Molecular genetic testing in myeloid neoplasms: yesterday, today, and tomorrow

Sophia Yohe, MD

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Disclosures

- I have no financial disclosures.

Objectives

- Choose appropriate molecular genetic testing for diagnosis of myeloid neoplasms
- Identify molecular genetic tests that predict prognosis in myeloid neoplasms
- Discuss the benefits and limitations of newer genetic tests in evaluating myeloid neoplasms

GENE LIST

ABL1	BARD1	CD79A	CSF1R	EZH2	FGFR2	HRAS	KEAP1	MLL2	NRAS	PRKDC	SMARCB1	TSC2
AKT1	BCL2	CD79B	CTCF	FAM123B (WTX)	FGFR3	IDH1	KIT	MPL	NTRK1	PTCH1	SMO	TSHR
AKT2	BCL2L2	CDC73	CTNNA1	FAM46C	FGFR4	IDH2	KLHL6	MRE11A	NTRK2	PTEN	SOCS1	VHL
AKT3	BCL6	CDH1	CTNNB1	FANCA	FLT1	IGF1R	KRAS	MSH2	NTRK3	PTPN11	SOX10	WISP3
ALK	BCOR	CDK12	DAXX	FANCC	FLT3	IKBKE	LRP1B	MSH6	NUP93	RAD50	SOX2	WT1
APC	BCORL1	CDK4	DDR2	FANCD2	FLT4	IKZF1	MAP2K1	MTOR	PAK3	RAD51	SPEN	XPO1
AR	BLM	CDK6	DNMT3A	FANCE	FOXL2	IL7R	MAP2K2	MUTYH	PALB2	RAF1	SPOP	ZNF217
ARAF	BRAF	CDK8	DOT1L	FANCF	GATA1	INHBA	MAP2K4	MYC	PAX5	RARA	SRC	ZNF703
ARFRP1	BRCA1	CDKN1B	EGFR	FANCG	GATA2	IRF4	MAP3K1	MYCL1	PBRM1	RB1	STAG2	
ARID1A	BRCA2	CDKN2A	EMSY (C11orf30)	FANCL	GATA3	IRS2	MCL1	MYCN	PDGFRA	RET	STAT4	
ARID2	BRIP1	CDKN2B	EP300	FBXW7	GID4 (C17orf39)	JAK1	MDM2	MYD88	PDGFRB	RICTOR	STK11	
ASXL1	BTK	CDKN2C	EPHA3	FGF10	GNA11	JAK2	MDM4	NF1	PDK1	RNF43	SUFU	
ATM	CARD11	CEBPA	EPHA5	FGF14	GNA13	JAK3	MED12	NF2	PIK3CA	RPTOR	TET2	
ATR	CBFB	CHEK1	EPHB1	FGF19	GNAQ	JUN	MEF2B	NFE2L2	PIK3CG	RUNX1	TGFBR2	
ATRX	CBL	CHEK2	ERBB2	FGF23	GNAS	KAT6A (MYST3)	MEN1	NFKBIA	PIK3R1	SETD2	TNFAIP3	
AURKA	CCND1	CIC	ERBB3	FGF3	GPR124	KDM5A	MET	NKX2-1	PIK3R2	SF3B1	TNFRSF14	
AURKB	CCND2	CREBBP	ERBB4	FGF4	GRIN2A	KDM5C	MITF	NOTCH1	PPP2R1A	SMAD2	TOP1	
AXL	CCND3	CRKL	ERG	FGF6	GSK3B	KDM6A	MLH1	NOTCH2	PRDM1	SMAD4	TP53	
BAP1	CCNE1	CRLF2	ESR1	FGFR1	HGF	KDR	MLL	NPM1	PRKAR1A	SMARCA4	TSC1	

SELECT REARRANGEMENTS

ALK	BCR	BCL2	BRAF	EGFR	ETV1	ETV4	ETV5
ETV6	EWSR1	MLL	MYC	NTRK1	PDGFRA	RAF1	RARA
RET	ROS1	TMPRSS2					

Alphabet Soup

Commonly mutated genes in myeloid neoplasms

Gene	Function	Disease
DNMT3A	DNA methylation	20%+ AML
TET2		MDS, MPN, AML
IDH1/2	Metabolic, ?DNA methylation	15-30% AML
EZH2	Histone modification	
PHF6		3% AML, TALL
ASXL1	Disrupt chromatin, ?histone	CMML, MDS, MPN, AML
SRSF2	Spliceosome	MDS
ZRSR2		MDS
U2AF1		MDS
CBL	Ubiquitination	AML, CMML

Limitations

- Inconsistency of results across studies
- Multivariate analysis
- Different genes tested
- Different testing methods
- Lack of replication
- Subgroup evaluation
- All mutations of a gene may not have similar effects
- Lack of randomized controlled trials

Myeloproliferative Neoplasms (MPN)

Myelodysplastic/myeloproliferative neoplasms (MPN/MDS)

Myeloproliferative Neoplasms

- Chronic myelogenous leukemia (CML)
- Polycythemia vera (PV)
- Primary myelofibrosis (PMF)
- Essential thrombocythemia (ET)

- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia, NOS (CEL)
- Mastocytosis
- Myeloproliferative neoplasm, unclassifiable

Myelodysplastic/myeloproliferative neoplasms

- Chronic myelomonocytic leukemia (CMML)
- Atypical CML (BCR-ALB1 negative)
- Juvenile myelomonocytic leukemia
- Myelodysplastic/myeloproliferative neoplasm, unclassifiable

