



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Leukemia and Myeloid Neoplasms

Evan C. Chen, MD

Attending Physician

Adult Leukemia Program, Division of Hematologic Malignancies

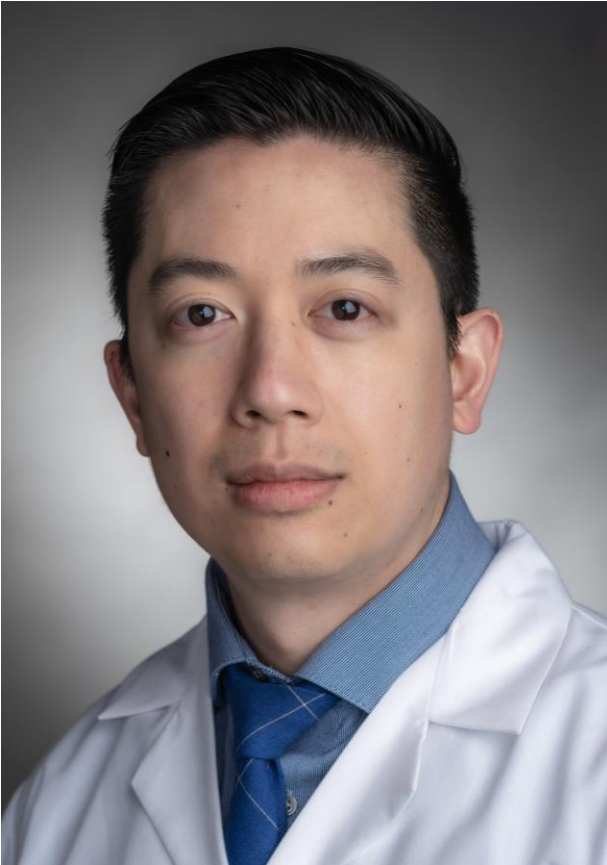
Dana-Farber Cancer Institute

Instructor in Medicine

Harvard Medical School



Evan C. Chen, MD



Attending Physician, Adult Leukemia Program, DFCI
Instructor in Medicine, Harvard Medical School

Education

Medical School – Stanford University

Internal Medicine – Massachusetts General Hospital

Hematology/Oncology – Dana-Farber/Mass General Brigham

Clinical Focus:

AML, ALL, MDS, MPN, MDS/MPN, AA, LGL, HCL

Research Focus:

Advanced myeloid neoplasms; novel therapies, especially cell therapy and leukemia epigenetics



DISCLOSURES

Advisory board/consulting:

- AbbVie
- Rigel
- Merck
- Guidepoint

Research funding:

- AbbVie
- Takeda
- ArcellX

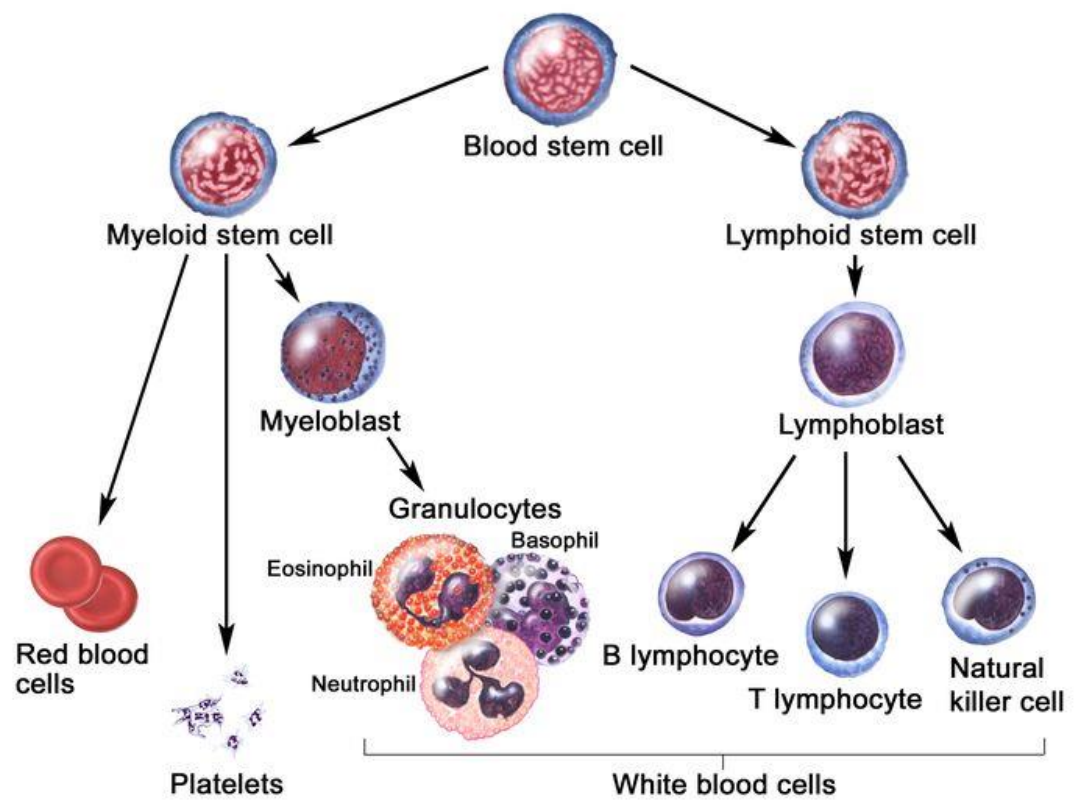


OBJECTIVES

- To understand the diagnostic testing of leukemias and myeloid neoplasms
- To understand the management of leukemias and myeloid neoplasms
- I highlight what I think are higher-yield topics



Hematologic malignancies overview



National Cancer Institute, 2007

Myeloid

Lymphoid



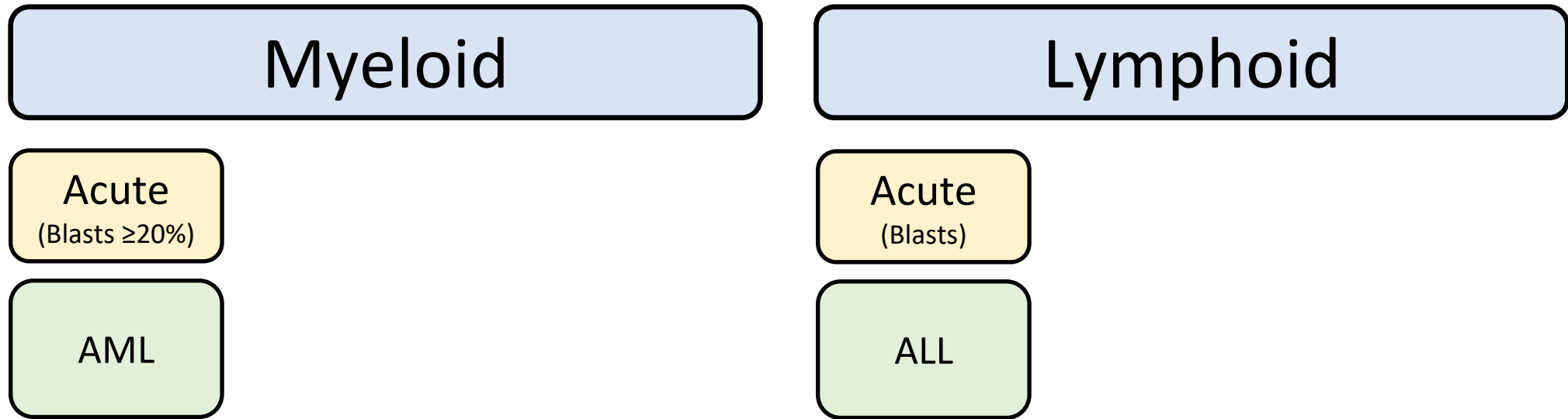
Hematologic malignancies overview

Myeloid

Lymphoid



Hematologic malignancies overview



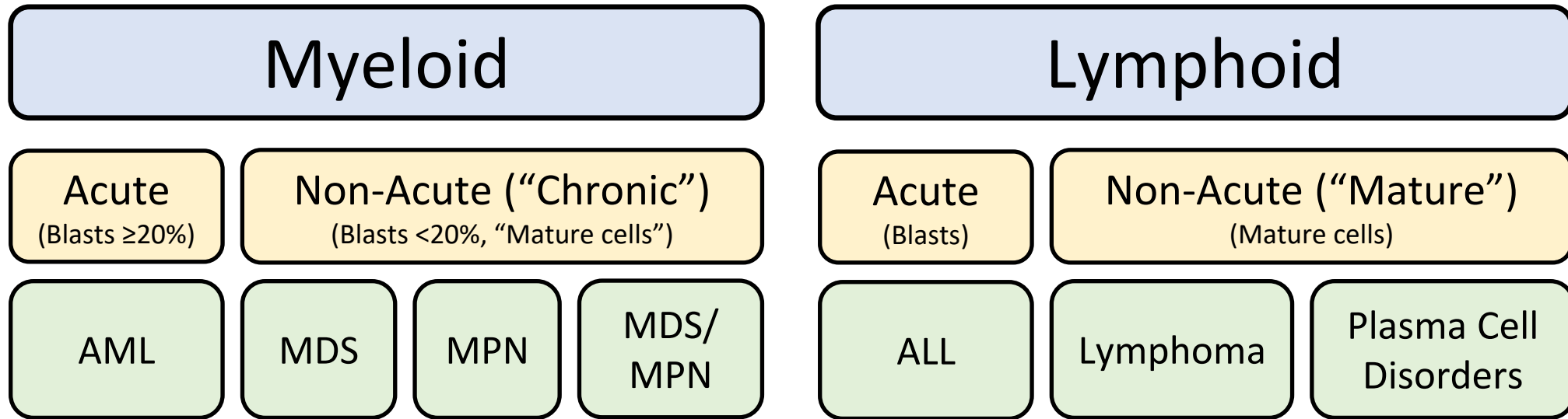
Terminology

AML = Acute myeloid leukemia

ALL = Acute lymphoblastic leukemia



Hematologic malignancies overview



Terminology

AML = Acute myeloid leukemia

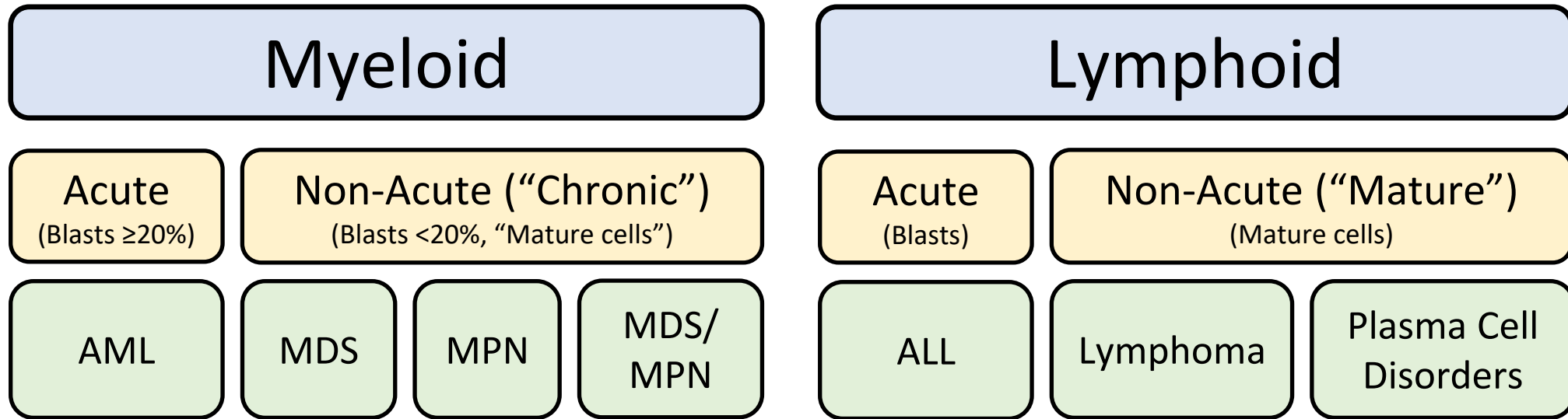
ALL = Acute lymphoblastic leukemia

MDS = Myelodysplastic syndrome

MPN = Myeloproliferative neoplasm



Hematologic malignancies overview



Terminology

Leukemia = Has a "circulating" component (e.g. lymphomas in "leukemic" phase)

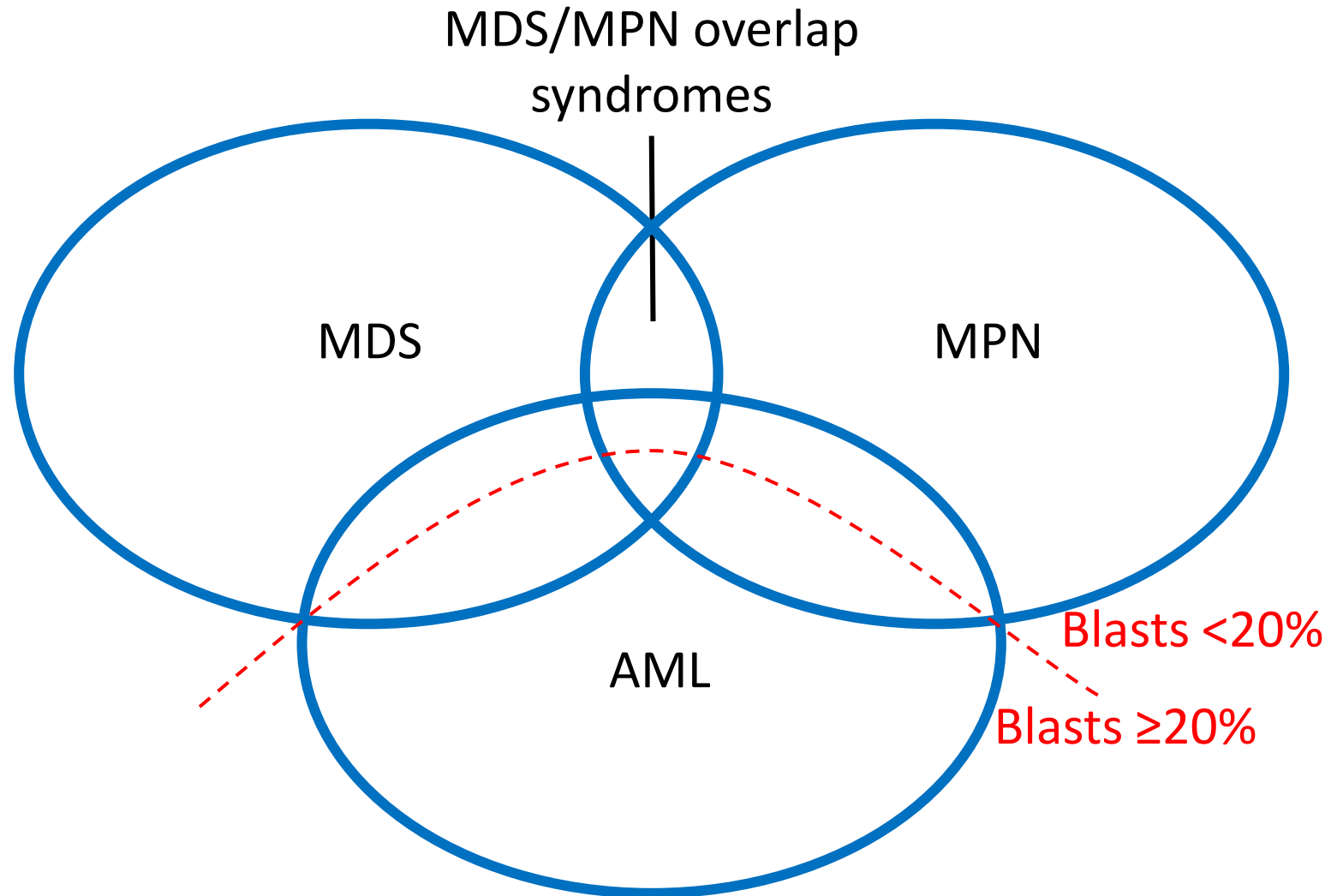
Lymphoma = Accumulates in lymphoid structures

Acute = Aggressive, needing urgent consultation, therapy w/in days-weeks

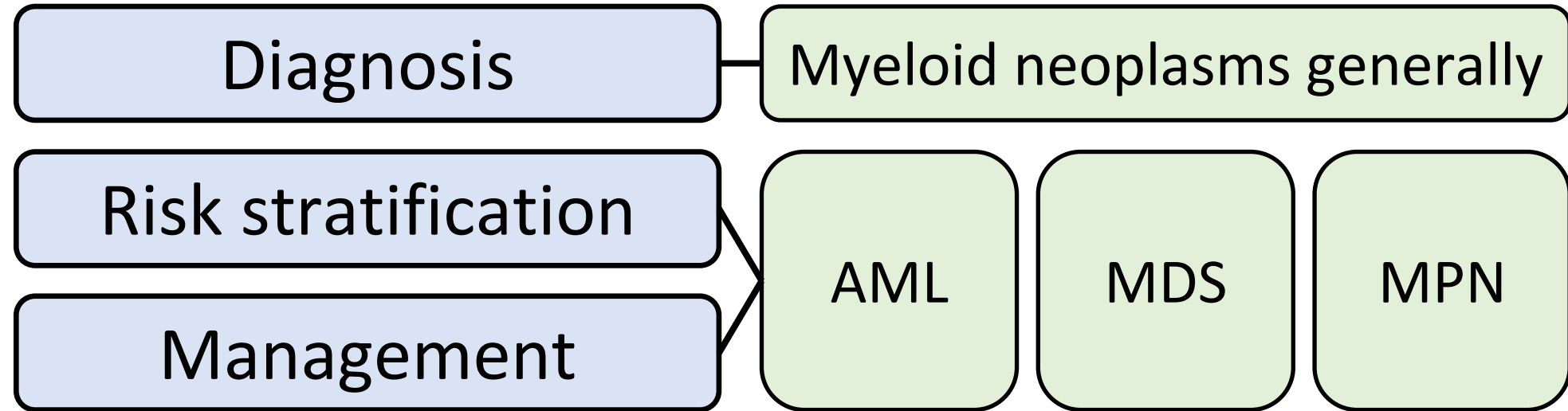
Chronic = More indolent, potential to progress to higher-risk disease



