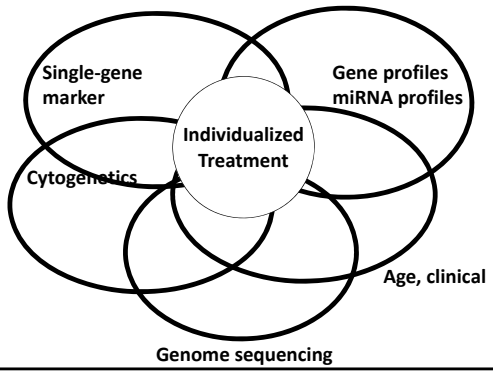


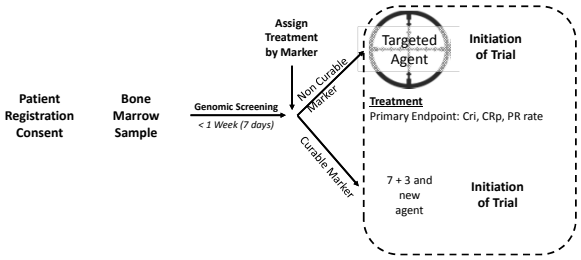
INNOVATIVE TRIAL DESIGN: LEUKEMIA & LYMPHOMA SOCIETY BEAT AML MASTER TRIAL

RATIONALE FOR MASTER TRIAL CONCEPT IN AML

- Overall intent to yield measurable efficiencies in terms of
  - Improving genomic screening of AML patients at the time of clinical trial entry
  - Feasibility of 7 day waiting period while genomic studies completed
  - Assign therapy on basis of molecular marker targetable with a novel agent
  - Different from other studies, also incorporate a marker negative arm so all patients are offered a opportunity to gain benefit
  - Improved timelines for drug biomarker testing of targeted agent and adaptation
  - Use chemotherapy only when benefit demonstrated (NPM1 mut/FLT3 wt; CBF AML)
- Multi-arm master protocol
  - Each arm independent from one another with consistent eligibility
  - Window design allows for testing of "large effects"
  - Focus initially on age >60 years as this group does poorly with 7/3 chemotherapy
- Designed to facilitate FDA approval of new drugs where big effects are observed

CLINICAL TRIAL DESIGN: PATIENT IDENTIFICATION

Phase 2, newly diagnosed AML patients, > 60 yrs



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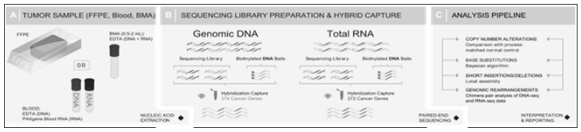
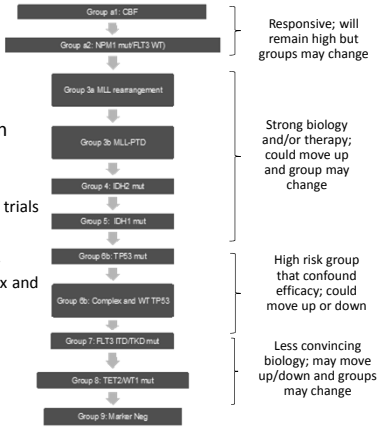
GENOMIC/BIOCHEMICAL PROFILING DETAILS



- **Use a centralized genomic/biochemical platforms to identify all known somatic alterations in a panel of newly diagnosed AML patients**
- **These will be done in a CLIA-approved lab**
- **< 7 day turn around time for profiling**
- **Use this data to "bin" patients into different trials, treatment assignments**
- **Exploratory profiling to link biomarkers with response/resistance**

Order chosen based upon

1. Responsive potential
1. Rationale or strong data in trials around biology
1. Higher risk group that may confound efficacy (Complex and TP53)
4. Less convincing biology
4. Marker Negative



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How is Therapy Assigned

1. Molecular and Cytogenetic Data Arrives with Top to bottom approach
2. Dominant clone at VAF > .3 chosen based upon classification
3. If no dominant clone at VAF > .3, go to .2 with top to bottom for assignment

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POTENTIAL TREATMENT GROUPS

Chemo Responsive
CBF: Samalizumab + 7/3 induction than by Ara-C + Samalizumab consolidation
NPM1 mut/Flt3 neg (Fit): Entospletinib (ENTO) + 7/3 induction then Ara-C + ENTO consolidation NPM1 mut/Flt3 neg (Unfit): ENTO followed by ENTO + Azacitidine if no response
Less Responsive Marker
MLL rearrangement: ENTO followed by ENTO + Azacitidine if no response MLL PTD: ENTO followed by ENTO + Azacitidine if no response
IDH1 mut: (Pending; hypermethylation group)
IDH2 mut: AG-221 followed by AG-221 + azacitidine if no response
TP53 mut: ENTO + Decitabine TP53 WT/Complex: Ento + Decitabine
FLT3 ITD/TKD: (Pending, marker negative) Hypermethylation (TET2, WT1, IDH1, IDH2): Azacitidine + BI 836858 Marker negative: Azacitidine + BI 836858 and Samalizumab + 7/3 induction than by Ara-C + Samalizumab consolidation

WHERE ARE WE NOW: CLINICAL SITES AND EXPANSION

5 Clinical Sites Recruited
- Memorial Sloan Kettering
- Oregon Health Sciences
- Ohio State University
- Dana Farber
- Mass General

Expand to at least 15-20 clinical sites as quickly as possible
- Additional sites will be selected via RFP process
- Review by LLS and CRO
- Anticipated April 2017

Other Active Trials in AML

- Syk inhibitor with chemotherapy in AML
- FLT3 inhibitor pacritinib with chemotherapy in AML (first in combination)
- Targeting IDH1 and IDH2 mutations in AML
  - Relapsed/refractory oral single-agent IDH1 and IDH2 inhibitors
  - New combination studies with chemotherapy in younger newly diagnosed patients
- Focus on developing immunotherapeutics
  - monoclonal Ab, CD33 targeting in AML (first in human, led by OSU)
  - Antibody-drug conjugates, CD33
  - Upcoming CD3-CD123 bispecific antibody trial (first in human)