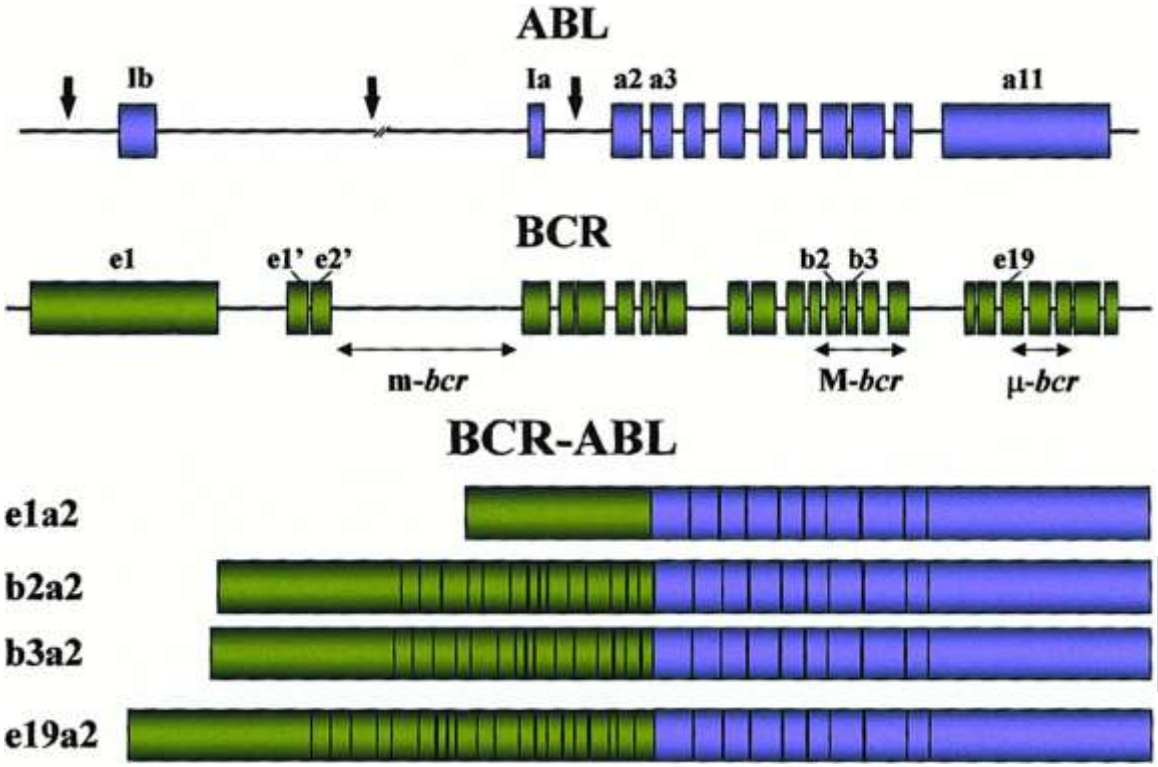
CML & the Philadelphia chromosome

46,XX,t(9;22)(q34;q11.2)

- CML is defined by the BCR-ABL1 fusion
- 90-95% detectable by karyotype
- Some variant translocations involve multiple chromosomes
- Some cryptic translocations occur