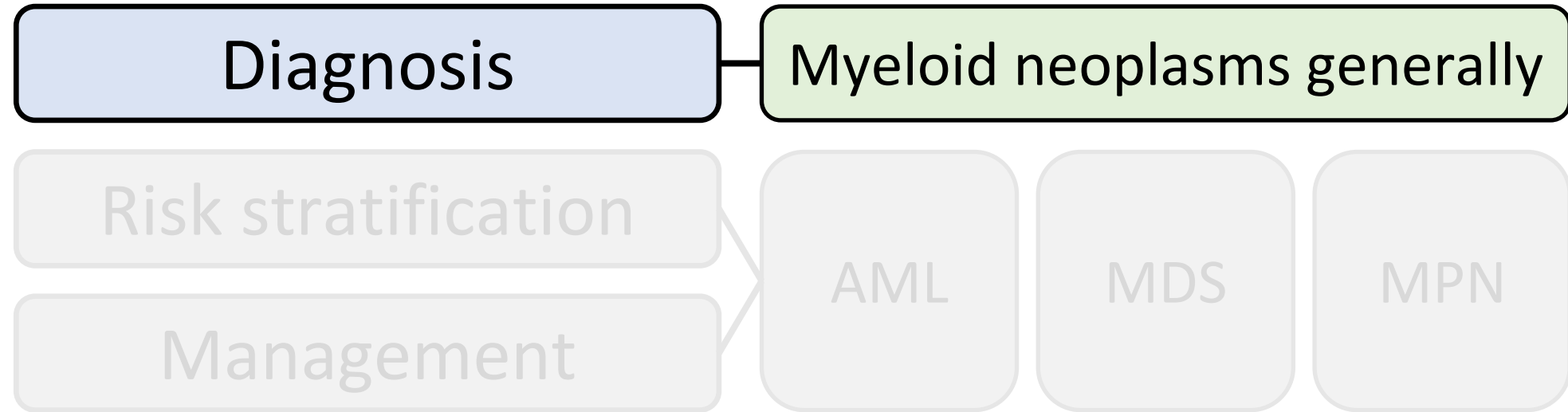
Myeloid malignancies overview



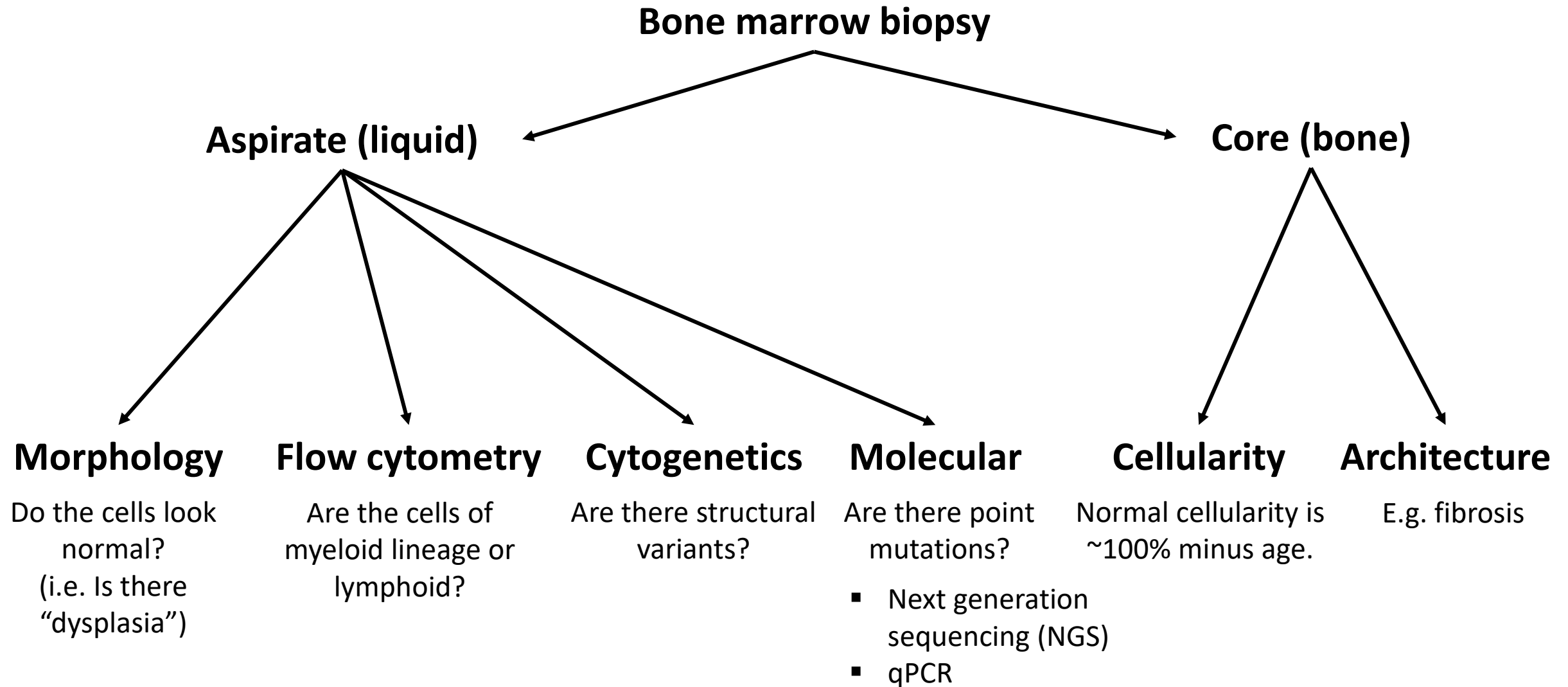
Outline



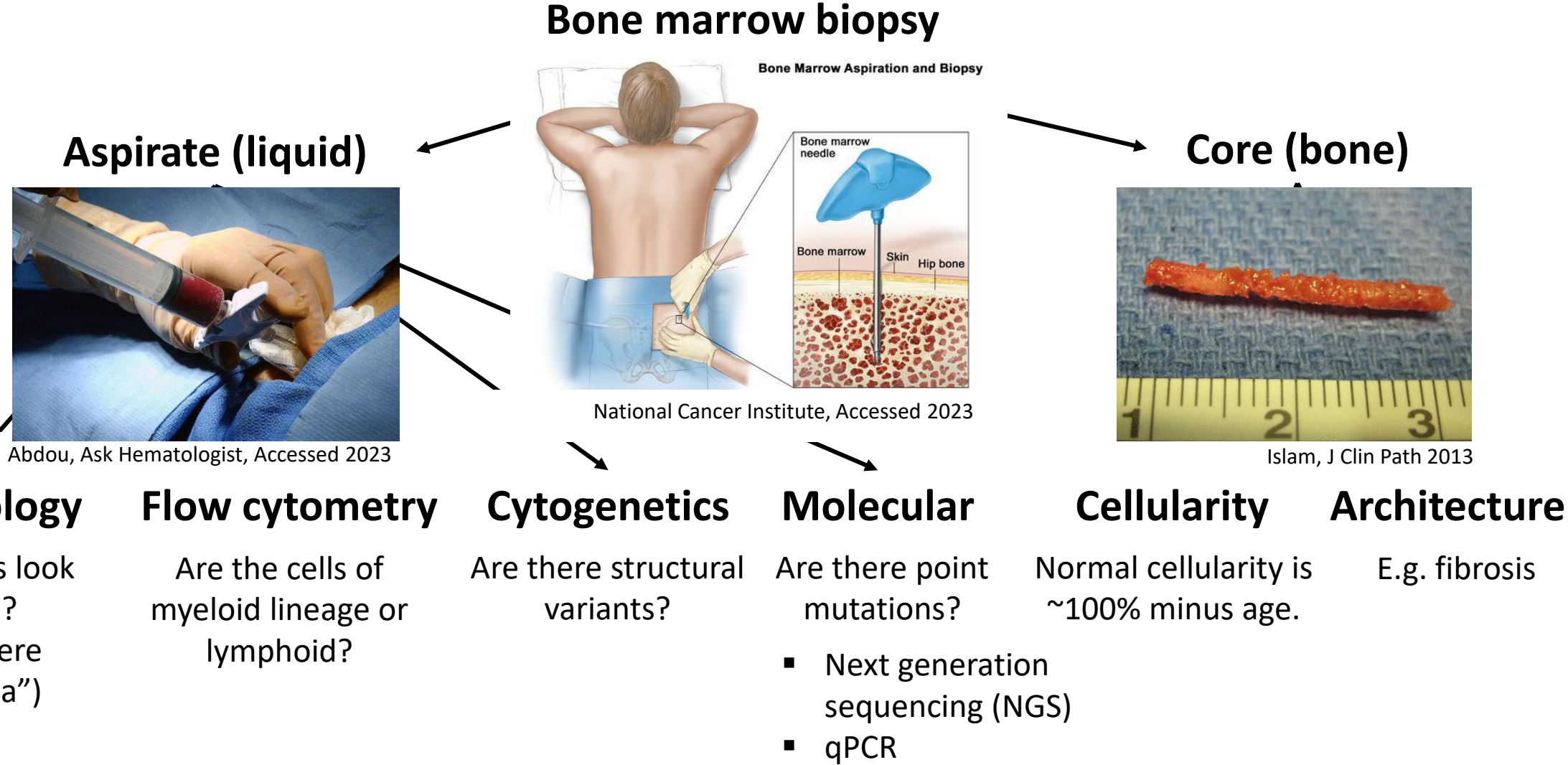
Outline



How do we diagnose myeloid malignancies?

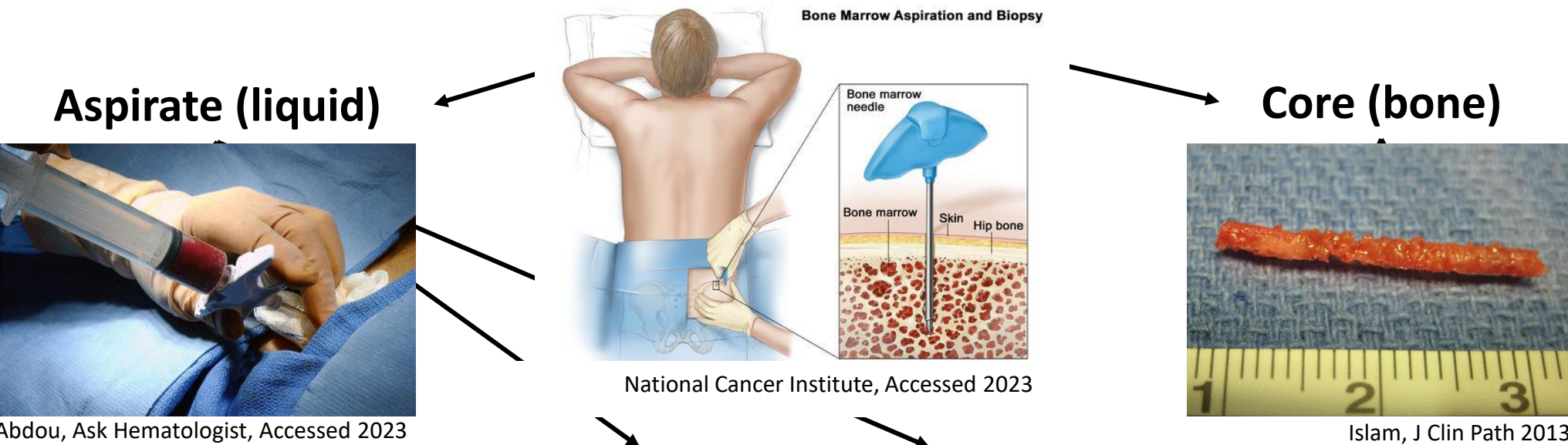


How do we diagnose myeloid malignancies?



How do we diagnose myeloid malignancies?

Bone marrow biopsy



Morphology

Do the cells look normal?
(i.e. Is there “dysplasia”)

Flow cytometry

Are the cells of myeloid lineage or lymphoid?

Cytogenetics

Are there structural variants?

Molecular

Are there point mutations?

- Next generation sequencing (NGS)
- qPCR

Cellularity

Normal cellularity is ~100% minus age.

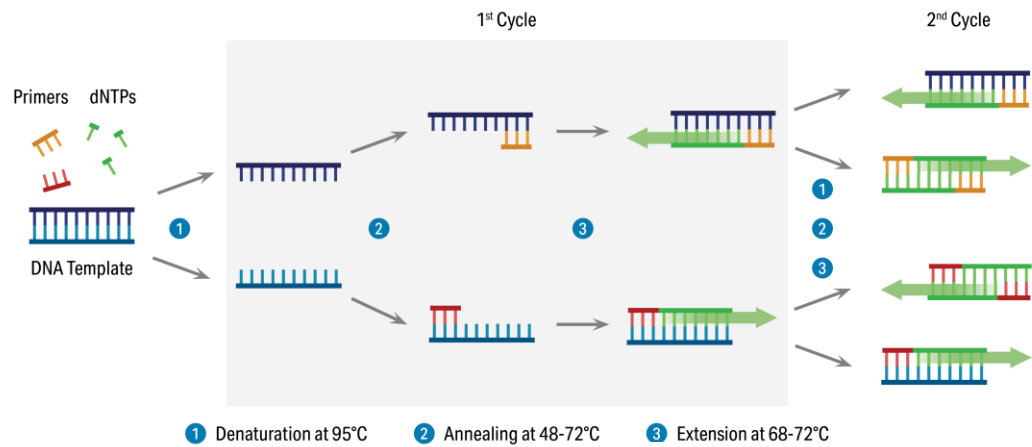
Architecture

E.g. fibrosis



qPCR vs NGS

Quantitative PCR (qPCR)



Aatbio.com, accessed May 1, 2024

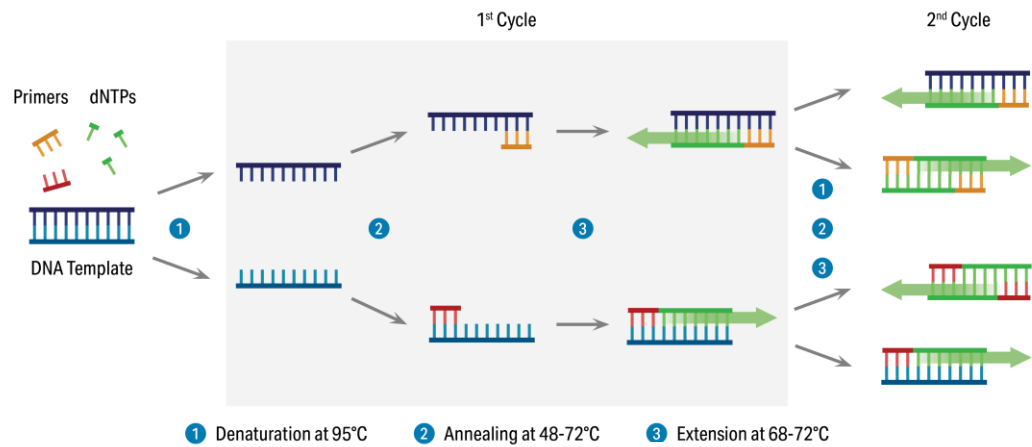
Test characteristic	Implications
Requires designing primers to amplify known target	Suited for known target
Many rounds of target amplification	Suitable for targets expressed at low levels High sensitivity
Time-consuming	Lower-throughput



Used for CML (detect BCR-abl mRNA) and APL (detect PML-RARa mRNA)

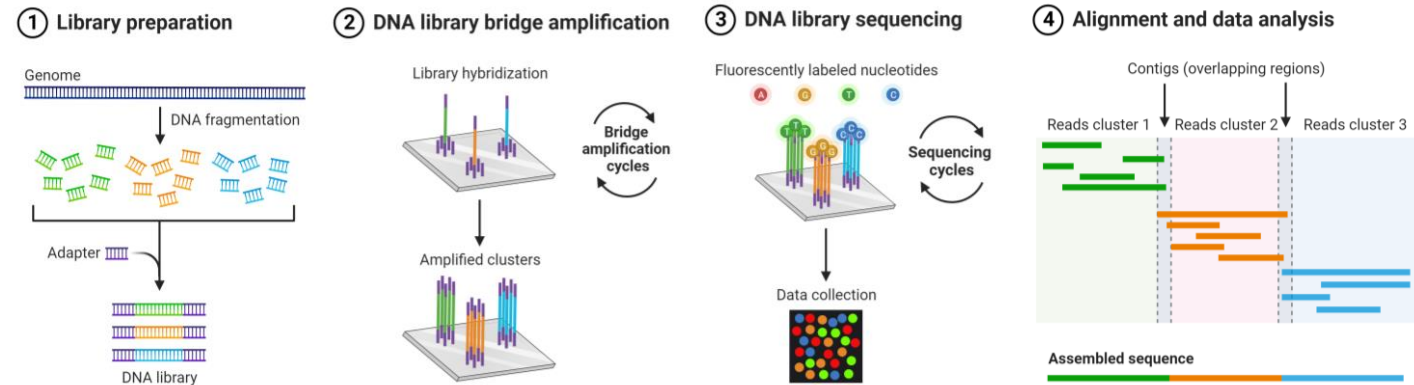
qPCR vs NGS

Quantitative PCR (qPCR)



Aatbio.com, accessed May 1, 2024

Next-generation sequencing (NGS)



Aatbio.com, accessed May 1, 2024

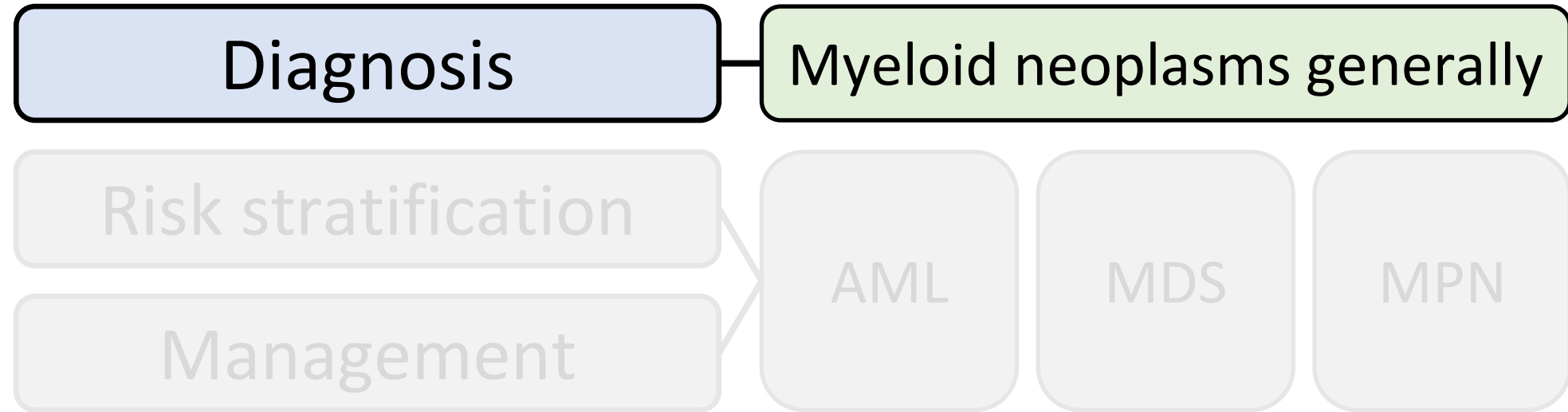
Test characteristic	Implications
Requires designing primers to amplify known target	Suited for known target
Many rounds of target amplification	Suitable for targets expressed at low levels High sensitivity
Time-consuming	Lower-throughput

Test characteristic	Implications
Does not require target-specific primers	Suited for target discovery
Fewer rounds of target amplification	Lower sensitivity
Multiplex capability	Higher-throughput

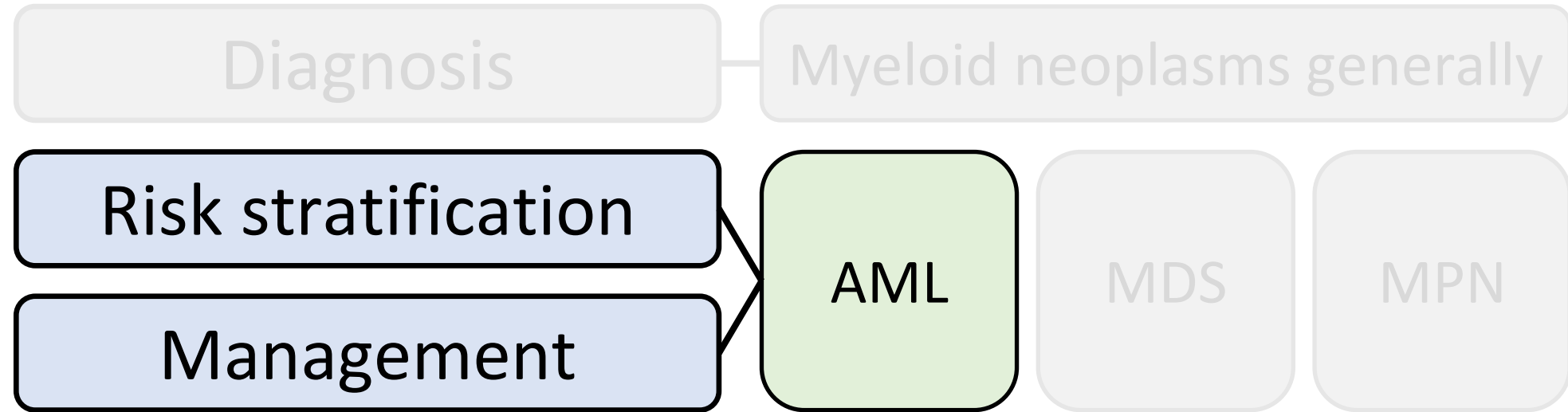


Used for CML (detect BCR-abl mRNA) and APL (detect PML-RARa mRNA)

Outline



Outline



Question 2

A 26-year-old female presents after 2 ER visits for vaginal bleeding, not improved. CBC shows pancytopenia. Fibrinogen is 60, INR is 1.9. She is found to have immature cells on her smear with Auer rods. What is her most likely diagnosis?

- a. Acute lymphoblastic leukemia
- b. Chronic myeloid leukemia
- c. Myelodysplastic syndrome
- d. Acute promyelocytic leukemia



Question 2

A 26-year-old female presents after 2 ER visits for vaginal bleeding, not improved. CBC shows pancytopenia. Fibrinogen is 60, INR is 1.9. She is found to have immature cells on her smear with Auer rods. What is her most likely diagnosis?

- a. Acute lymphoblastic leukemia
- b. Chronic myeloid leukemia
- c. Myelodysplastic syndrome
- d. **Acute promyelocytic leukemia**

APL is characterized by younger age, circulating promyelocytes with granules and Auer rods, and coagulopathy. The diagnosis is confirmed by the presence of t(15;17).

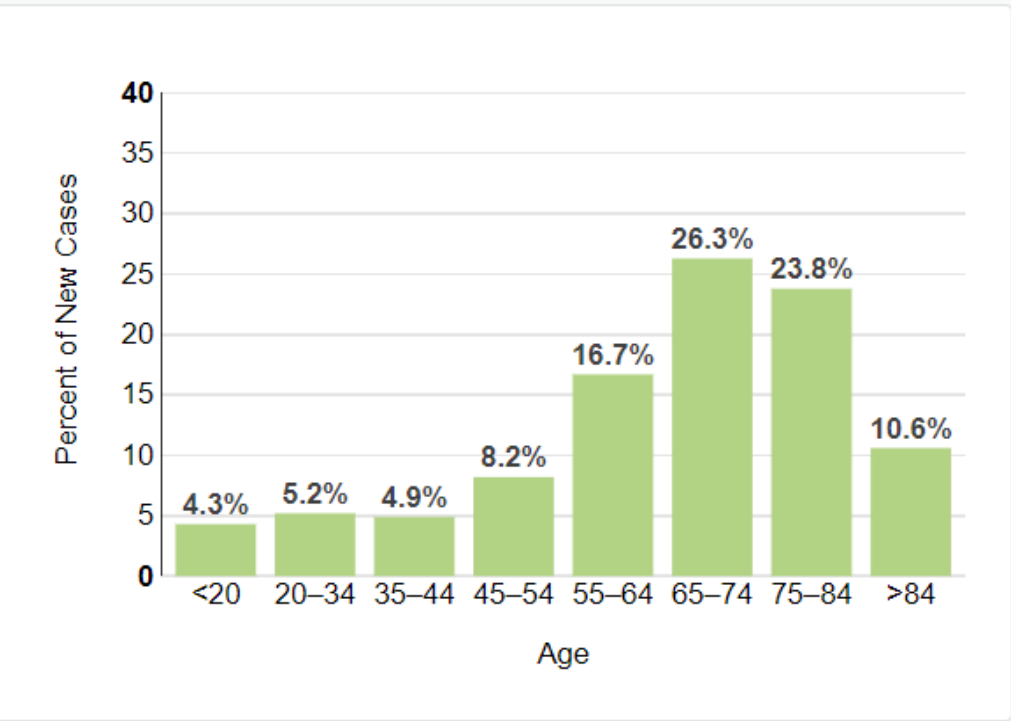


Acute myeloid leukemia is a rare cancer of older adults

Estimated New Cases in 2024	20,800
% of All New Cancer Cases	1.0%

Estimated Deaths in 2024	11,220
% of All Cancer Deaths	1.8%

5-Year Relative Survival
31.9%
2014–2020

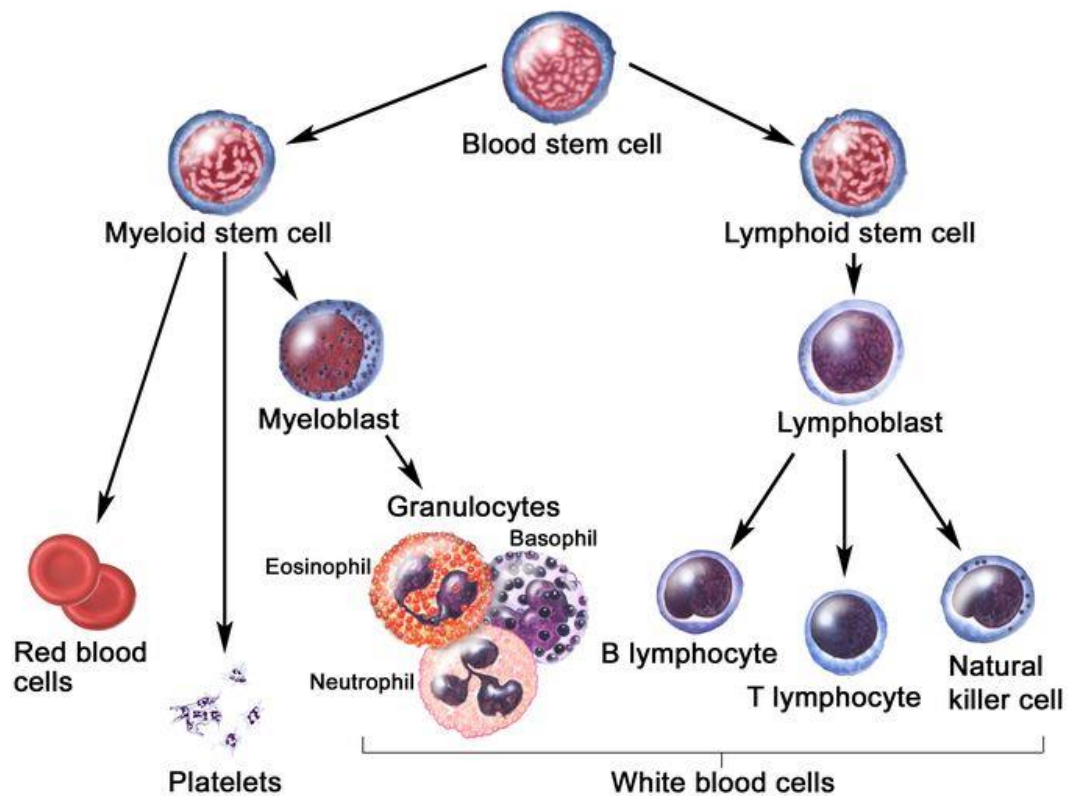


Acute myeloid leukemia is most frequently diagnosed among people aged 65–74.

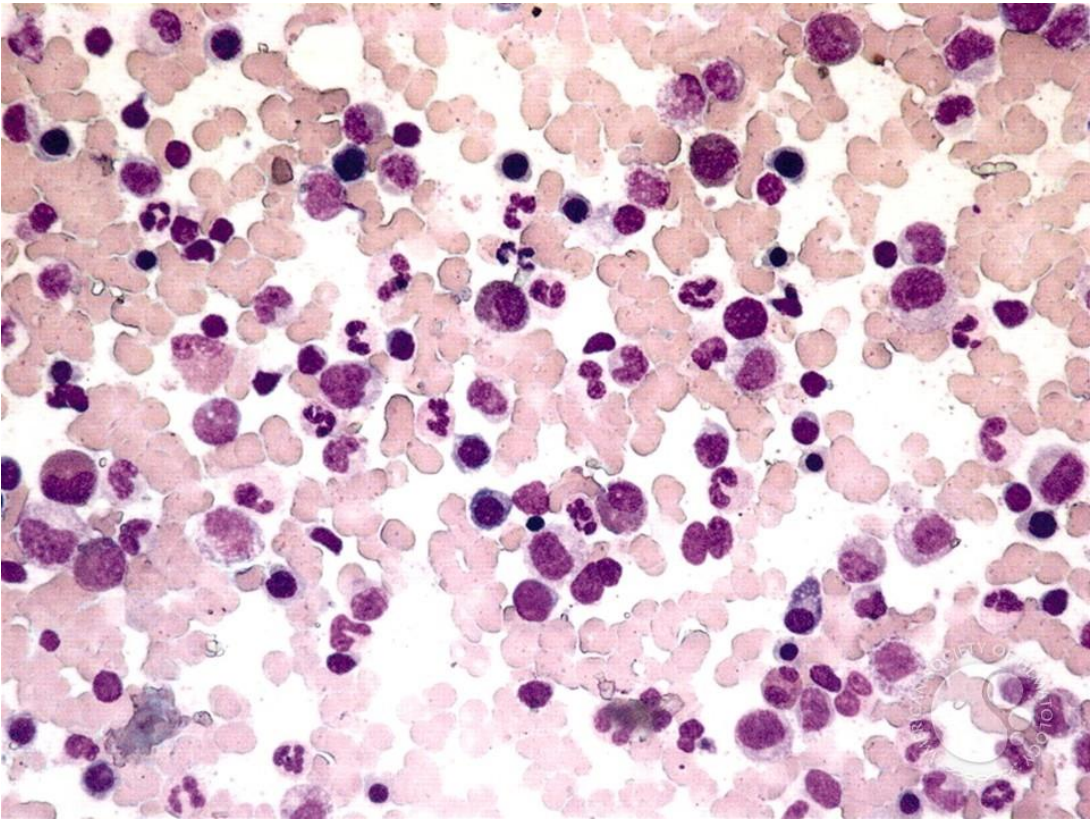
Median Age At Diagnosis
69



AML involves a perturbation of myeloblast differentiation



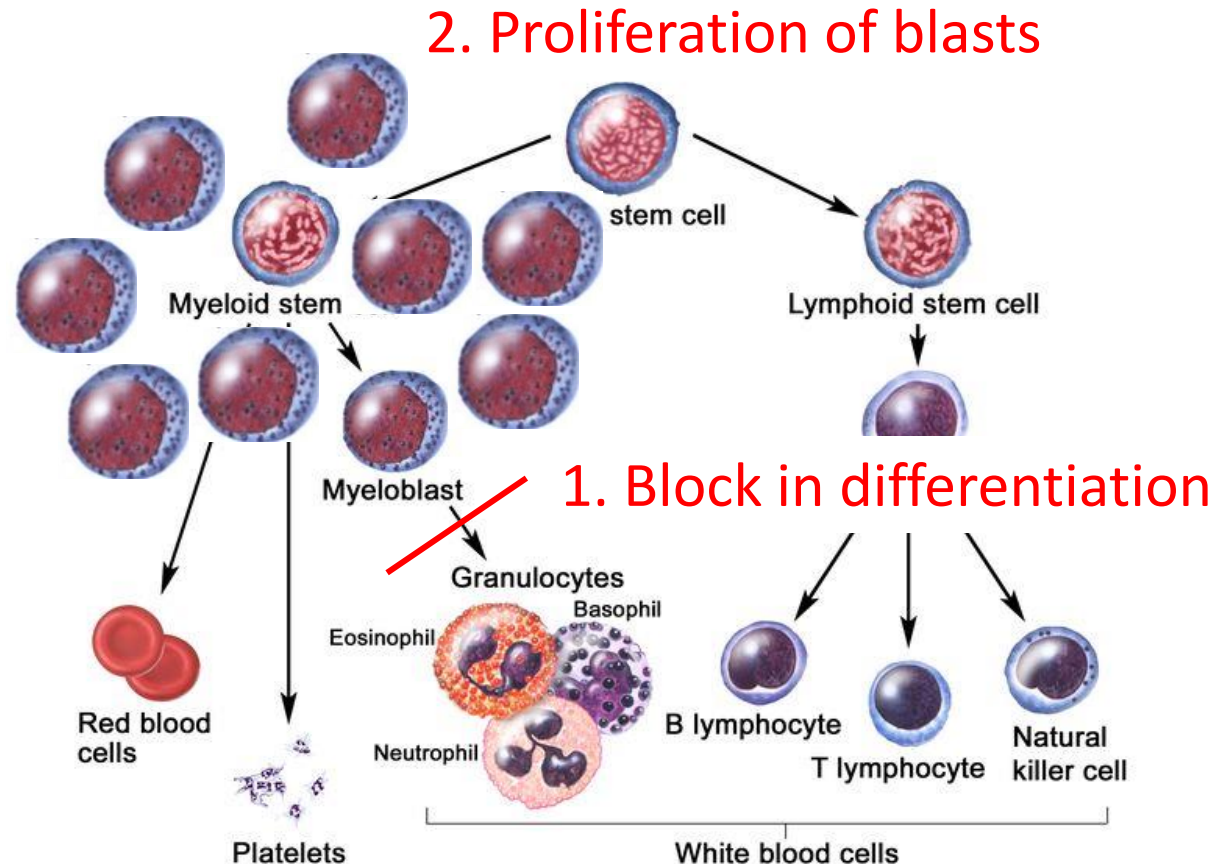
National Cancer Institute, 2007



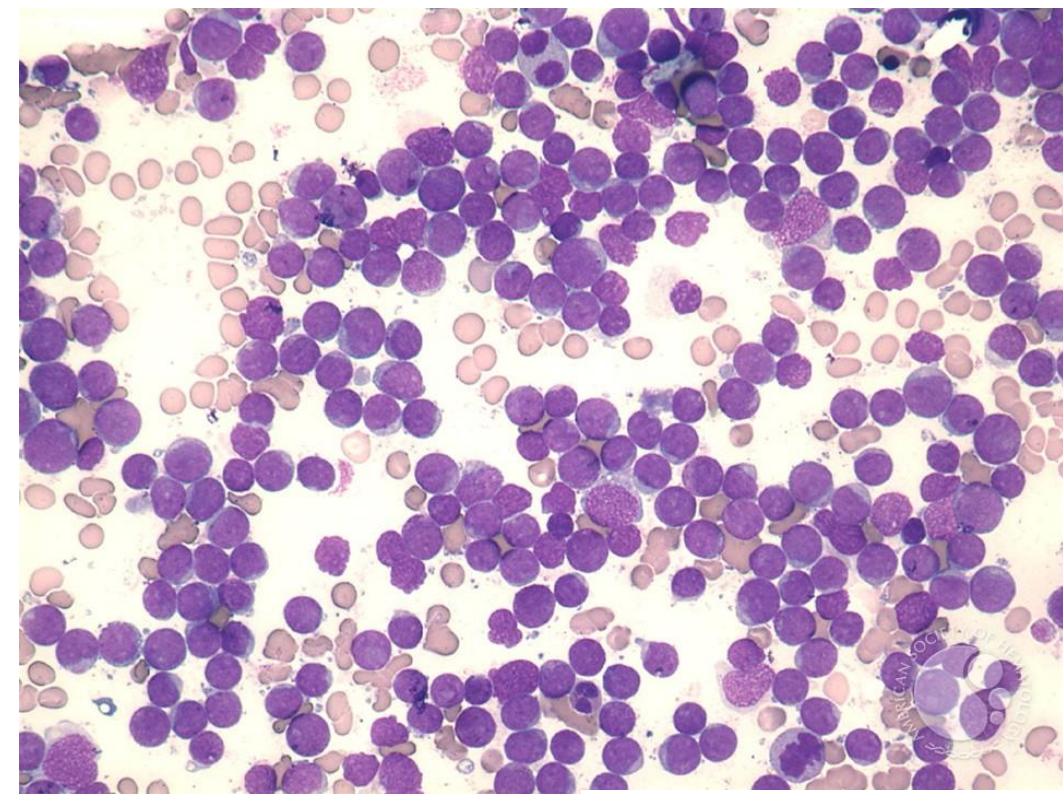
Heterogeneous appearance
(normal)

ASH Images

AML involves a perturbation of myeloblast differentiation



National Cancer Institute, 2007



ASH Images

Uniform appearance

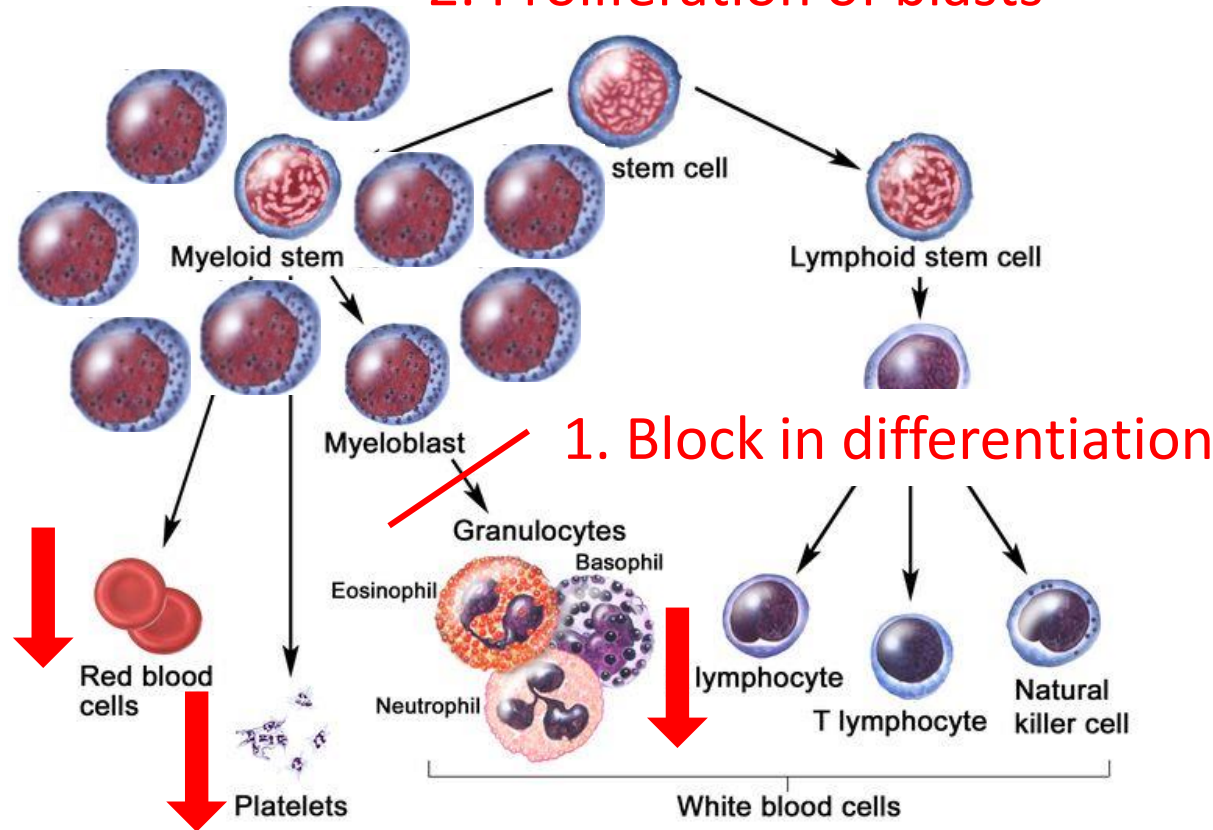
Large cells, high N:C ratio, fine chromatin