Cytogenetics Laboratory, University of Minnesota Medical Center, Fairview

BCR and ABL breakpoints



m-bcr p190 -> ALL

CML with monocytosis

M-bcr p210 -> CML

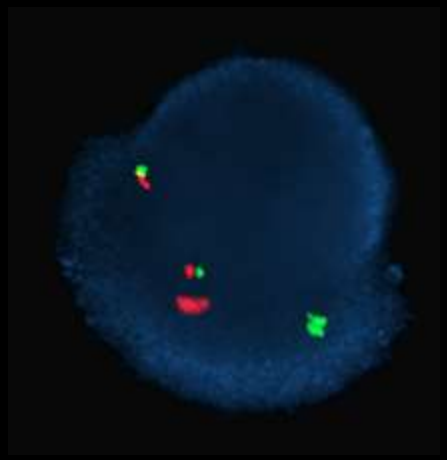
ALL 40% adult/10% peds

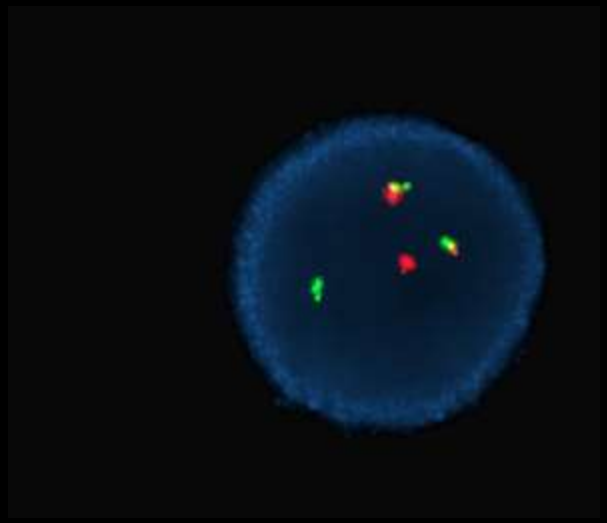
μ-bcr p230 -> CML with neutrophilia

CML with thrombocytosis

Deininger M W N et al. Blood 2000;96:3343-3356

BCR ABL1





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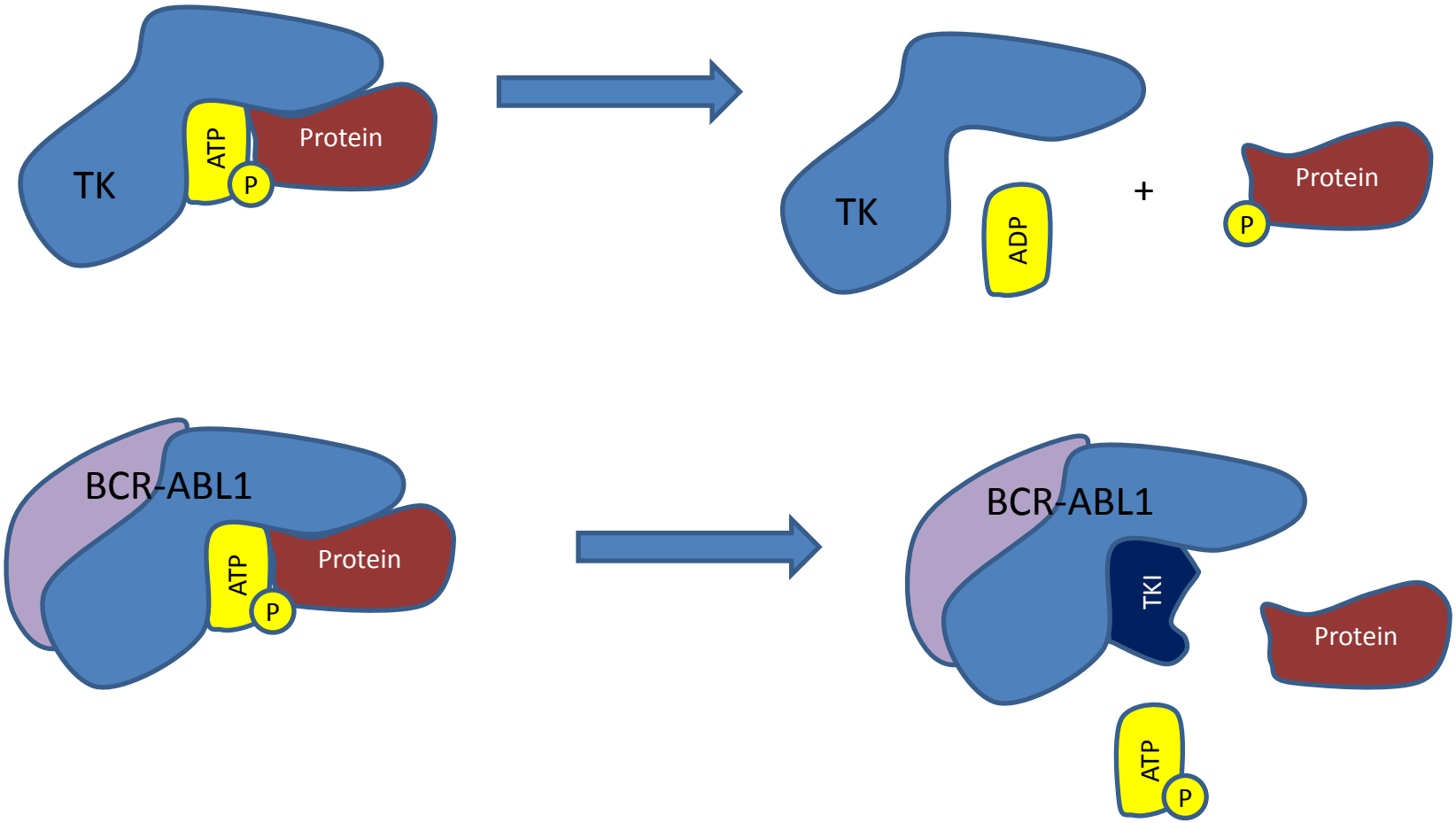
PCR for BCR-ABL1

- RNA starting material
  - RNA is less stable than DNA
    - Specimen must be processed in 72 hrs
    - Need fresh specimen (no paraffin)
- Qualitative: present or absent
- Quantitative: required for CML follow-up

Diagnosis of CML

- Karyotype should be performed on bone marrow
  - Allows detection of other abnormalities (baseline)
- Quantitative PCR (baseline)
- FISH
  - On peripheral blood if bone marrow not obtained
  - Rare cases where an alternate breakpoint is suspected and PCR for the breakpoint is not available
  - If FISH can be performed more quickly than PCR

Tyrosine kinase activity and tyrosine kinase inhibitors (TKI)



Follow up of CML

- Cytogenetics & PCR
  - 3 mo, 6 mo, 12 mo, 18 mo
  - Some time points may be omitted if the prior testing shows a good response
  - More frequent after transplant
- Clonal evolution
  - Development of a new karyotypic abnormality not present at diagnosis
  - Indicates accelerated phase

Cytogenetic & Molecular Response

Cytogenetic Response

Major (MCyR)

- Complete (CCyR)
  - No Ph+ metaphases
- Partial
  - 1-35% Ph+ metaphases
- Minor
  - >35% Ph+ metaphases

Molecular Response

- Complete
  - No detectable BCR-ABL1 by QPCR using international scale (IS)
- Major (MMR)
  - $\geq$ 3 log reduction by QPCR using IS

- Response to TKI is the most important prognostic factor

NCCN Guidelines version 1.2013
Chronic myelogenous leukemia

TKI resistance

- Primary or secondary
- Multiple causes
  - BCR-ABL1 kinase domain mutations
  - Drug transport/metabolism
  - Clonal evolution
  - Pathways that bypass BCR-ABL1

Indications for BCR-ABL1 kinase domain mutational analysis

- At 3 or 6 months
  - No PCyR or BCR-ABL1 $\geq$ 10%
- At 12-18 months
  - No CCyR
- Anytime
  - Hematologic or cytogenetic relapse
  - 1 log increase BCR-ABL1 & loss of MMR
  - Accelerated or blast phase

NCCN Guidelines version 1.2014
Chronic myelogenous leukemia

Why is testing important

Mutation	Treatment Recommendation
T315I	Ponatinib (preferred), omacetaxine, HSCT, or clinical trial
V299L	Consider ponatinib or nilotinib or omacetaxine**
T315A	Consider ponatinib, nilotinib, imatinib*, bosutinib, or omacetaxine**
F317L/V/I/C	Consider ponatinib, nilotinib, or bosutinib, or omacetaxine**
Y253H, E255K/V, F359V/C/I	Consider ponatinib, dasatinib, or bosutinib, or Omacetaxine**
Any other mutation	Consider ponatinib, high dose imatinib, dasatinib, nilotinib, bosutinib, or omacetaxine**

*if mutation develops on dasatinib
**Option with resistance or intolerance to $\geq$ 2 TKIs

NCCN Guidelines version 1.2014
Chronic myelogenous leukemia

Jak2 V617F & myeloid neoplasia

- 95% of polycythemia vera
- 50-60% of essential thrombocythemia and primary myelofibrosis
- Rarely found in other clonal myeloid neoplasms (CMML, MDS, AML, MDS/MPN - RARS-T)
- Rules out a reactive cause

JAK2 exon 12 mutation & PV

- Multiple mutations
  - All are adjacent to the pseudokinase domain
  - Codons 536-547
- Morphology
  - increased erythropoiesis
  - may not show panmyelosis
- Sequencing*, HRM, melting curve, dHPLC

When to test for exon 12 mutation

- Scenario 1 -
  - Increased red cell volume
  - EPO decreased
  - Negative for Jak V617F mutation
- Scenario 2 – very rare
  - Suspected pre-polycythemic phase
  - Negative for Jak V617F mutation
  - EPO decreased

MPL & ET/PMF

- Thrombopoeitin receptor
- W515K/L mutation leads to gain of function
  - Similar downstream effects of JAK2 V617F
  - Found in about 5% of PMF and 1% of ET*
  - W515R/A/N & S505N
- Not all MPL mutations lead to gain of function

Mastocytosis and KIT (c-kit) mutations

- D816V
  - Present in 95+% of adults with SM*
  - Present in only 1/3 of CM in children
- Other point mutations of KIT
  - Rare in adults with SM
  - Common in children with CM
  - D816Y, D816H, D816F

Lymphoid & myeloid disorders with eosinophilia and abnormalities of PDGFRA, PDGFRB, & FGFR1

- Varied morphology and don't always have eosinophilia
- PDGFRA
  - Cryptic deletion 4q12 (CHIC2) leads to FIP1L1-PDGFRA rearrangement
  - Test by FISH or RT-PCR
  - Sensitive to TKI (imatinib)
- PDGFRB
  - 5q31~33 PDGFRB rearrangements, most common t(5;12)
  - Test by cytogenetics, with confirmatory FISH or RT-PCR
  - Sensitive to TKI (imatinib)
- FGFR1
  - 8p11 rearrangement with multiple partners
  - Test by cytogenetics or FISH
  - Not responsive to TKI

Neutrophilia and CSF3R mutations

- 60% to 80% of CNL and aCML
  - T618I is the most common mutation
  - Rare in AML (1%)
  - Nonsense mutations in 30-40% severe congenital neutropenia
  - One study: CSF3R T618I specific for CNL
    - 100% of WHO defined CNL
    - 6% of suspected CNL that did not meet WHO criteria
    - 0% in MGUS associated CNL, aCML, suspected aCML
  - Another study: CNL and aCML

AKA: CD114, GCSF receptor

SETBP1 mutations

- Involved in DNA replication
- Found in ~30% of aCML
- Found in 6% CMML
- Rare in AML and MDS

CMML

- Rule out BCR-ABL1 (p190)
- Rule out PDGFRB, esp t(5;12)
- 20-40% of patients have clonal cytogenetics
  - +8, -7/7q, 12p abnormalities
- Gene mutations are common
  - May help differentiate from reactive
  - ASXL1, CBL, EZH2, Jak2, KRAS/NRAS, RUNX1, SRSF2, TET2
  - ASXL1 & SRSF2 associated with poor prognosis

Diagnosis of JMML

Category 1 (all)	Category 2 (at least one)*	Category 3 (two if there are no category 2)
BCR/ABL1 negative	Somatic RAS or PTPN11 mutation	WBC >10 K
>1 K monocytes	Diagnosis of NF1 or NF1 mutation	Circulating myeloid precursors
<20% blasts	Monosomy 7	Increased hbg F for age
Splenomegaly*		Other clonal cytogenetics
		GM-CSF hypersensitivity

Proposed additions to the WHO 2008 criteria
JMML Symposium, Atlanta, GA, 2008
Patients need either categories 1 & 2 or categories 1 & 3
CBL mutation

*Only 7% of JMML patients do not present with splenomegaly; however, virtually all develop it within weeks to months

Loh. Hematology 2010;2010: 357-362.