Generally, AML is diagnosed when myeloblasts $\geq 20\%$



AML involves a perturbation of myeloblast differentiation

2. Proliferation of blasts



National Cancer Institute, 2007

Clinical presentation

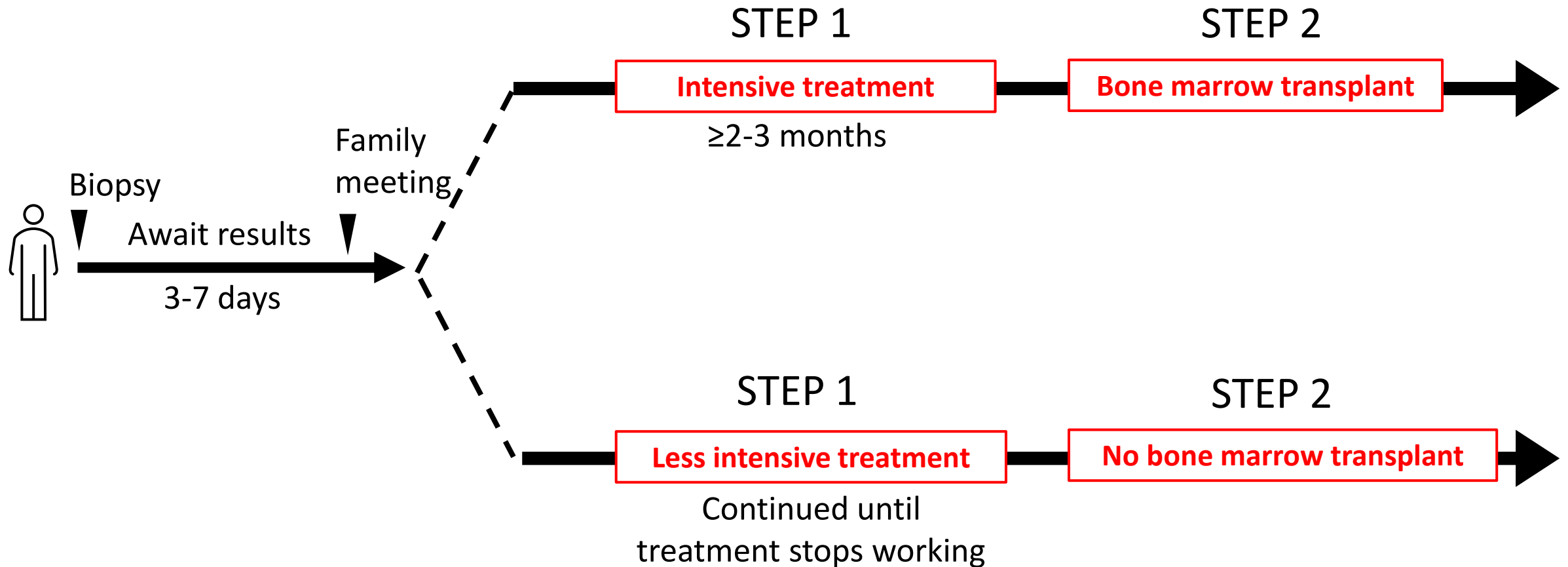
↓Neutropenia = ↑Infections

↓Anemia = ↑Fatigue

↓Thrombocytopenia = ↑Bleeding/Bruising



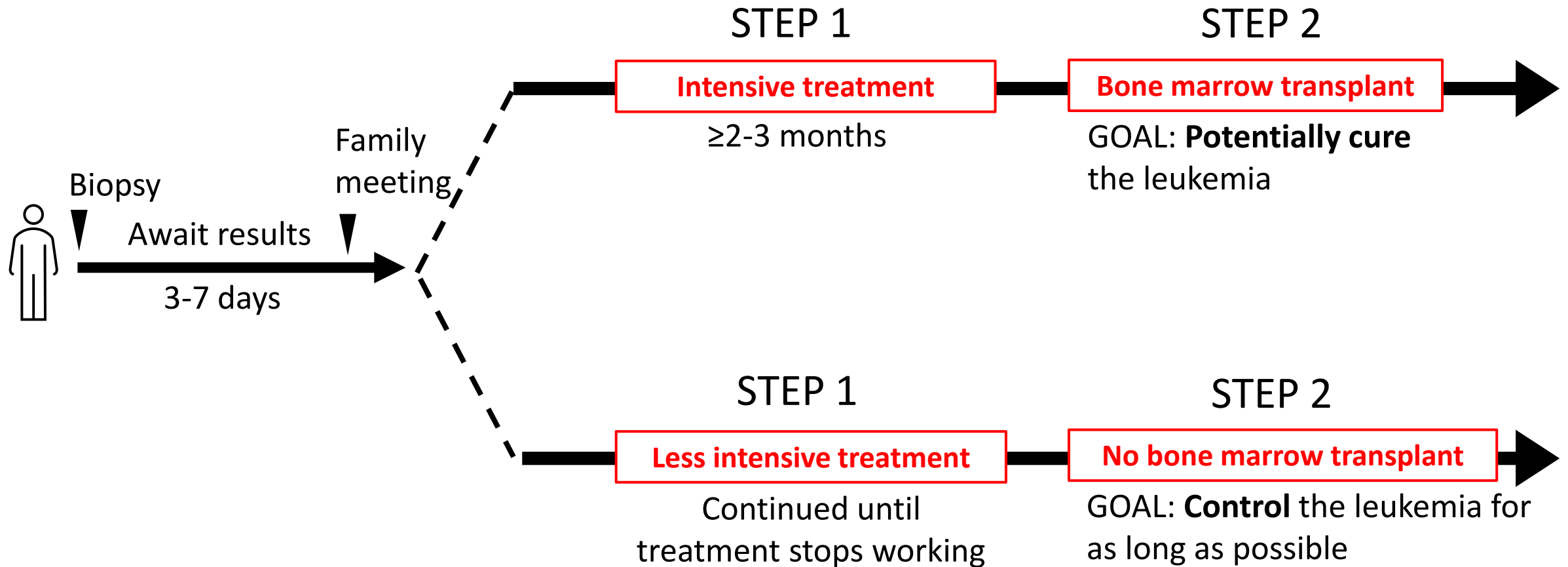
Major patterns of AML therapy



- STEP 2 affects STEP 1, so we start by discussing STEP 2 first



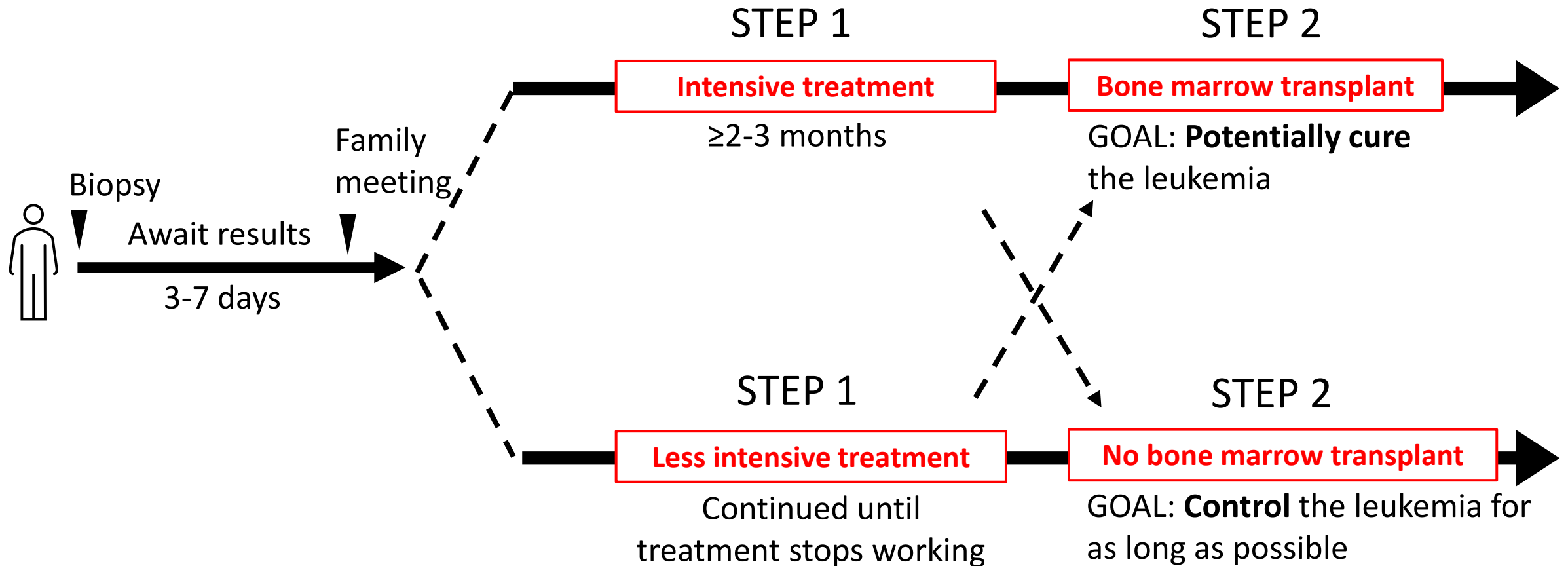
Major patterns of AML therapy



- Our decision for STEP 2 determines our treatment GOAL



Major patterns of AML therapy

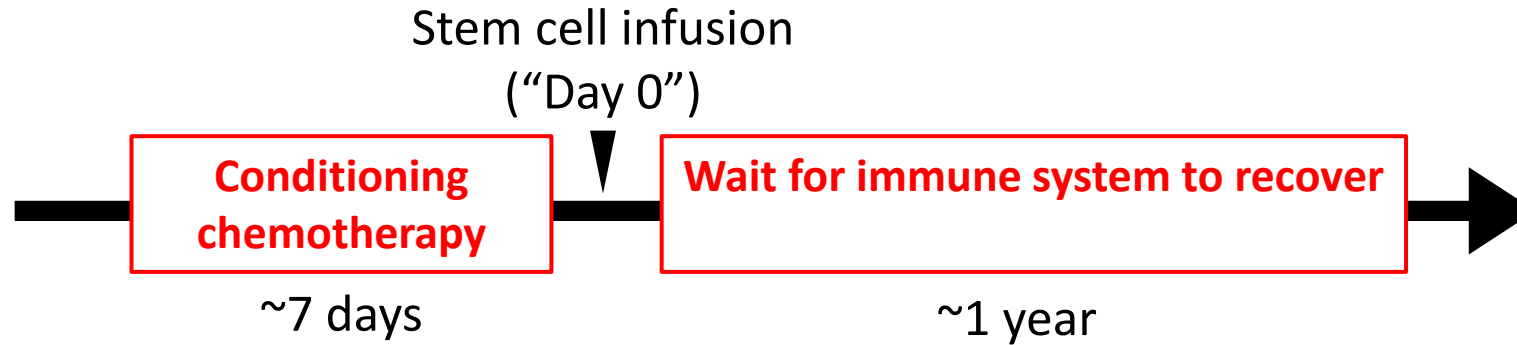


- We may change our decision later about about STEP 2, but it is helpful to have an initial idea

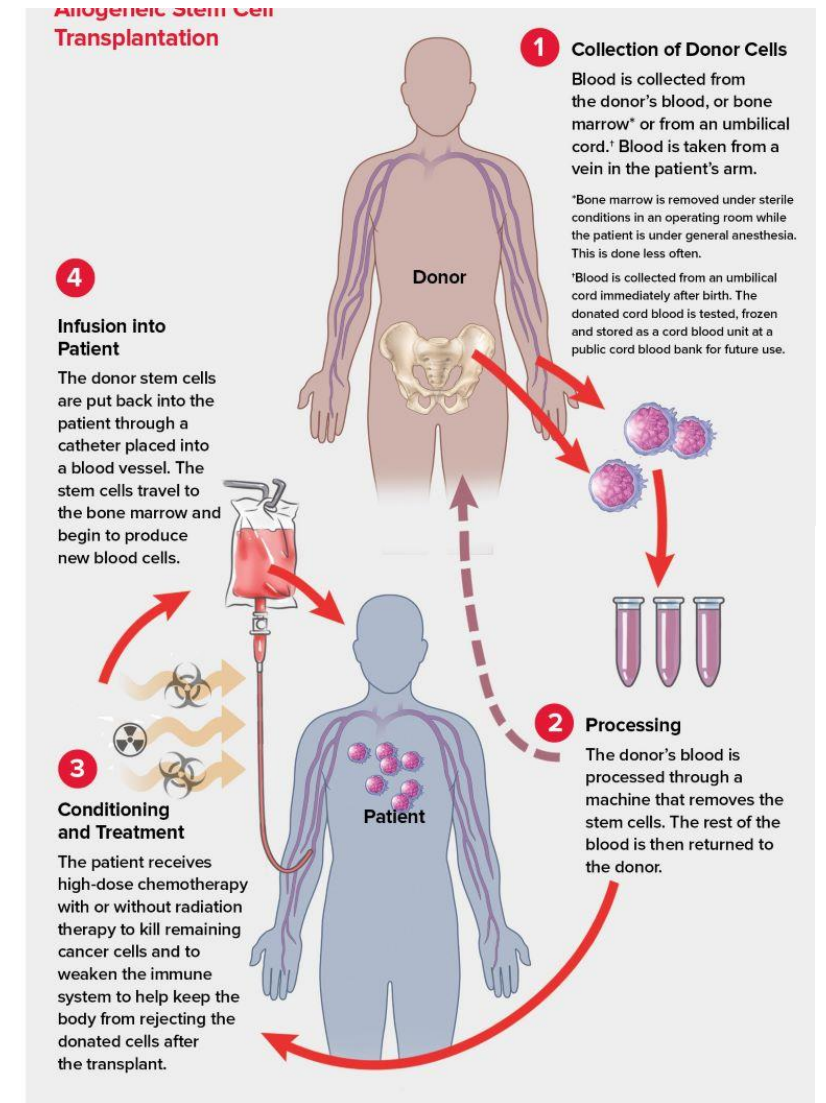


A brief note about bone marrow transplant (BMT)

Synonyms: transplant, bone marrow transplant (BMT), stem cell transplant (SCT), hematopoietic cell transplant (HCT), hematopoietic stem cell transplant (HSCT)



- For AML, we use **allogeneic** transplant, NOT autologous



A brief note about bone marrow transplant (BMT)

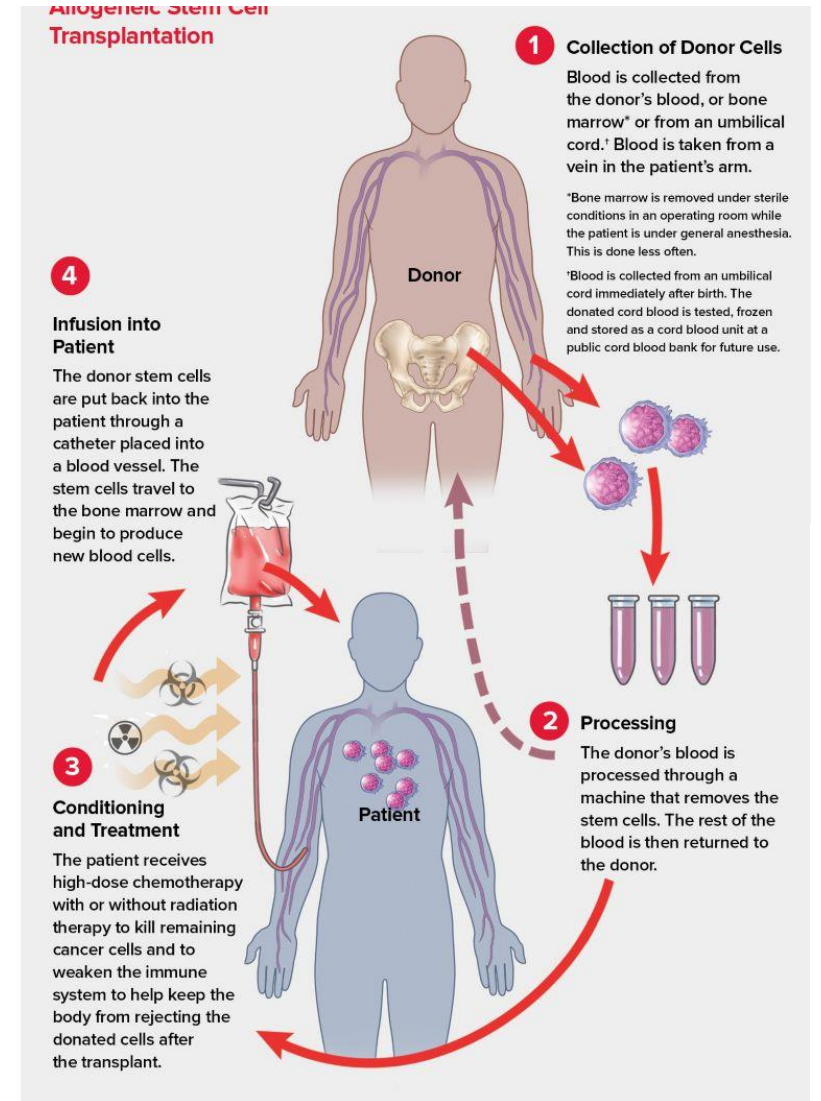
Synonyms: transplant, bone marrow transplant (BMT), stem cell transplant (SCT), hematopoietic cell transplant (HCT), hematopoietic stem cell transplant (HSCT)

A BMT is **not** a surgery (unlike a kidney, lung, or heart transplant). For most types of AML, it offers the only **chance** at a cure

- Success ranges from 20-70%, depending on the specific type of AML

But treatment is **intense** and there is a **risk of transplant-related mortality**

- Serious infections
- Graft-versus-host disease
- May require long initial hospital stay (3-4 weeks)
- Prolonged debilitation and recovery (~1 year)



A brief note about bone marrow transplant (BMT)

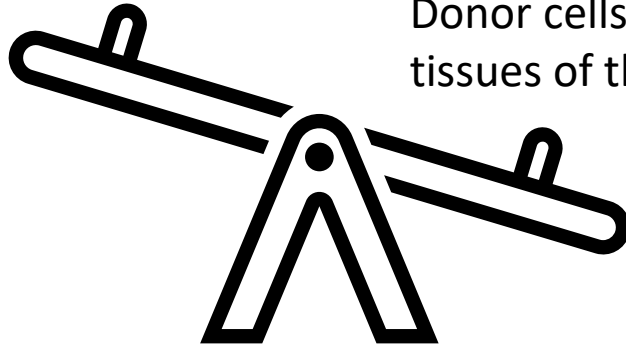
Synonyms: transplant, bone marrow transplant (BMT), stem cell transplant (SCT), hematopoietic cell transplant (HCT), hematopoietic stem cell transplant (HSCT)

Graft versus Leukemia effect (GvL)

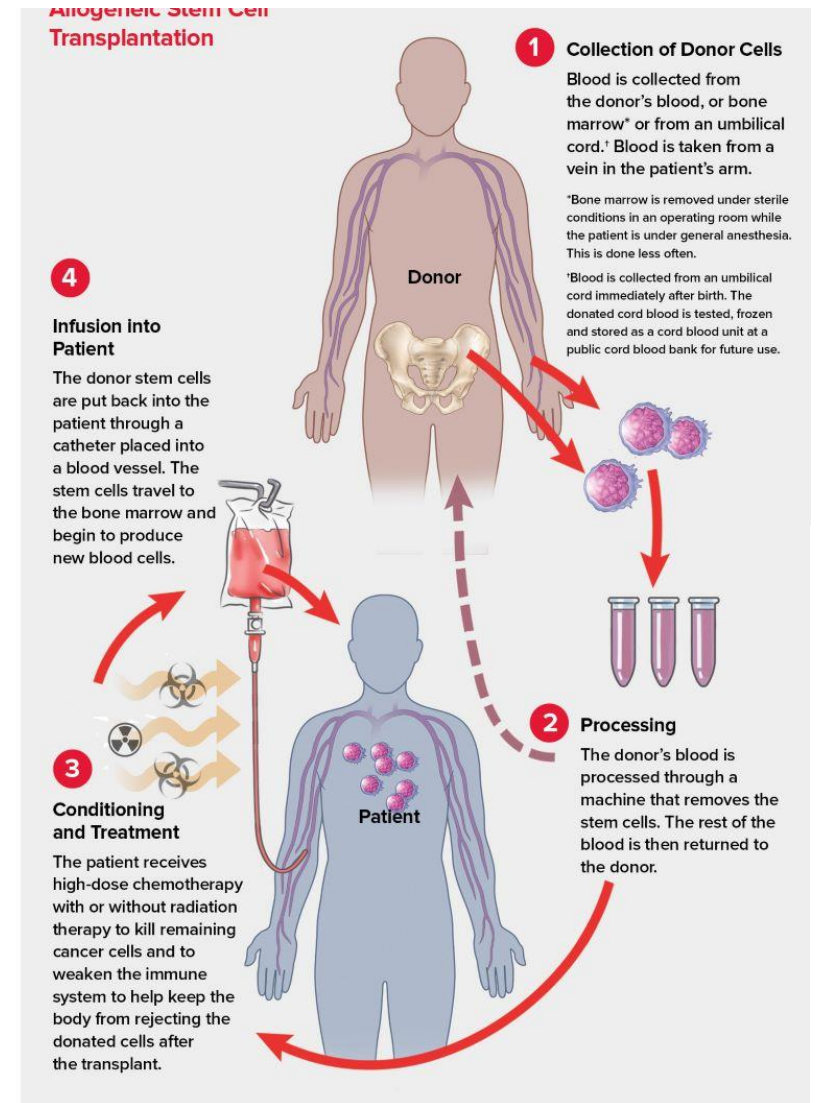
Donor cells can attack residual
AML of the patient – **BENEFICIAL**

Graft versus Host disease (GvHD)

Donor cells can also attack healthy
tissues of the patient – **HARMFUL**



Requires titrating immunosuppressive therapy to balance GvL and GvHD



A brief note about bone marrow transplant (BMT)

Synonyms: transplant, bone marrow transplant (BMT), stem cell transplant (SCT), hematopoietic cell transplant (HCT), hematopoietic stem cell transplant (HSCT)

Therefore,

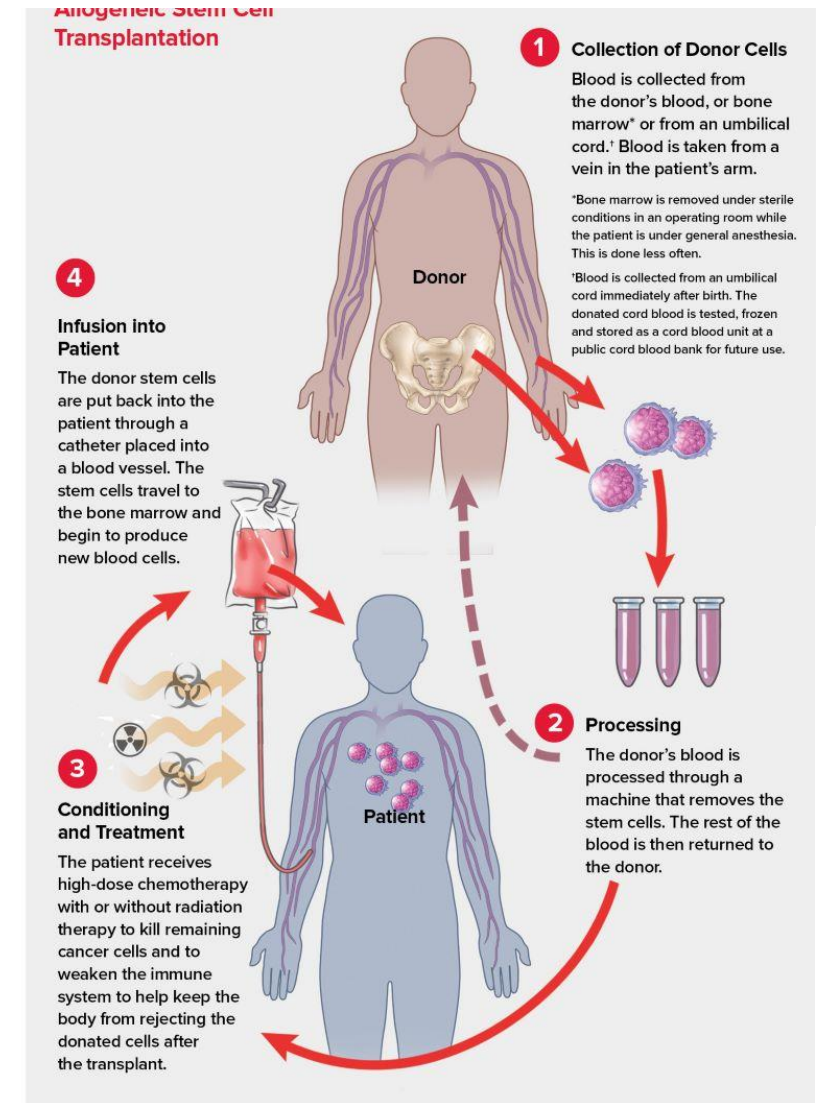
not everyone is safe for a BMT

- Must otherwise be in good health with good organ function
- Must have a 24/7 caretaker, especially first 100 days after transplant