Myelodysplastic syndromes

- Clonal stem cell diseases
  - Ineffective hematopoiesis leading to cytopenias
  - Dysplasia
  - Increased risk of AML
- Diagnosis
  - Persistent cytopenias
  - Morphologic evidence of dysplasia
  - Cytogenetic abnormalities may provide presumptive evidence

Presumptive evidence for MDS

- Refractory cytopenia, no morphologic dysplasia, AND recurring cytogenetic abnormality

Unbalanced	Balanced
-7/7q	t(11;16)(q23;p13.3)
-5/5q	t(3;21)(q26.6;q22.1)
i(17q) or t(17p)	t(1;3)(p36.3;q21.2)
-13/13q	t(2;11)(p21;q23)
del(11q)	inv(3)(q21q26.2)
del(12p) or t(12p)	t(6;9)(p23;q34)
del(9q)	
idic(X)(q13)	

Not presumptive evidence: +8, del(20q), -Y

WHO 2008

Karyotype versus FISH

- Good karyotype (20 metaphases)
  - FISH discrepant in 1-2%
  - FISH may be false positive (especially low level positives)
  - FISH may pick up additional abnormalities in complex karyotype
- Poor karyotype (<20 metaphases)
  - FISH discrepant in ~14%
- Recommendation: FISH only if karyotype inadequate*

Prognosis in MDS

- Prognosis guides therapy
  - IPSS, IPSS-R, WPSS, MDAPSS, LR-MDAPSS
    - Cytogenetics
    - Cytopenias
    - Blasts
  - Age
  - Comorbidities
  - Performance status

IPSS and IPSS-R

International Prognostic Scoring System (IPSS)[s,t]

Survival and AML evolution					
	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)[u]	<5	5-10	---	11-20	21-30
Karyotype[v]	Good	Intermediate	Poor		
Cytopenia[w]	0/1	2/3			

IPSS Risk category (% IPSS pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
LOW (33)	0	5.7	9.4
INT-1 (38)	0.5-1.0	3.5	3.3
INT-2 (22)	1.5-2.0	1.1	1.1
HIGH (7)	≥ 2.5	0.4	0.2

Revised International Prognostic Scoring System (IPSS-R)[x]

	Score value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics[y]	Very good	–	Good	–	Intermediate	Poor	Very poor
Marrow blasts (%)	≤2	–	>2-<5	–	5-10	>10	–
Hemoglobin	≥10	–	8-<10	<8	–	–	–
Platelets	≥100	50-<100	<50	–	–	–	–
ANC	≥0.8	<0.8	–	–	–	–	–

IPSS-R Risk category (% IPSS-R pop.)	Overall score	Median survival (y) in the absence of therapy	25% AML progression (y) in the absence of therapy
VERY LOW (19)	≤ 1.5	8.8	Not reached
LOW (38)	>1.5-3	5.3	10.8
INT (20)	>3-4.5	3	3.2
HIGH (13)	>4.5-6	1.6	1.4
VERY HIGH (10)	>6	0.8	0.7

Cytogenetics and Prognosis

IPSS

Prognosis	Cytogenetic abnormality
Good	Normal, isolated –Y, -5q, -20q
Intermediate	Everything else
Poor	Complex (≥3) and chr7 abnormalities