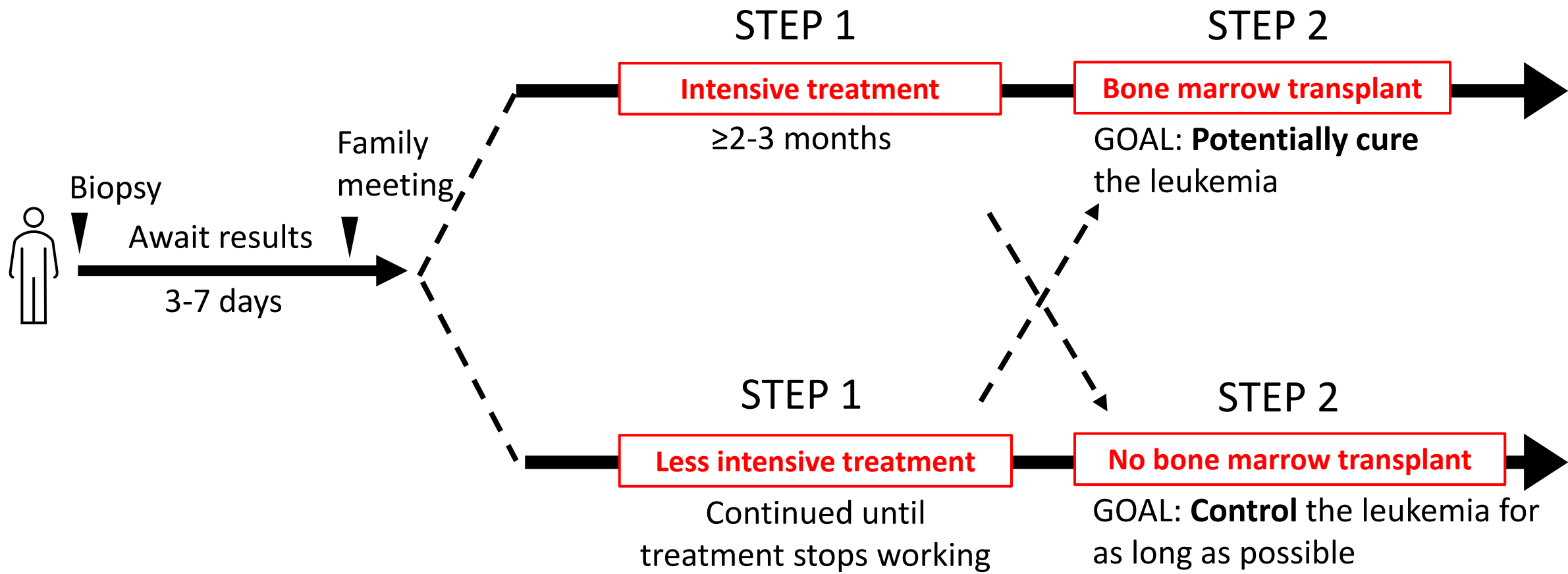
not everyone wants a BMT (goals of care)

not everyone will benefit from a BMT

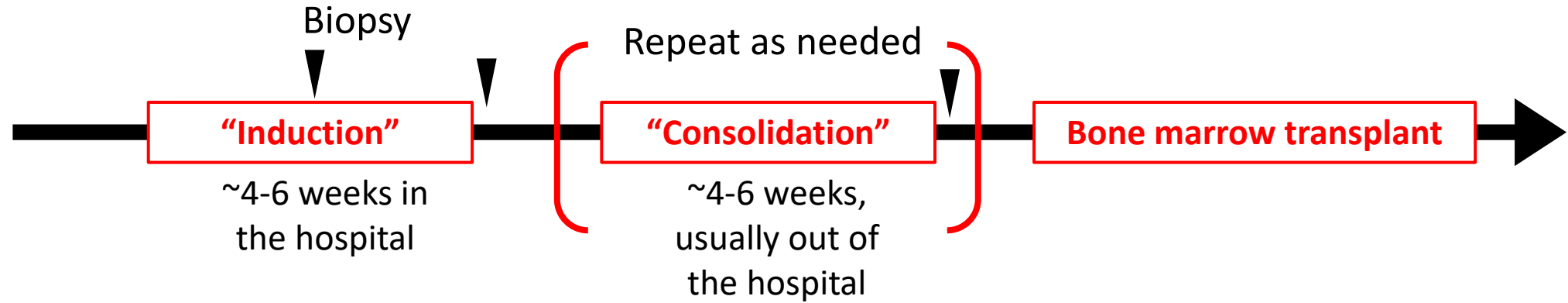
- Success ranges from 20-70%, which may/may not justify the risks



Major patterns of AML therapy



Intensive treatment



What is the goal of “induction”?

To induce a **remission**, defined as:

- Bone marrow blasts <5% (normal)
- No circulating blasts
- No extramedullary disease
- ANC $\geq 1000/\mu\text{L}$
- Platelets $\geq 100,000/\mu\text{L}$

What is the goal of “consolidation”?

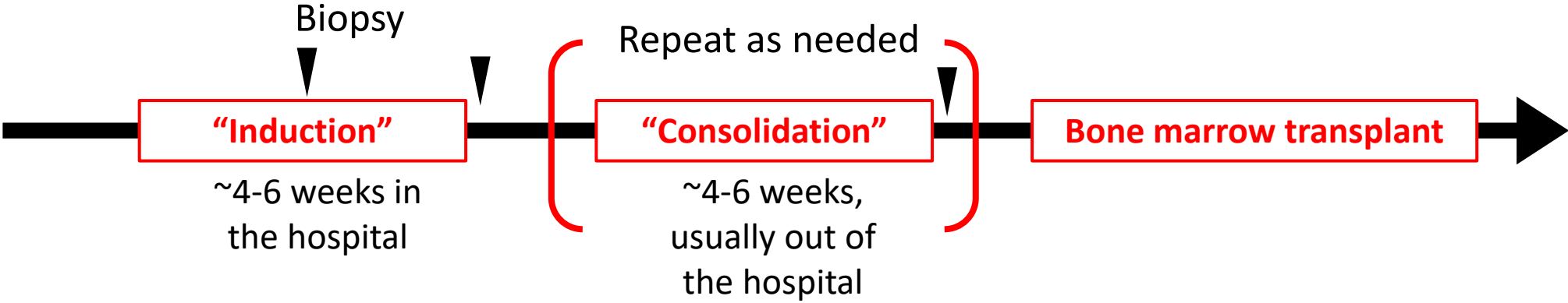
To consolidate, or reinforce, the remission and prevent relapse while waiting for a transplant.

How do we check for response?

With repeat bone marrow biopsies



Intensive treatment



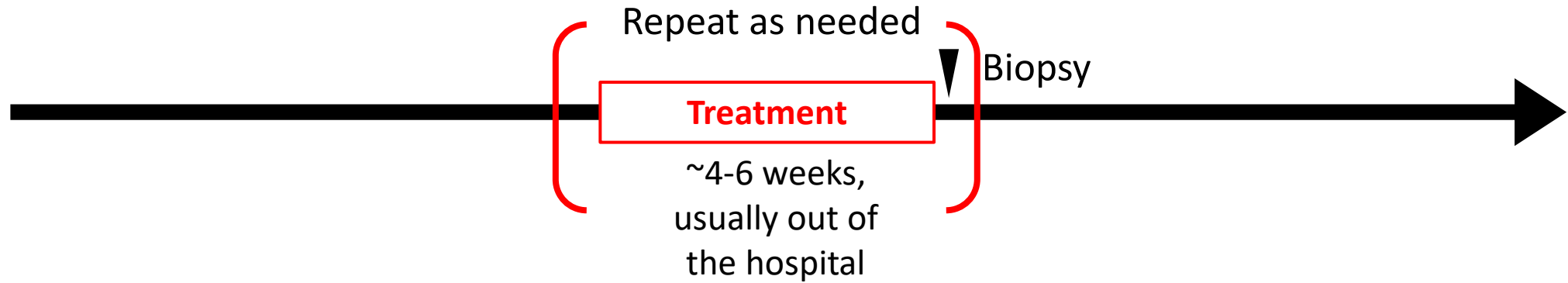
What treatments do we administer?

There is variations in practice patterns

Induction	Consolidation
Cytarabine + anthracycline (e.g. "7+3" = 7-days of cytarabine + 3 days of daunorubicin)	Cytarabine (e.g. "HiDAC" = high-dose cytarabine)
CPX-351 (Liposomal formulation of cytarabine and daunorubicin)	CPX-351



Less-intensive treatment



What treatments do we administer?

Therefore, the goal with less-intensive treatments is to **control** the leukemia for as long as possible, rather than to achieve a cure

Continuous therapies until loss of response or intolerance

Venetoclax + Azacitidine

Ivosidenib + Azacitidine

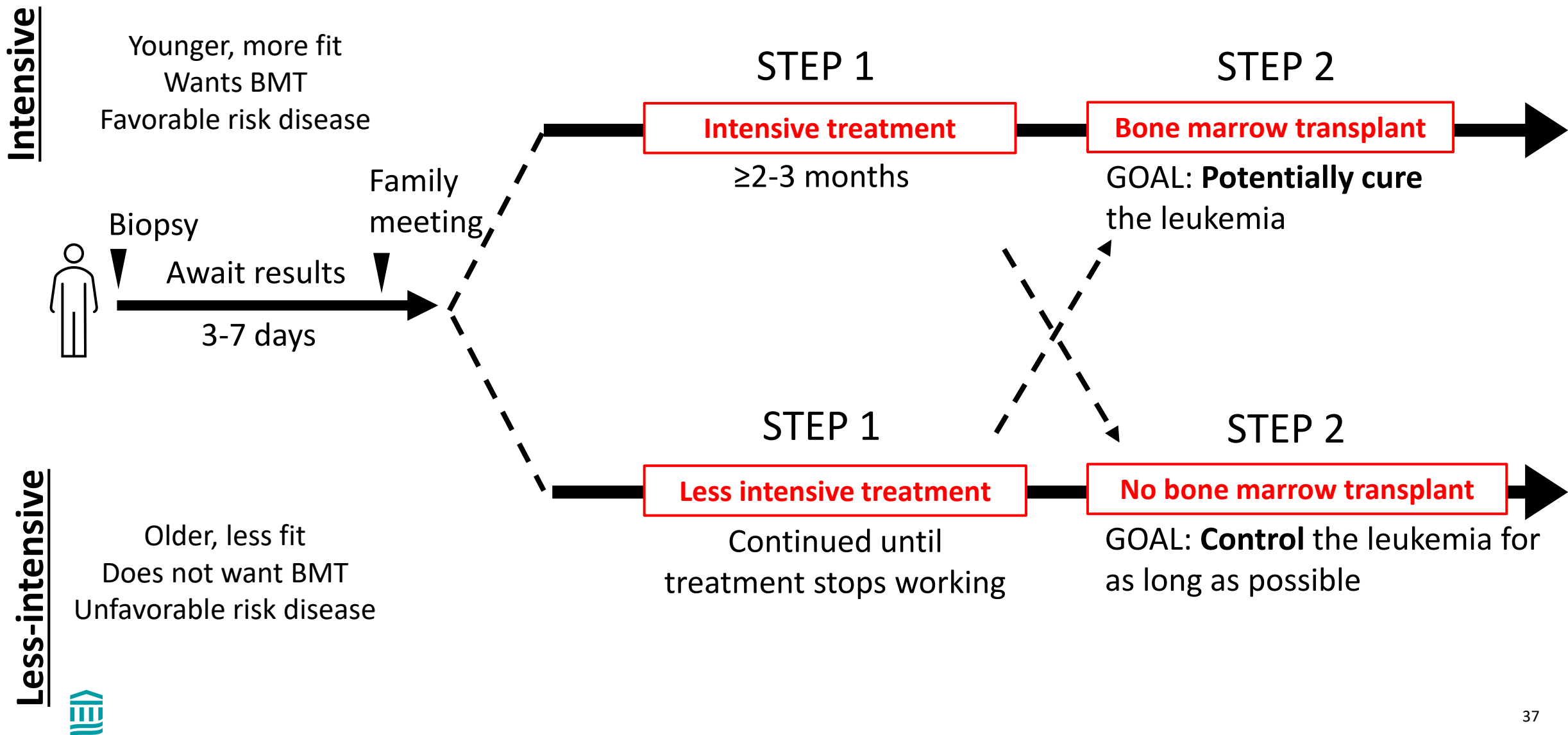
Azacitidine monotherapy

Decitabine monotherapy

Supportive care



Major patterns of AML therapy - Summary



AML prognostic factors guide management

	Risk factor	Choice of initial therapy	Decision with subsequent BMT
Age and comorbidities	<60	Intensive	✓, if patient is fit
	≥75 or significant medical comorbidities	Less intensive	X, since patient unfit
Goals of care	Curative (plan for BMT)	Intensive	✓, if patient is fit
	Palliative (no plan for BMT)	Less intensive	X, since palliative
Disease genetics	Favorable-risk: <ul style="list-style-type: none"> ▪ Acute promyelocytic leukemia – t(15;17) ▪ Core binding factor – t(8;21) , inv(16), t(16;16) ▪ <i>NPM1</i>-mut without <i>FLT3</i>-ITD ▪ bZIP in-frame <i>CEBPa</i>-mut 	Intensive	X, cure possible without BMT
	Unfavorable-risk: <ul style="list-style-type: none"> ▪ Monosomal karyotype ▪ Chromosome 5, 7, or 17 abnormality ▪ Complex karyotype (≥3 abnormalities) ▪ “Secondary-type” mutations in <i>ASXL1</i>, <i>BCOR</i>, <i>EZH2</i>, <i>RUNX1</i>, <i>SF3B1</i>, <i>SRSF2</i>, <i>STAG2</i>, <i>U2AF1</i>, <i>ZRSR2</i> ▪ <i>KMT2A</i>-rearranged – t(v;11q23.3) except t(9;11) ▪ Mutations in <i>TP53</i> 	Debated Intensive or less intensive	✓, if patient is fit

Common scenarios for AML (newly-diagnosed)

Diagnosis/Scenario	Induction	Consolidation	Subsequent BMT?
Acute promyelocytic leukemia [t(15;17)]	ATRA + ATO	ATRA + ATO	Cure possible w/o BMT
Favorable risk	7+3 + gemtuzumab ozogamicin	HiDAC + gemtuzumab ozogamicin	Cure possible w/o BMT
<i>FLT3</i> -mut, fit patient	7+3 + midostaurin or quizartinib	Cytarabine + midostaurin or quizartinib	Recommended
Antecedent MDS or MPN (secondary-AML) Therapy-related AML	CPX-351	CPX-351	Recommended
Unfavorable risk	No standard of care 7+3 Venetoclax + Azacitidine Azacitidine or Decitabine monotherapy		Generally recommended
Age >75 or significant medical comorbidities	Venetoclax + Azacitidine		Generally not feasible
<i>IDH1</i> -mut, unfit patient	Ivosidenib + Azacitidine Venetoclax + Azacitidine		Generally not feasible
Became unfit for BMT after intensive chemo	7+3 or CPX-351	Oral azacitidine (CC-486)	N/A



Common scenarios for AML (relapsed/refractory)

Diagnosis/Scenario		Subsequent BMT?
<i>FLT3</i> -ITD or <i>FLT3</i> -TKD	Gilteritinib	If patient is fit, age ≤75 years, and wants it
<i>IDH1</i> mutations	Ivosidenib, Olutasidenib	
<i>IDH2</i> mutations	Enasidenib	
<i>KMT2A</i> rearrangements	Revumenib (recently approved)	
CD33-positive	Gemtuzumab ozogamicin	
Fit, no targeted therapies	Salvage chemotherapy, such as: MEC (mitoxantrone + etoposide + cytarabine) CLAG (cladribine + cytarabine + G-CSF) FLAG-Ida ± Ven (fludarabine + cytarabine + G-CSF + Idarubicine ± venetoclax)	
Unfit, no targeted therapies	Azacitidine or Decitabine monotherapy Low-dose cytarabine (LDAC) Supportive care	



Common drugs and mechanisms

Diagnosis/Scenario	Mechanism	
Anthracycline (ex. Daunorubicin, idarubicin)	Disrupts topoisomerase II -> dsDNA breaks cannot be repaired	
Cytarabine, i.e. “Ara-C” (HiDAC = high-dose Ara C)	Nucleoside disrupts DNA synthesis	
Venetoclax	Inhibitor of the anti-apoptotic protein BCL-2	
Hypomethylating agents (ex. Azacitidine, decitabine)	Inhibitor of DNA methyltransferase (DNMTi)	
Gemtzumab ozogamicin	CD33-directed antibody-drug conjugate	
Midostaurin, gilteritinib	TKI for FLT3-ITD and FLT3-TKD mutations (type 1 inhibitor)	
Quizartinib	TKI for FLT3-ITD only (type 2 inhibitor)	
Ivosidenib	TKI against mut-IDH1	Mut-IDH1/2 aberrantly converts α-KG to the oncometabolite 2-HG, which disrupts DNA methylation and inhibits differentiation.
Enasidenib	TKI against mut-IDH2	
Oludasidenib	TKI against mut-IDH1	
Revumenib	Menin inhibitor (recently approved)	
Glasdegib	Inhibitor of SMO and hedgehog signaling cascade	
CC-486 (oral azacitidine)	DNMTi, not bioequivalent to IV/SQ azacitidine	



Abbreviations: TKI = tyrosine kinase inhibitor, DNMTi = DNA methyltransferase inhibitor, ITD = internal tandem repeats, TKD = tyrosine kinase domain

A note about Acute Promyelocytic Leukemia (APL)

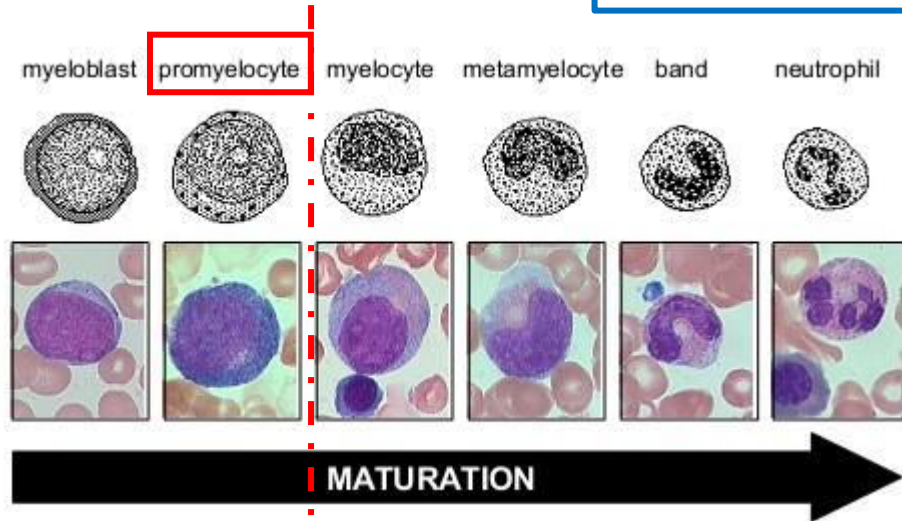
HIGH CURE RATES

+

HIGH EARLY MORTALITY IF NOT TREATED
(esp. CNS hemorrhage)

=

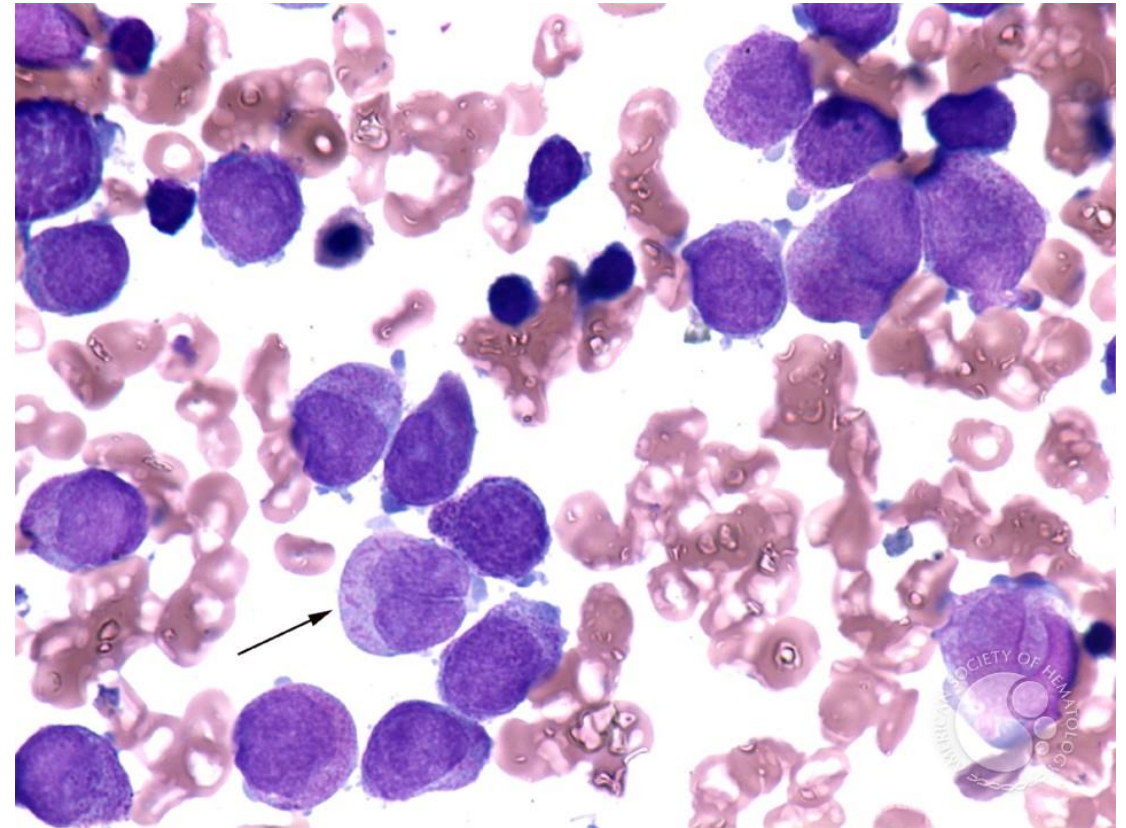
CAN'T MISS DIAGNOSIS



A block in differentiation

Medical-labs.net

- Rare subtype of acute myeloid leukemia (10-15%)
- Characterized by t(15;17), PML::RAR α
- Clinical presentation:
 - Usually younger patients (~40 y/o)
 - Pancytopenia
 - Clinical signs of bleeding/bruising
 - Evidence of coagulopathy (e.g. DIC—prolonged PT/PTT, low fibrinogen)
- Treatment: ATRA (retinoic acid) + ATO (arsenic)



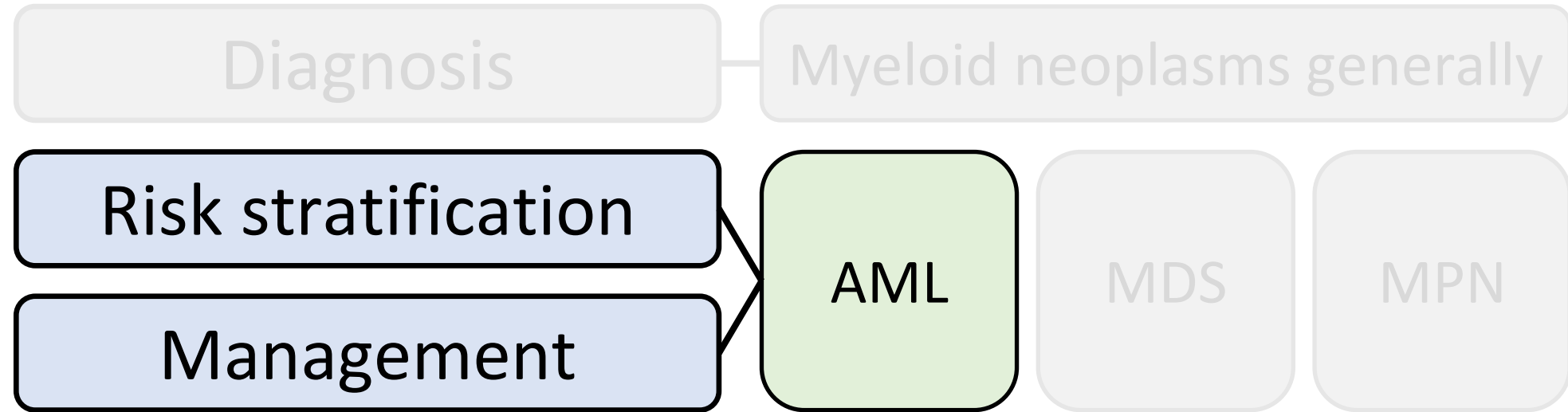
Heterogeneous appearance

ASH Image Bank

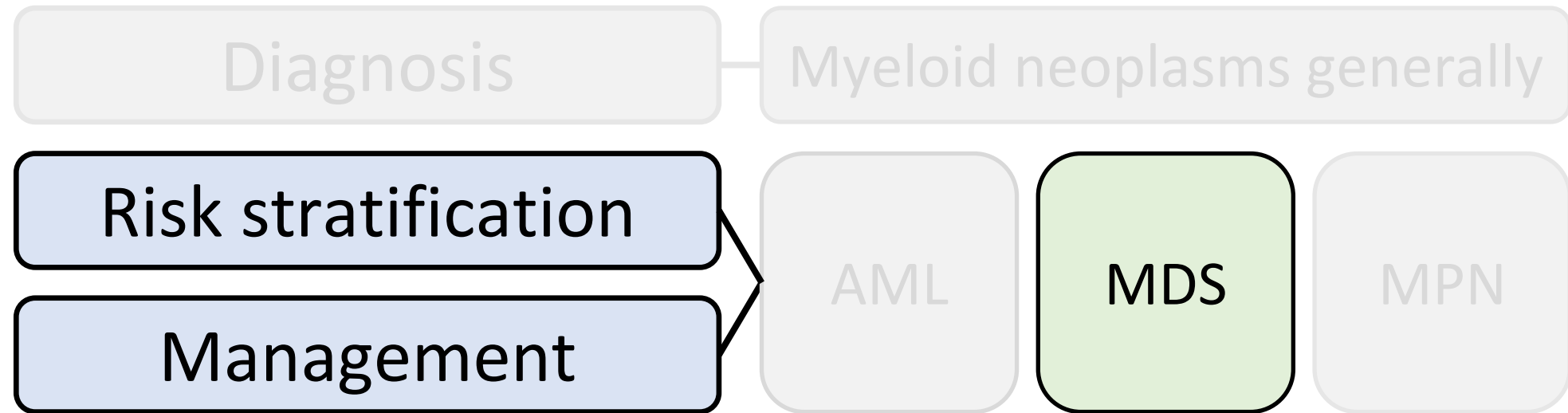
Typical variant: Bilobed nuclei, azurophilic granules, Auer rods



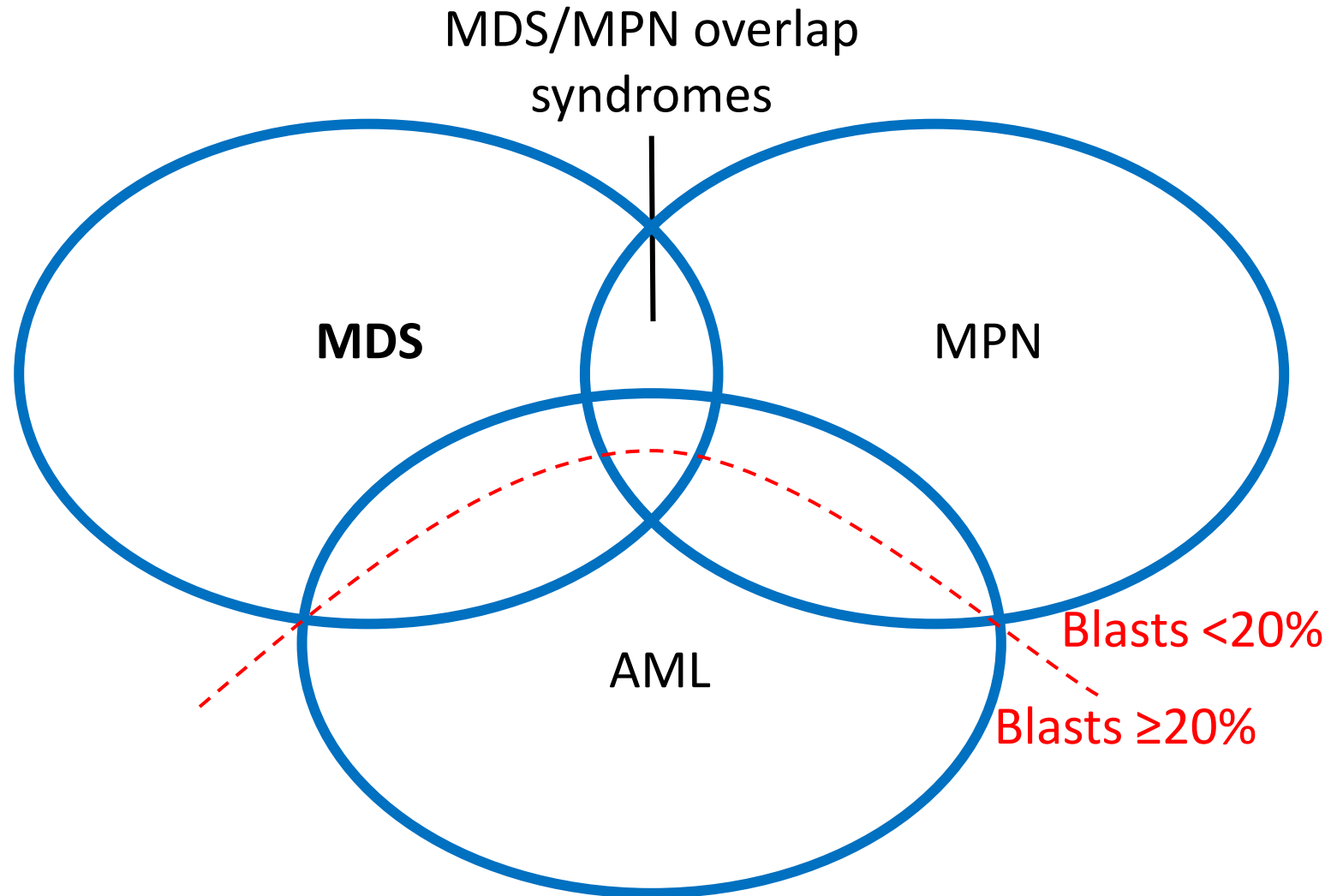
Outline



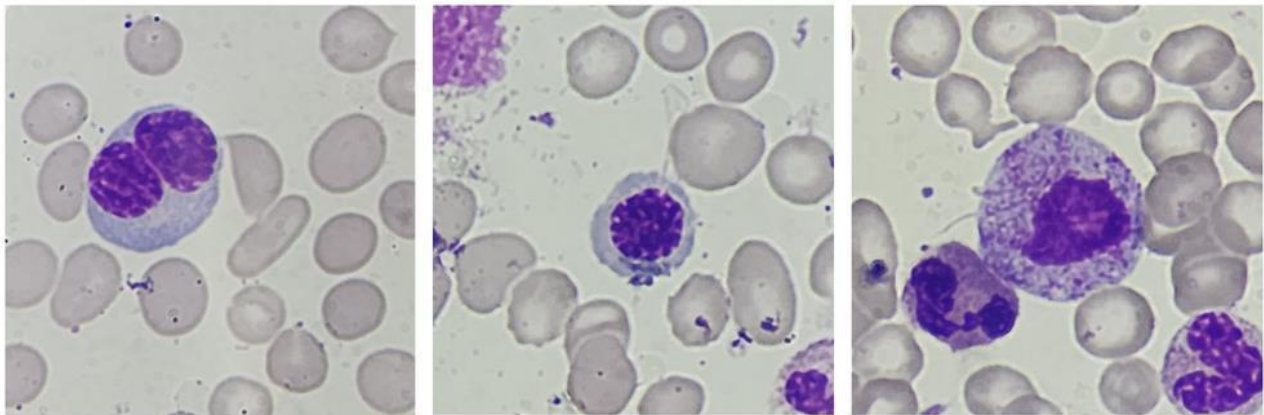
Outline



Myeloid malignancies overview



Myelodysplastic syndromes is a heterogeneous disorder



ASH Image Bank

Dysplasia (mis-shapedened) cells

E.g. Pelger huet-like abnormality, nucleated erythrocytes, hyposegmented granulocytes (left to right)

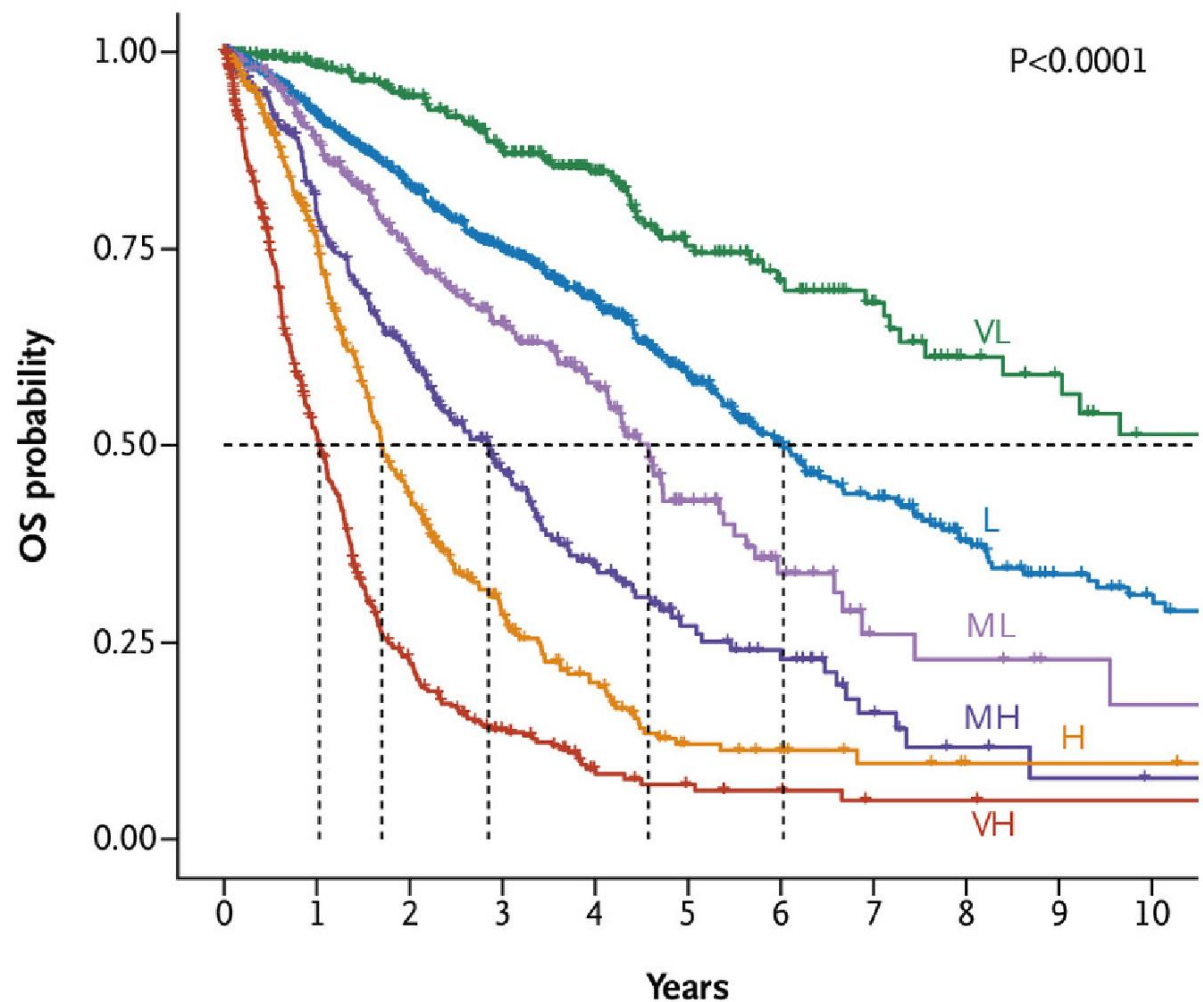
Clinical presentation

- Older age (~70 y/o)
- Chronically progressive cytopenias and symptoms
- Fatigue, weight loss

Diagnostic criteria	
Chronic cytopenia	Hgb <10, ANC <1.8, Plt <100, blasts <20%
+	
Dysplasia	≥10% in ≥1 lineage
or	
Specific cytogenetic abnormalities, such as:	Complex karyotype
	-7/del(7q)
	Del(5q)
or	
Specific genetic abnormalities	Del5q
	SF3B1-mut
	Biallelic TP53-mut
or	
Increased blasts	BM ≥5% - <20%
	Blood ≥2% - <20%



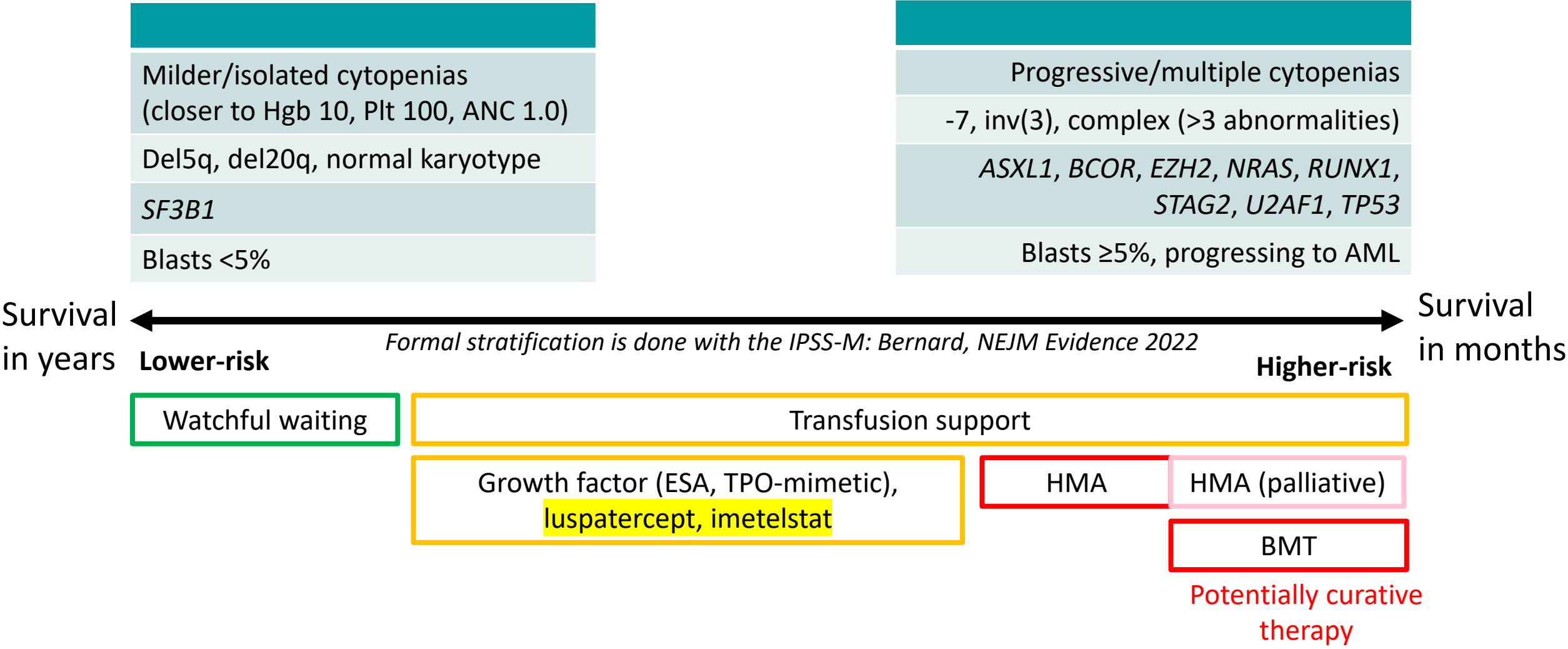
A range of “severity”



VL = Very low, L = Low, ML = Moderately low, MH = Moderately high, H = High, VH = Very high