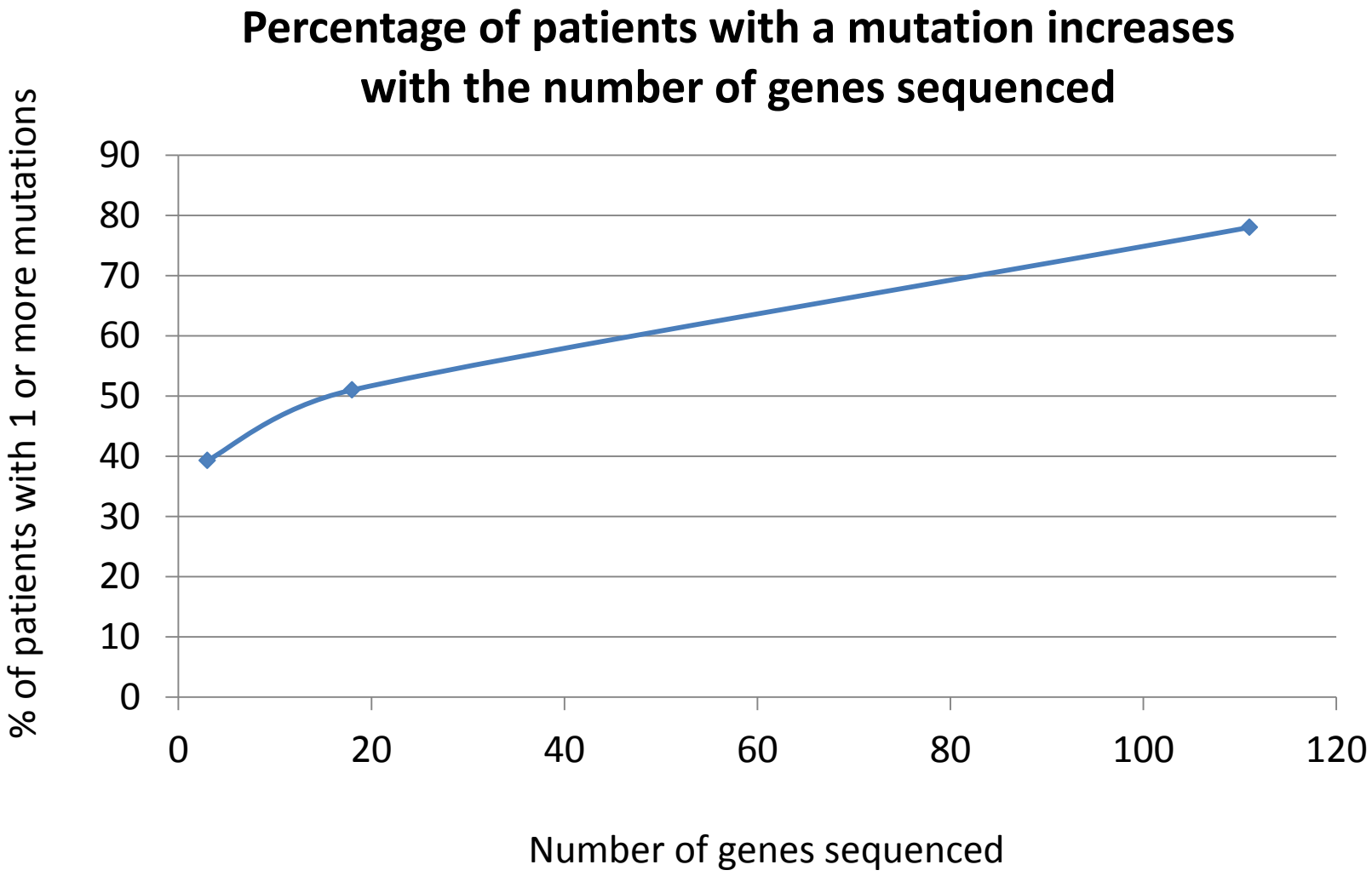
IPSS-R

Prognosis	Cytogenetic abnormality
Very good	Isolated –Y or -11q
Good	Normal Isolated -5q, -12p, -20q 2 abnormalities one of which is -5q
Intermediate	Isolated -7q, +8, i(17q), +19, other 2 abnormalities (without -5q, -7, or -7q)
Poor	Isolated inv(3), t(3q), -3q, -7 2 abnormalities one of which is -7, -7q or 3 3 abnormalities (complex)
Very poor	Complex (>3)

Does gene mutation testing help:

- Diagnose MDS with normal morphology and cytogenetics?
- Detect MRD when cytogenetics is normal?
- Add prognostic value?
  - Intermediate: behave more like low or high risk
  - Identify low risk patients with more aggressive dz
  - Identify unique subgroups of MDS

Gene mutations in MDS



Myelodysplastic syndromes

- A patient presents with persistent cytopenias. A bone marrow biopsy is performed and does not show clear evidence of dysplasia.

Gene mutations and diagnosis of MDS

- No evidence for or against at this time
  - Some patient with no mutations
  - No prospective evaluations
- TET2 is associated with clonal myeloid hematopoiesis in elderly females
  - Skewed X inactivation (clonal)
  - No evidence of clinical disease
  - Unclear if clinical disease will develop at a later time

Gene mutations and MRD

- Limited number of studies
  - Mutations may be present in a subclone
  - Founder or driver mutation versus passenger mutation
  - Transcript levels WT1 &/or PRAME
  - Splicesome mutations

Prognostic effect of gene mutations

- Poor prognosis
  - More mutations
  - TP53
  - SRSF2, ZRSR2, U2AF1: Spliceosome genes
  - TP53, EZH2, ETV6, RUNX1, ASXL1
    - Presence worsened IPSS group by one
- In IPSS low risk MDS
  - EZH2, NRAS, ASXL1 = worse prognosis
  - Using LR-MDAPSS only EZH2 retained impact

Unique subsets of MDS

- Isolated 5q- syndrome
  - Typically respond to lenalidomide
  - TP53 mutations in 5q- syndrome have higher risk of AML and may not respond to lenalidomide therapy
- SF3B1 mutations and ring sideroblasts (RARS or RARS-T)
  - Iron stains
  - RARS/RARS-T with mutated SF3B1 have better prognosis than those with wild type

Molecular genetic testing in AML

- Categorization
- Prognosis
  - Guide aggressiveness of therapy
- Association with response to therapy
- Does NOT play a role in directing targeted therapy except for PML/RARA

Treatment for AML

- Aggressiveness of therapy depends on
  - Age
  - Performance status
  - Comorbidities
  - Cytogenetic & molecular risk group
  - Subtype of AML (APL, history of MDS, therapy-related)

NCCN guidelines

Prognostic stratification

Risk group	Cytogenetic results	Molecular results
Better/favorable	t(15;17) inv(16)/t(16;16) t(8;21)	+NPM1 with neg FLT3-ITD OR Isolated biallelic CEPBA IF Cytogenetics are normal
Intermediate	Normal Isolated trisomy 8 t(9;11)	KIT (c-KIT) mutation WITH inv(16)/t(16;16) or t(8;21)
Poor	Complex Monosomal -5/5q, -7/7q 11q23 [except t(9;11)] inv(3)/t(3;3) t(6;9) t(9;22)	Normal cytogenetics AND +FLT3-ITD

NCCN AML guideline 2.2013

Acute promyelocytic leukemia (APL)

- Confirm diagnosis by FISH or PCR
  - t(15;17) PML/RARA
  - Variant translocations of RARA
- PCR follow up for MRD after consolidation
  - If low risk for relapse and PCR negative further monitoring by PCR may not be needed
  - Confirm a positive test on BM within 4 wks
  - Q3mo testing for 2 years if:
    - High-risk for relapse
    - Age >60
    - Disrupted consolidation &/or maintenance therapy
    - Non-confirmed positive PCR test

FLT3

- Receptor tyrosine kinase
- Internal tandem duplication (ITD)
  - Found in 28-34% of normal karyotype AML
  - Associated with worse prognosis

- Tyrosine kinase domain point mutations
  - Early studies showed prognostic significance
  - Most later studies have not

NPM1

- Multi-function protein that shuttles from nucleus to cytoplasm
- Mutation is common in AML
  - ~1/3 all AML and ~1/2 or normal karyotype
  - Most common mutation is 4 bp insertion (60-70%)
  - Mutations lead to cytoplasmic localization
    - Detectable by IHC
- Good prognosis in absence of FLT3 ITD

CEBPA

- CCAAT/enhancer binding protein alpha
  - Transcription factor that binds to promoters and enhancers
- Mutation associated with good prognosis
  - Double versus single mutation controversy
  - Controversial effect of FLT3 ITD
    - No effect or negative

CEBPA

- 2 types of mutation
  - C terminus b-ZIP domain
    - In-frame indels
    - Disrupt DNA binding or dimerization
  - N terminus
    - Frameshift mutation leading to loss of longer isoform of CEBPA
    - Continued expression of shorter isoform which inhibits the longer isoform (dominant negative effect)

Mutations in other genes

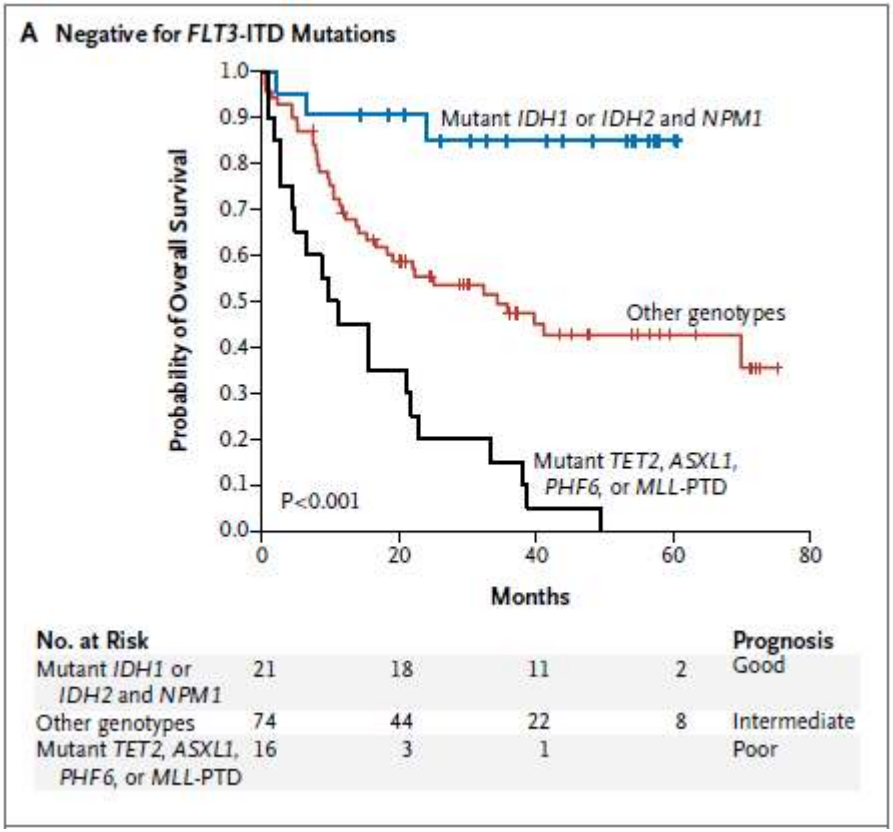
- Poor Prognosis
- ASXL1
- KRAS/NRAS**
- TET2
- DNMT3A**
- TP53
- PHF6
- MLL PTD

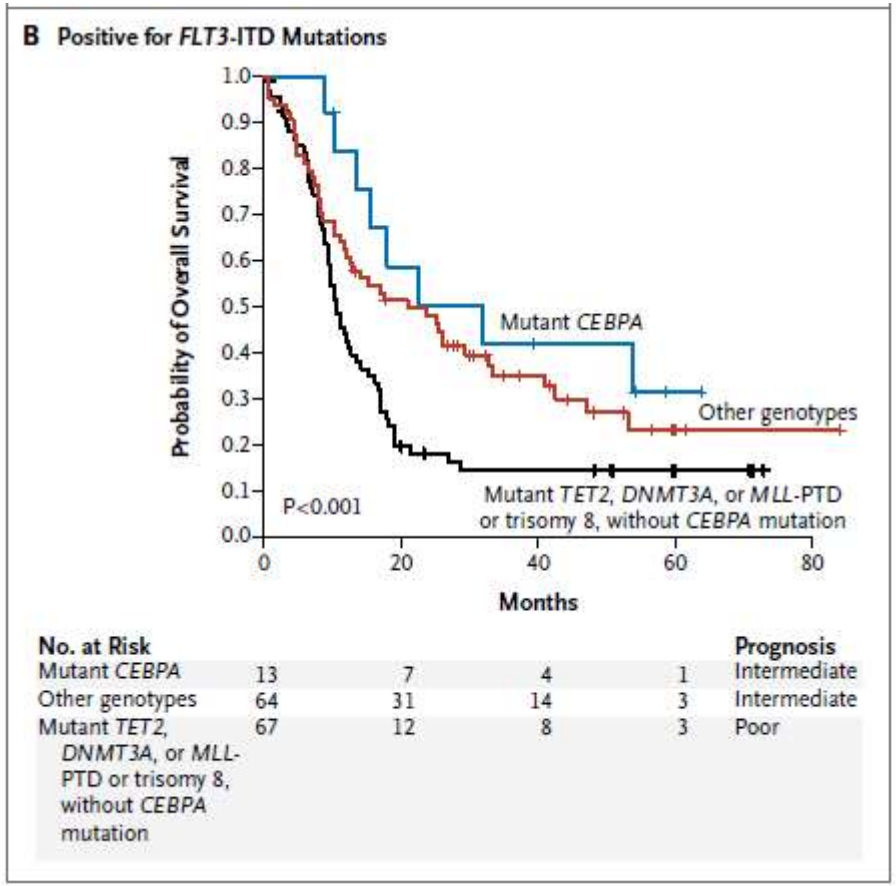
- Unclear effect
  - RUNX1*
  - WT1

- Better prognosis
  - IDH1/2 with NPM1 (neg FLT3 ITD)