Management centers on risk stratification



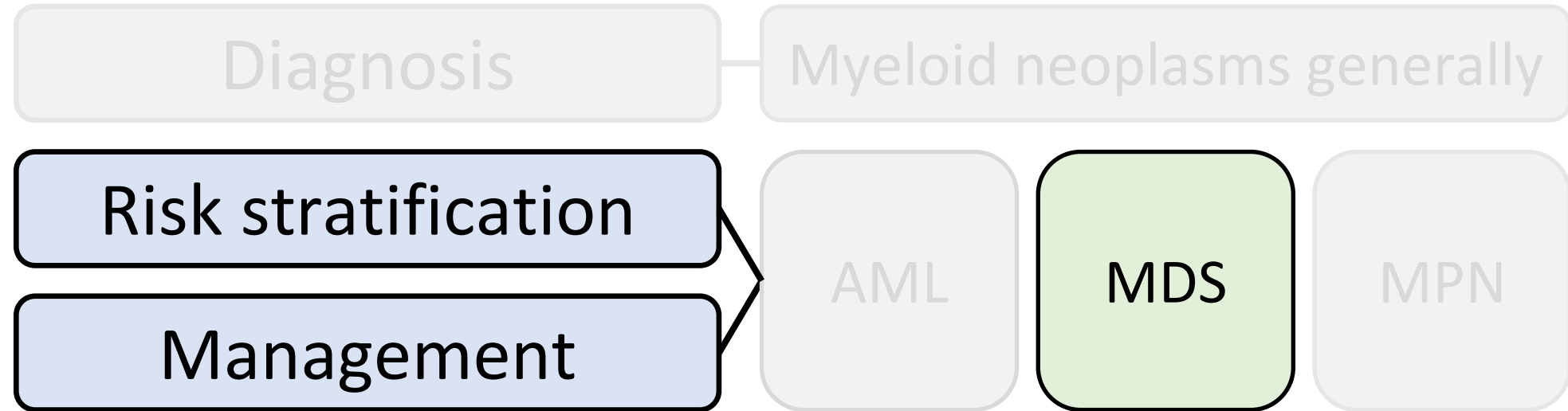
Abbreviations: HMA = hypomethylating agents (see slide 34)

Common treatment scenarios for MDS

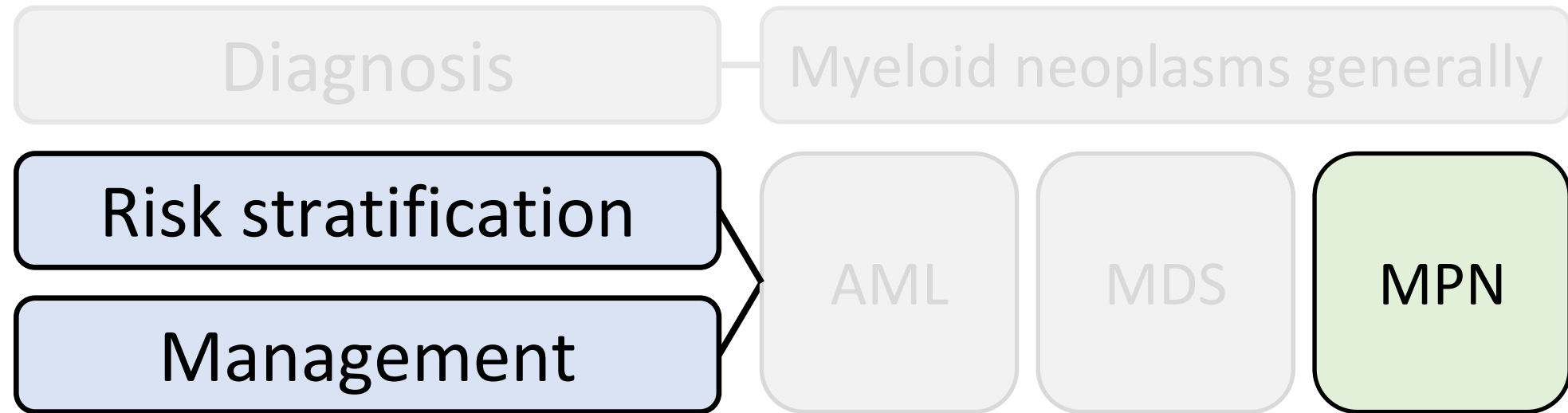
Diagnosis/Scenario	Management		Notes
Lower-risk MDS, transfusion independent	Watchful waiting		Not all MDS patients need treatment!
Lower-risk MDS, transfusion dependent	Anemia, EPO <500	ESA	ESA = erythropoietin stimulating agent
	Anemia (most effective ring sideroblasts and/or <i>SF3B1</i> -mut present)	Luspatercept	Fusion protein that binds TGF- β , prevents downstream signaling, and promotes erythroid maturation
	Del5q	Lenalidomide	Binds to CRBN to direct E3 ubiquitin ligase degradation of CSK1 α
	Anemia refractory or ineligible to ESA	Imetelstat (recently approved)	Telomerase inhibitor
	Thrombocytopenia	TPO-mimetic	TPO = thrombopoietin
Higher-risk MDS	BMT eligible	BMT	Potentially curative therapy
	BMT ineligible	Hypomethylating agent (azacitidine or decitabine)	Inhibitor of DNA methyltransferase (DNMTi)



Outline



Outline



Question 2

A 54-year-old male presents with WBC 230 K/uL. He denies bruising, bleeding. He has a large spleen. Hemoglobin and platelets are normal. Bone marrow biopsy demonstrates chronic myeloid leukemia. What is the hallmark chromosomal finding of this diagnosis?

- a. MLL (11q23) rearrangement
- b. 9;22 translocation (Philadelphia chromosome)
- c. 15;17 translocation
- d. Loss of chromosome 7



Question 2

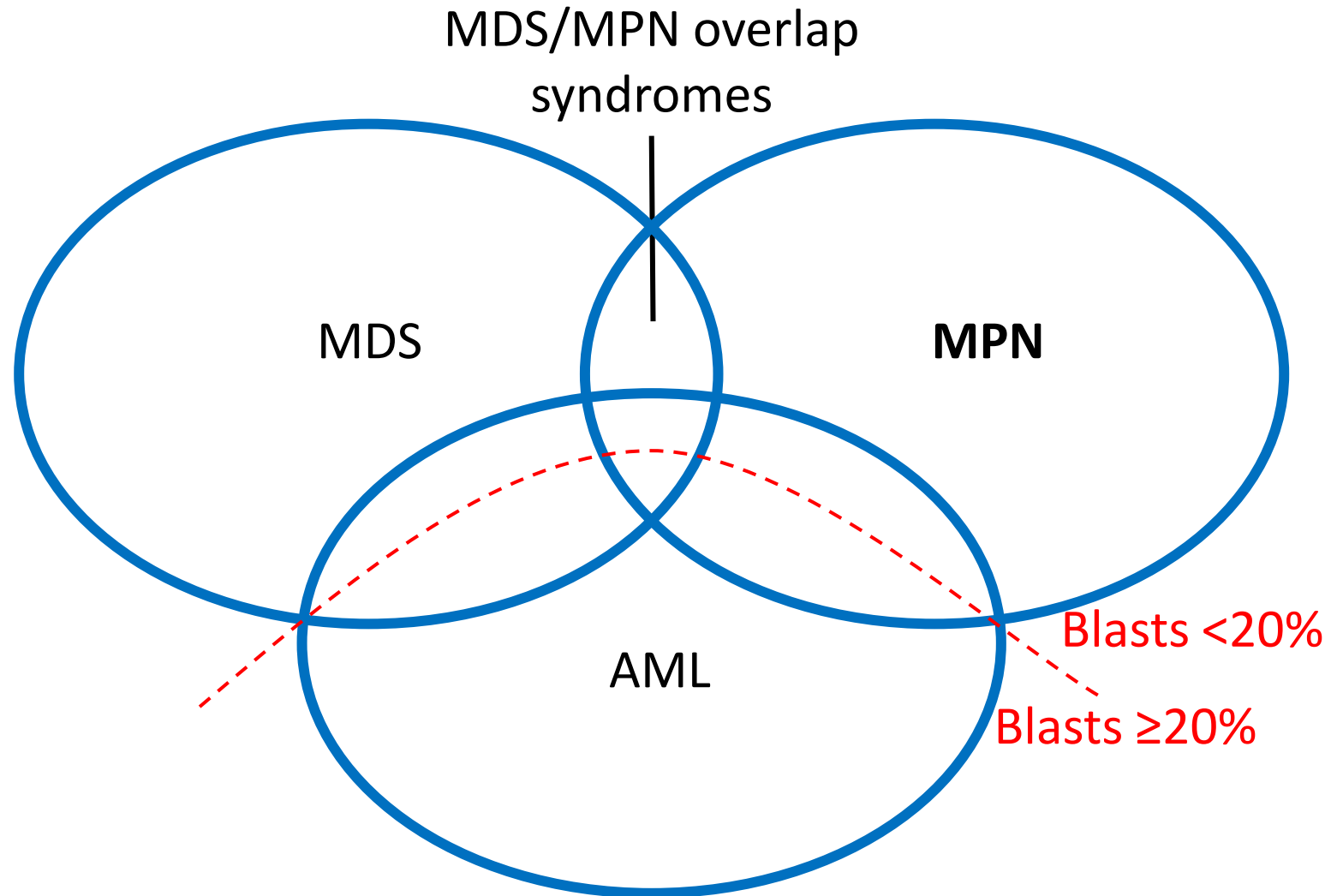
A 54-year-old male presents with WBC 230 K/uL. He denies bruising, bleeding. He has a large spleen. Hemoglobin and platelets are normal. Bone marrow biopsy demonstrates chronic myeloid leukemia. What is the hallmark chromosomal finding of this diagnosis?

- a. MLL (11q23) rearrangement
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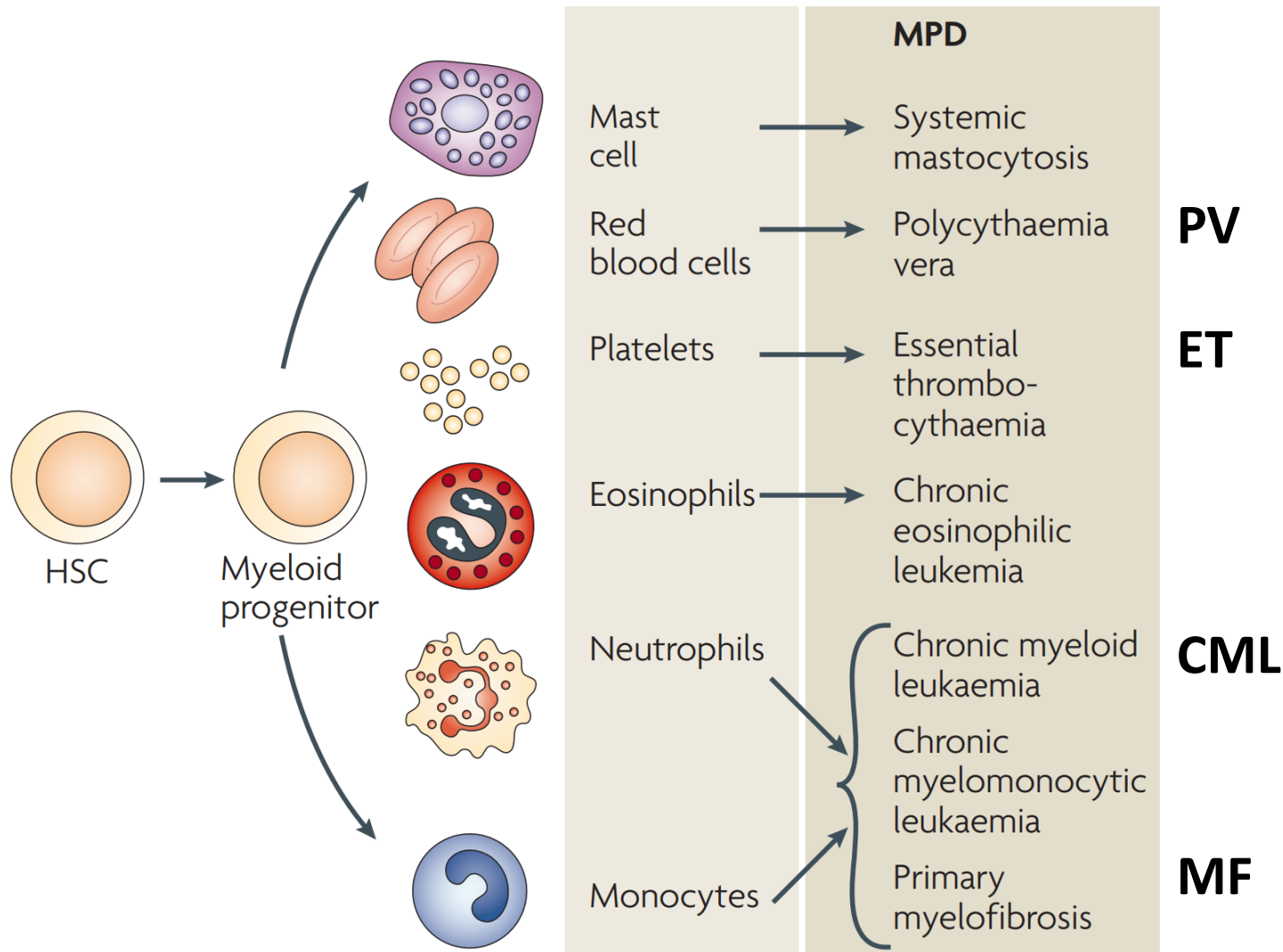
Chronic Myeloid Leukemia is DEFINED by the presence of the Philadelphia chromosome and is required for diagnosis



Myeloid malignancies overview



Myeloproliferative neoplasms



The “classic” MPNs

- Philadelphia chromosome-negative: **PV, ET, MF**
- Philadelphia chromosome-positive: **CML**

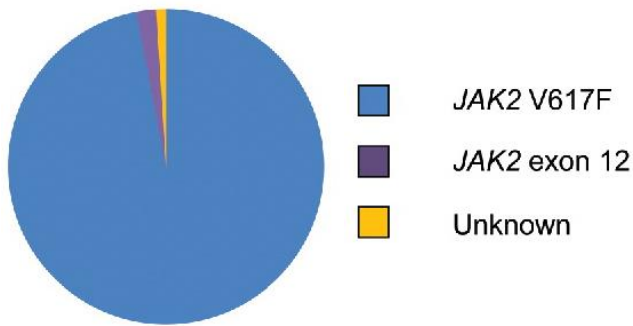
Levine, Nat Rev Cancer 2007



Myeloproliferative neoplasms

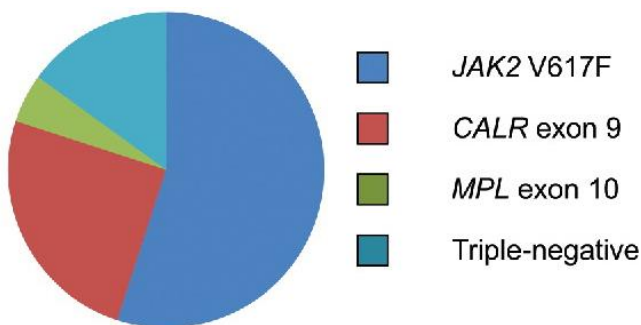
Polycythemia vera (PV)

↑Hgb (↑WBC)



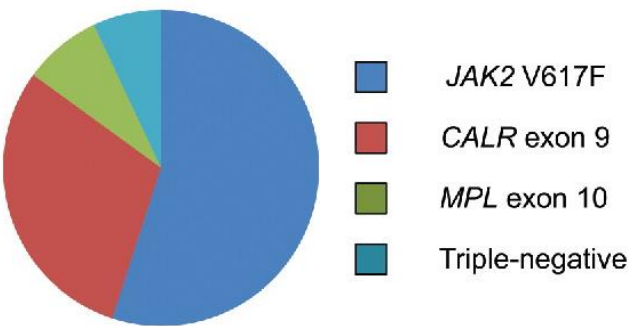
Essential Thrombocythemia (ET)

↑Plt (↑WBC)



Myelofibrosis (MF)*

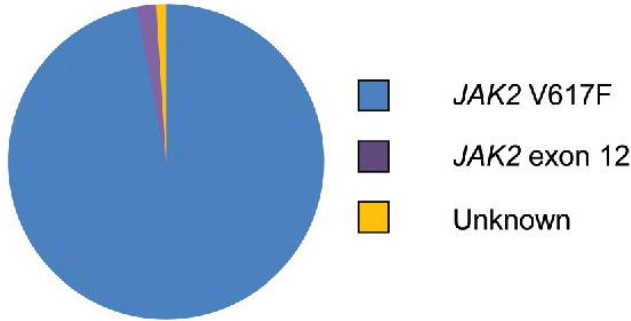
↓Hgb, ↓Plt (↑WBC, then ↓)



Myeloproliferative neoplasms

Polycythemia vera (PV)

↑Hgb (↑WBC)



~5%/10 yrs

Myelofibrosis (MF)*

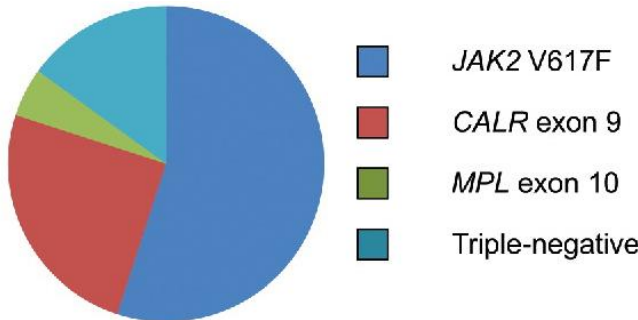
↓Hgb, ↓Plt (↑WBC, then ↓)

Varies

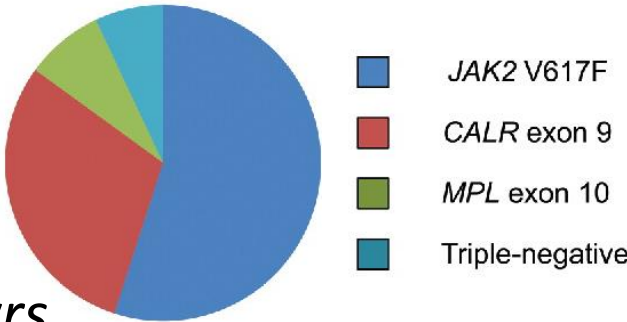
Secondary
-AML

Essential Thrombocythemia (ET)

↑Plt (↑WBC)



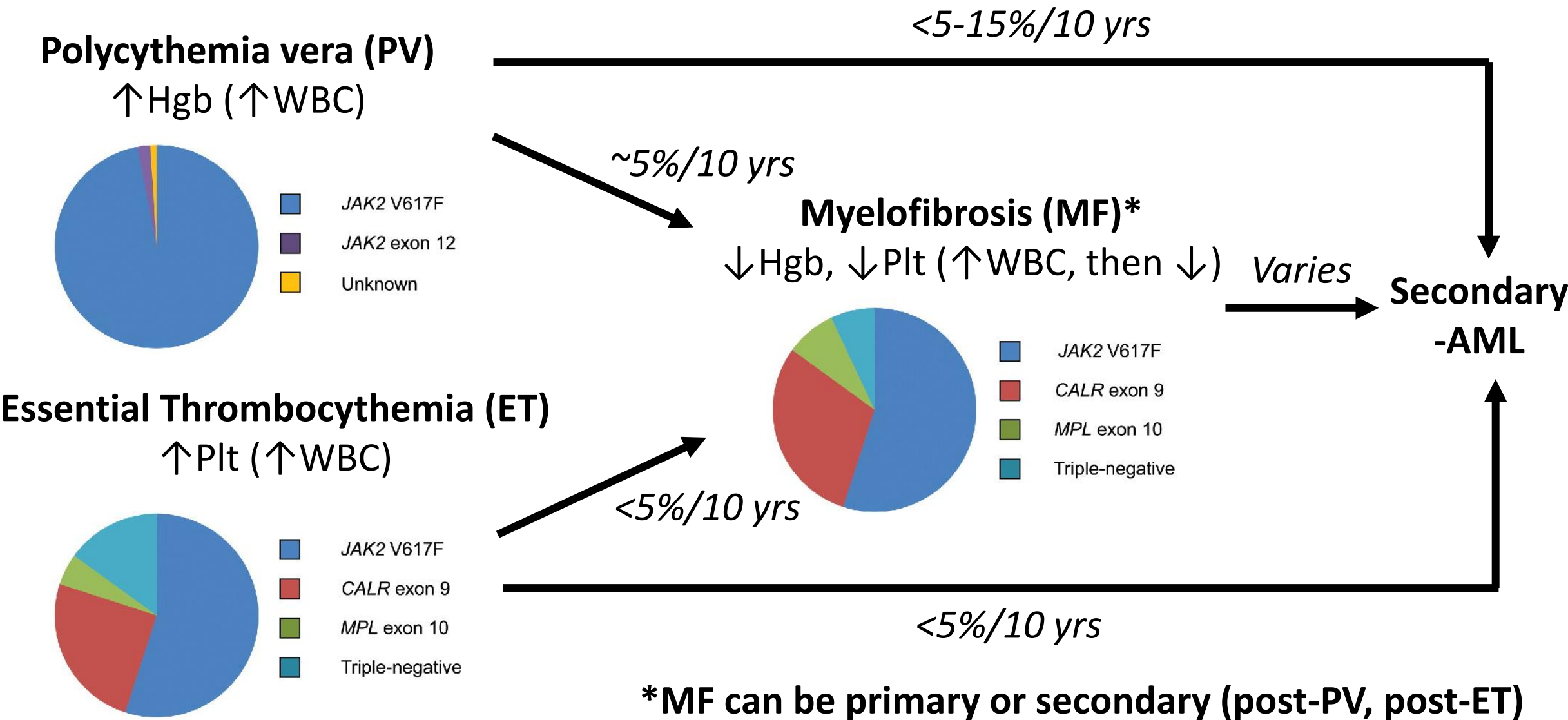
<5%/10 yrs



***MF can be primary or secondary (post-PV, post-ET)**



Myeloproliferative neoplasms



Myeloproliferative neoplasms

Polycythemia vera (PV)

Major criteria

Hgb >16.5 g/dL or Hct >49% (men)

Hgb >16.0 g/dL or Hct >48% (women)

BM biopsy with:

- Panmyelosis (trilineage growth)
- Pleomorphic megakaryocytes (differences in size)

JAK2 mutation

Minor criteria

Low EPO

Diagnose PV:

All 3 major criteria or First 2 major + minor criterion

Essential thrombocythemia (ET)

Major criteria

Platelet ≥ 450 K/uL

BM biopsy with:

- Mainly megakaryocyte proliferation
- Megakaryocytes with hyperlobulated nuclei

Not meeting criteria for other MPNs

JAK2, *CALR*, or *MPL* mutation

Minor criteria

Other clonal marker (e.g. abnormal karyotype)

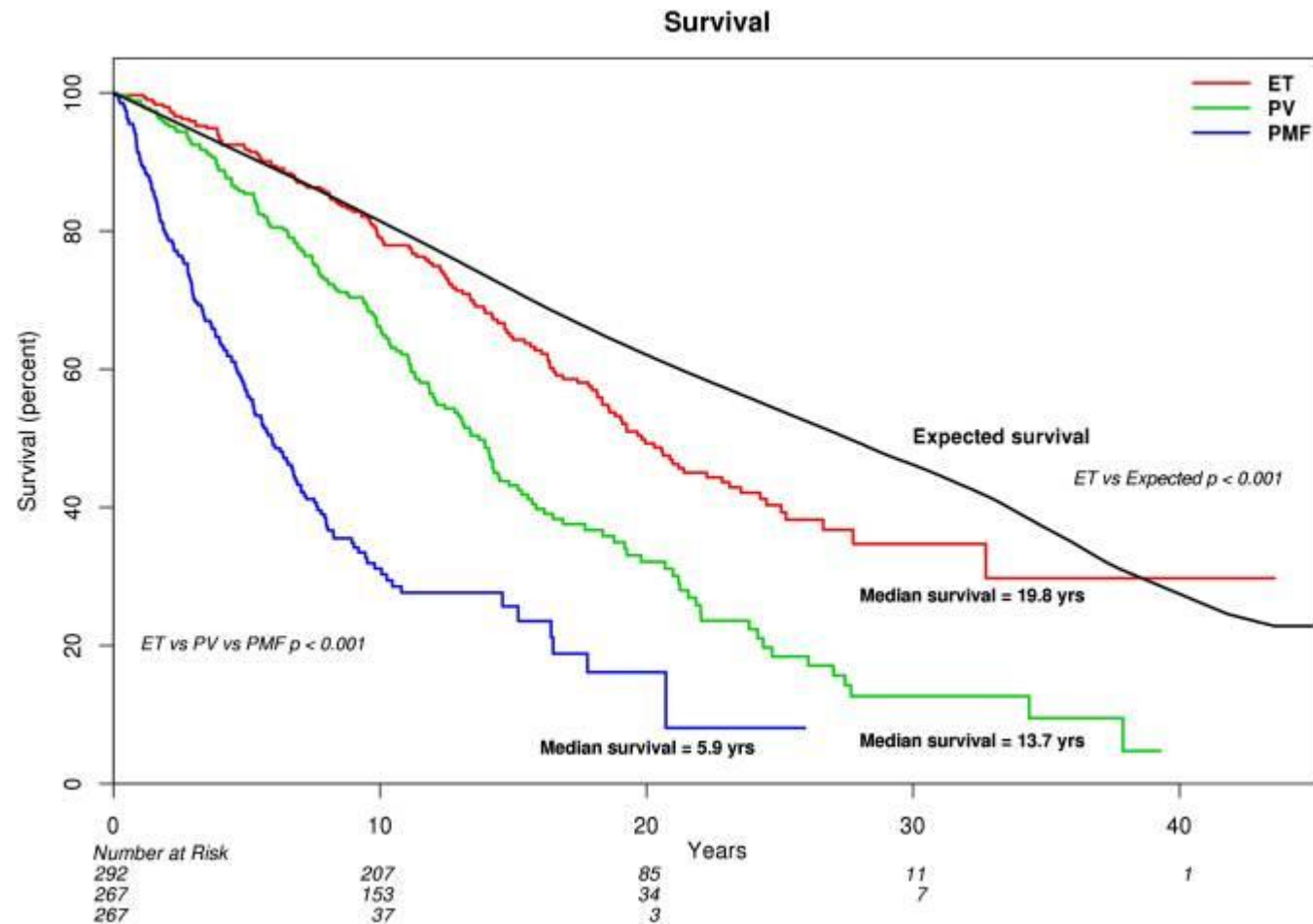
Absence of evidence of reactive thrombocytosis

Diagnose ET:

All 4 major criteria or First 3 major + 1 minor criterion



A range of “severity”



ET = Essential thrombocythemia, PV = Polycythemia vera, PMF = Primary myelofibrosis

Tefferi, Blood 2014



Management centers on:

- 1) Long-term: Monitoring for disease progression to secondary MF or AML
- 2) Short-term: Preventing thrombosis (venous, arterial, cardiac, CNS)**



Polycythemia vera management

Risk	Age?		Prior thrombosis?	Give aspirin?	Start cytoreduction (e.g. hydroxyurea)?
Low	≤60 y/o	AND	X	Yes	No*, <u>phlebotomy</u> alone for <u>goal Hct <45%</u>
High	>60 y/o	<u>OR</u>	✓	Yes	Yes, with <u>hydroxyurea</u> for <u>goal Hct <45%</u>

*Cytoreduction indicated for Hct not well-controlled by phlebotomy alone.

Essential thrombocythemia management

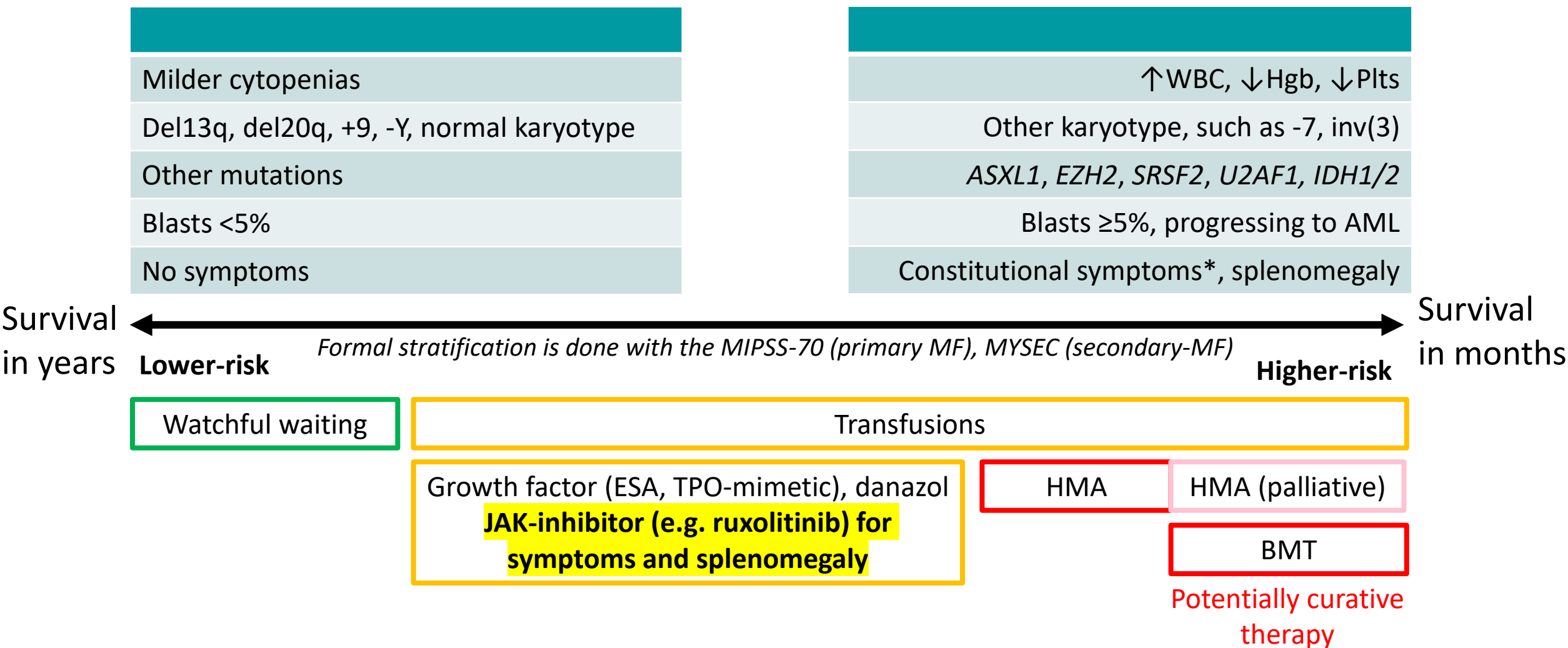
Risk	Age?		JAK2-mut?		Prior thrombosis?	Give aspirin?	Start cytoreduction?
Very low	≤60 y/o	AND	X	AND	X	Yes if vasomotor symptoms	No*
Low	≤60 y/o	AND	✓	AND	X	Yes	No*
Intermediate	>60 y/o	AND	X	AND	X	Yes	No*
High	>60 y/o	AND	✓	<u>OR</u>	✓	Yes	Yes, hydroxyurea

*Cytoreduction separately indicated for 1) Acquired von Willebrand syndrome (usually platelets >1-1.5 million) or major bleeding, 2) Vasomotor symptoms not improving to aspirin.



For all patients, also optimize CV risk factors (diet, exercise, smoking cessation)

Myelofibrosis management



*Fative, fever, nightsweats, weight loss, arthralgias, myalgias, difficulty with concentration
Abbreviations: HMA = hypomethylating agents (see slide 34)



List of JAK inhibitors for myelofibrosis

Drug	Indication	Common uses
Ruxolitinib	<ul style="list-style-type: none"> 1st-line MF Platelets ≥ 50 K/uL 	<ul style="list-style-type: none"> Earliest approved JAK inhibitors Thrombocytopenia and anemia are expected and commonly dose-limiting
Fedratinib	<ul style="list-style-type: none"> 1st or 2nd-line MF Platelets ≥ 50 K/uL Black-box warning of Wernicke's encephalopathy (thiamine repletion) 	
Pacritinib	<ul style="list-style-type: none"> 1st or 2nd-line MF Platelets < 50 K/uL is ok 	<ul style="list-style-type: none"> For patients with thrombocytopenia (Post-hoc analysis suggests benefit to anemia as well)
Momelotinib	<ul style="list-style-type: none"> 1st or 2nd-line MF Platelets > 25 K/uL 	<ul style="list-style-type: none"> For patients with anemia Decreases RBC transfusion dependency



A note about Chronic Myeloid Leukemia (CML)

MULTIPLE EFFECTIVE
TREATMENT OPTIONS

+

EXCELLENT LONG-TERM
OUTCOMES

=

CAN'T MISS DIAGNOSIS

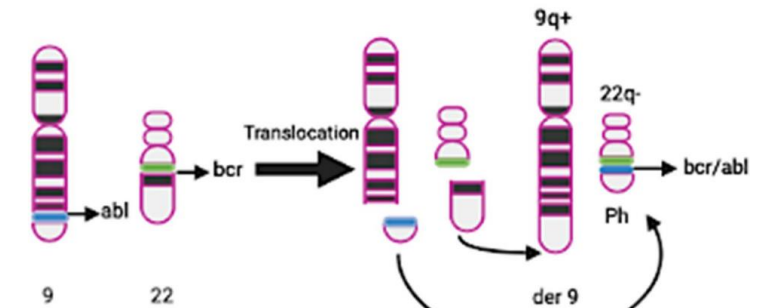
Philadelphia chromosome, t(9;22) → BCR-abl fusion protein

Presentation:

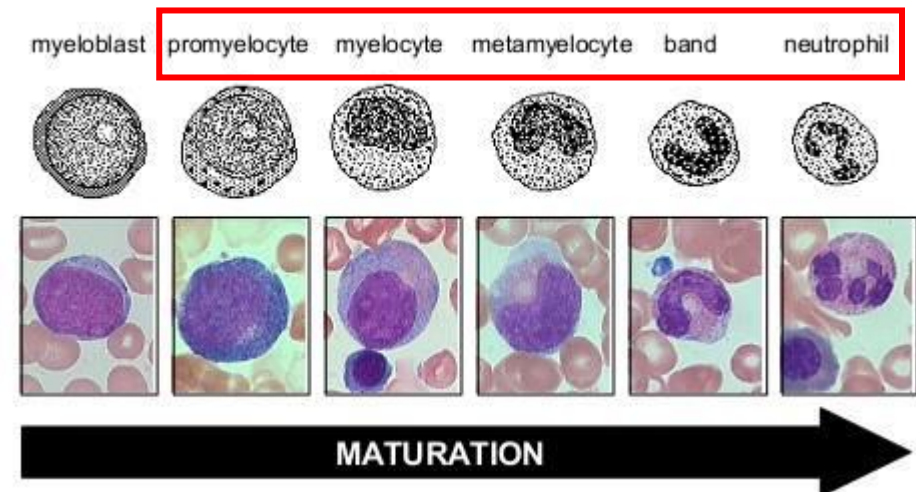
- ↑granulocytes (particularly neutrophils) and their precursors, not blasts

Diagnosis:

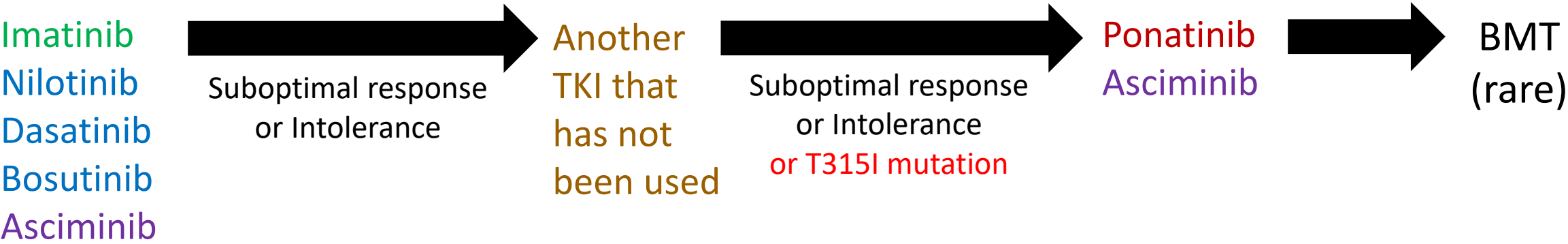
- **Flow cytometry:** to exclude acute leukemia, if suspected
- **Bone marrow biopsy (required)**
 - To confirm chronic phase disease
 - Karyotype to confirm t(9;22)
 - Karyotype to identify additional cytogenetic abnormalities that may be prognostic
- **qPCR for BCR-abl mRNA**



Karasu, Medical Oncology 2021

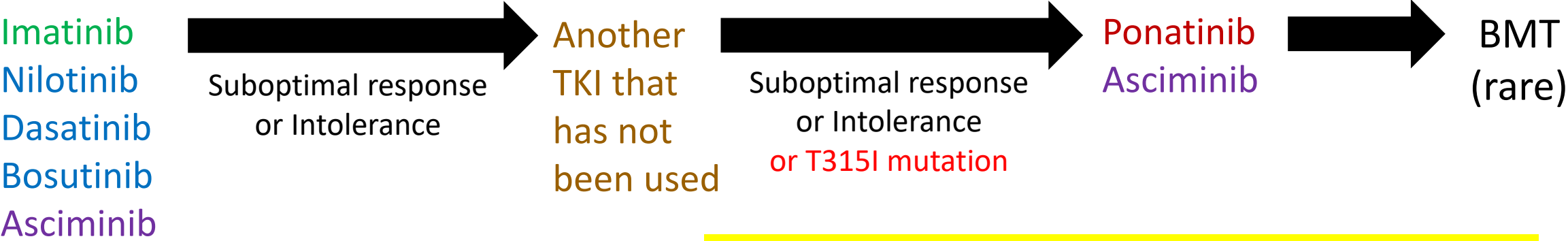


A note about Chronic Myeloid Leukemia (CML)



TKI	Class	Characteristic toxicity	General class toxicity
Imatinib	ATP-competitive, 1 st -gen	Generally well-tolerated Renal toxicity	QTc prolongation LFT elevation Renal impairment Electrolyte wasting Nausea/diarrhea Edema (extremities, periorbital)
Dasatinib	ATP-competitive, 2 nd -gen	Pleural effusion Pulmonary arterial HTN	
Bosutinib	ATP-competitive, 2 nd -gen	Diarrhea	
Nilotinib	ATP-competitive, 2 nd -gen	Arteriovascular disease Pancreatitis Hyperglycemia	
Ponatinib	ATP-competitive, 3 rd -gen Active against T315I mutation	Arteriovascular disease	
Asciminib	Allosteric inhibitor Active against T315I mutation	HTN Pancreatitis	

A note about Chronic Myeloid Leukemia (CML)



TKI	Class
Imatinib	ATP-competitive, 1 st -gen
Dasatinib	ATP-competitive, 2 nd -gen
Bosutinib	ATP-competitive, 2 nd -gen
Nilotinib	ATP-competitive, 2 nd -gen
Ponatinib	ATP-competitive, 3 rd -gen Active against T315I mutation
Asciminib	Allosteric inhibitor Active against T315I mutation

How to choose between 1st vs 2nd gen TKI in the first line setting?

- No difference in overall survival
- Differences in tolerability
- 2nd gen achieves deeper responses more quickly
 - This enables a shorter time to trying TKI discontinuation (≥3 years total TKI, ≥2 years of deep molecular remission)
- If intolerant to a 2nd gen, ok to switch to another 2nd gen TKI
- If resistant to a 2nd gen, another 2nd gen unlikely to be effective; consider asciminib, ponatinib

Common treatment scenarios for frontline CML

Scenario	Mechanisms/Notes
Younger patient hoping to not be on TKI lifelong	2 nd -gen TKI Avoid nilotinib due to arterial occlusive events
Patient planning to have children	2 nd -gen TKI to achieves deeper responses more quickly and increases opportunity for safe treatment discontinuation prior to pregnancy
Older patient with comorbidities and concerns of tolerance	Imatinib
Higher-risk disease (peripheral blasts, high platelets, splenomegaly)	2 nd -gen TKI
CHF or pulmonary comorbidities	Avoid dasatinib
Diabetes mellitus	Avoid nilotinib
Coronary artery disease, prior thrombosis	Avoid nilotinib



Practical pearls for referral

Scenario	Disposition
Acute leukocytosis + other cytopenias + poorly-appearing	Urgent referral to specialist or ED presentation (?acute leukemia)
Acute pancytopenia + poorly-appearing	Urgent referral to specialist or ED presentation (?acute leukemia)
Acute/subacute leukocytosis + NO cytopenias + clinically WELL-appearing, without clear secondary causes	Urgent referral to specialist or ED presentation (?CML vs. acute leukemia)
Chronically progressive cytopenias	Evaluate for secondary causes of cytopenias Refer to specialist +/- bone marrow biopsy (?MDS)

Acute: Days-to-weeks, **Subacute**: Weeks-to-months, **Chronic**: Months-to-years



Take-Aways

- A bone marrow evaluation includes multiple tests including 1) cell morphology review, 2) cell lineage determination (myeloid vs. lymphoid) by flow cytometry, and 3) genetic testing.
- AML treatment includes 1) conventional intensive chemotherapy (typically for favorable-risk AML or patients fit for subsequent BMT), and 2) less-intensive regimens (for older, frailer patients, typically ineligible for BMT). Revumenib is a newly approved drug for *KMT2A*-rearranged AML.
- MDS management ranges from observation for lower-risk patients without transfusion dependence to chemotherapy + BMT considerations for higher-risk patients. Imetelstat is a newly approved drug for lower-risk MDS.
- ET/PV management centers on thromboprevention with 1) aspirin (+phlebotomy for PV) and 2) hydroxurea for patients higher-risk patients.
- CML and APL are very testable diagnoses; know their typical presentation, defining genetic event, and general management.



Thank you

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