*Poor prognosis in AML with normal karyotype
**May also predict response to cytarabine or azacytidine/decitibine

Intermediate cytogenetic risk AML

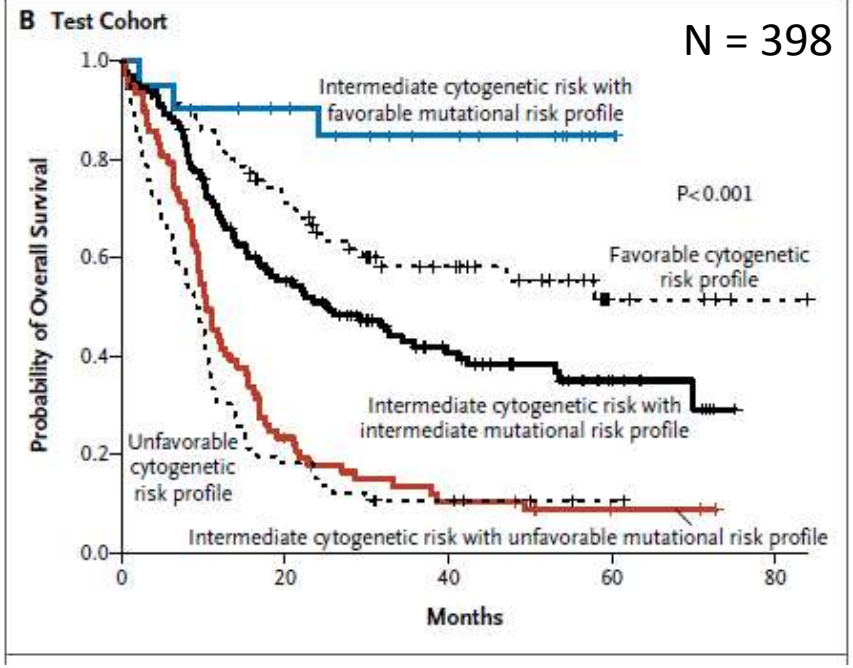


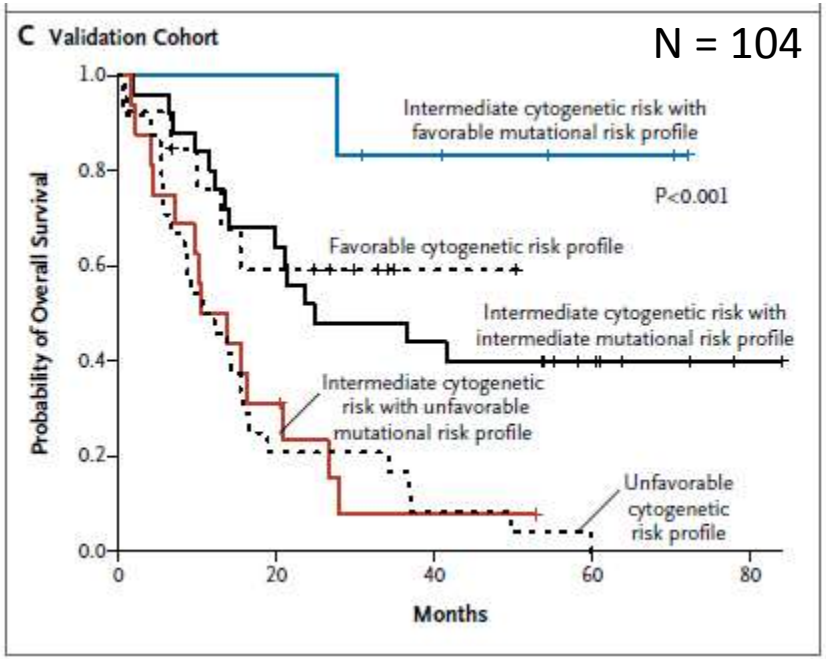


NEJM 2012;366:1079-1089.

A Revised Risk Stratification

Cytogenetic Classification	Mutations		Overall Risk Profile
Favorable	Any		Favorable
Normal karyotype or intermediate-risk ctyogenetic lesions	*FLT3*-ITD-negative	Mutant *NPM1* and *IDH1* or *IDH2*	Favorable
	FLT3-ITD-negative	Wild-type *ASXL1*, *MLL*-PTD, *PHF6*, and *TET2*	Intermediate
	FLT3-ITD-negative or positive	Mutant *CEBPA*	Intermediate
	FLT3-ITD-positive	Wild-type *MLL*-PTD, *TET2*, and *DNMT3A* and trisomy 8–negative	Intermediate
	FLT3-ITD-negative	Mutant *TET2*, *MLL*-PTD, *ASXL1*, or *PHF6*	Unfavorable
	FLT3-ITD-positive	Mutant *TET2*, *MLL*-PTD, *DNMT3A*, or trisomy 8, without mutant *CEBPA*	Unfavorable
Unfavorable	Any		Unfavorable





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