MDS/MPN

Case-based approach of CMML

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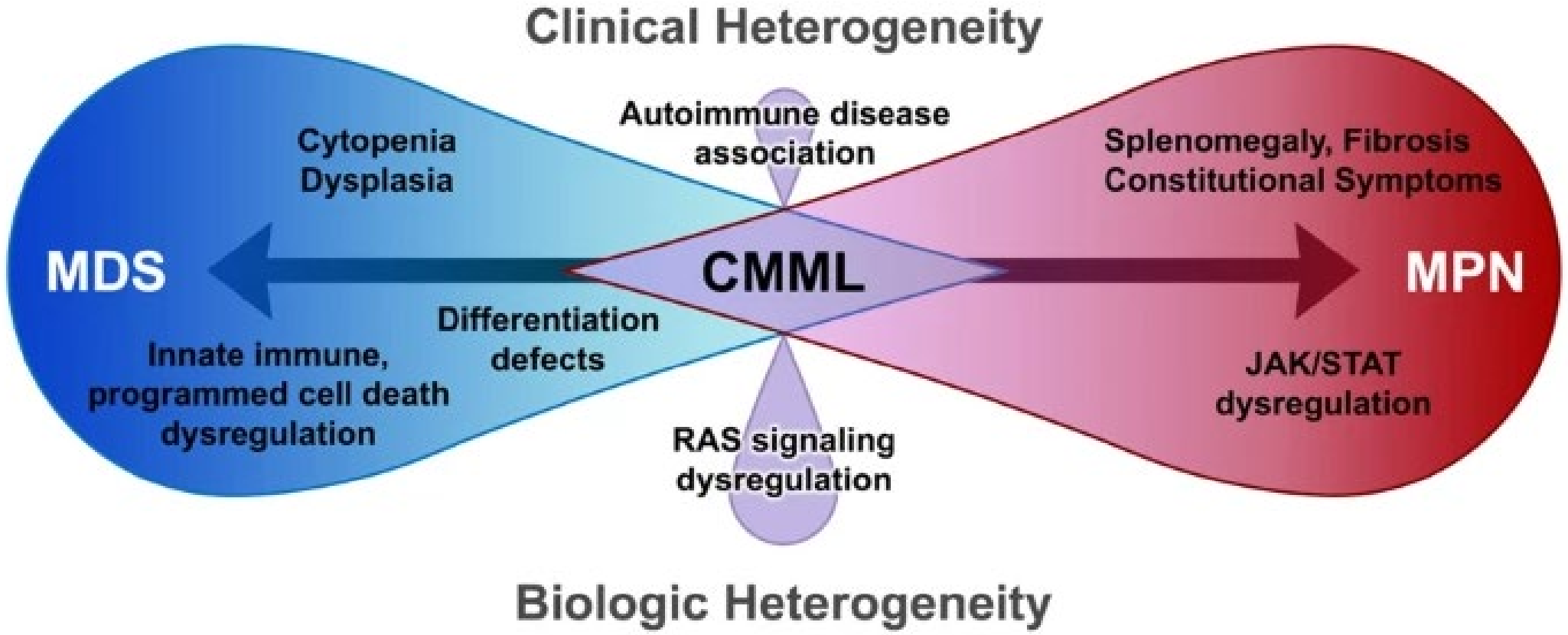
Overview

- Introduction MDS/MPN
- Definition CMML
- Approach to monocytosis
- Peripheral blood morphology
- Routine cellcounter and peripheral blood flowcytometry
- Bonemarrow aspirate cytology and corebiopsy evaluation
- Molecular testing

MDS/MPN



Chan et al. Chronic myelomonocytic leukemia diagnosis and management. Leukemia. 2021 Jun;35(6):1552-1562.

WHO 2016 Classification	WHO 2022 Classification	ICC 2022 Classification
Chronic myelomonocytic leukemia	Chronic myelomonocytic leukemia	Chronic myelomonocytic leukemia
		Clonal cytopenia with monocytosis of undetermined significance Clonal monocytosis of undetermined significance
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*$^-$	Myelodysplastic/myeloproliferative neoplasm with neutrophilia	Atypical chronic myeloid leukemia
Juvenile myelomonocytic leukemia (JMML)		
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)	Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis	Myelodysplastic/myeloproliferative neoplasm with thrombocytosis and *SF3B1* mutation
		Myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis, not otherwise specified
MDS/MPN, unclassifiable	Myelodysplastic/myeloproliferative neoplasm, not otherwise specified	Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

Fontana et al. Myelodysplastic Syndromes/Myeloproliferative Overlap Neoplasms and Differential Diagnosis in the WHO and ICC 2022 Era: A Focused Review. Cancers (Basel). 2023 Jun 13;15(12):3175.

WHO 2022

- **Prerequisite criteria**

1. Persistent absolute (≥0.5 × 10^9/ L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]

- **Supporting criteria**

1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]

Khoury et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703-1719.

ICC 2022

Monocytosis defined as monocytes ≥ 0.5 × 10^9/L and ≥ 10% of the WBC
Cytopenia (thresholds same as MDS)*
Blasts (including promonocytes) < 20% of the cells in blood and bone marrow
Presence of clonality: abnormal cytogenetics and/or presence of at least one myeloid neoplasm associated mutation of at least 10% allele frequency†
In cases without evidence of clonality, monocytes ≥ 1.0 × 10^9/L and > 10% of the WBC, and increased blasts (including promonocytes),‡ or morphologic dysplasia, or an abnormal immunophenotype consistent with CMML would be required for its diagnosis.
Bone marrow examination with morphologic findings consistent with CMML (hypercellularity due to a myeloid proliferation often with increased monocytes), and lacking diagnostic features of acute myeloid leukemia, MPN or other conditions associated with monocytosis§
No *BCR::ABL1* or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

Arber et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022 Sep 15;140(11):1200-1228.

Diagnostic criteria for clonal monocytosis of undetermined significance (CMUS)

Persistent monocytosis defined as monocytes ≥ 0.5×10^9/L and ≥ 10% of the WBC
Absence or presence of cytopenia (thresholds same as for MDS)*
Presence of at least one myeloid neoplasm associated mutation of appropriate allele frequency (ie, ≥2%)†
No significant dysplasia, increased blasts (including promonocytes) or morphologic findings of CMML on bone marrow examination‡
No criteria for a myeloid or other hematopoietic neoplasm are fulfilled
No reactive condition that would explain a monocytosis is detected

Subclassifications

- Important for prognosis: WBC count and blast%

- WBC ≥13 × 10^9/L MPN-CMML
- WBC < 13 x 10^9/L MDS-CMML

- CMML-1 (<5% in PB and/or <10% in BM)
- CMML-2 (5%-19% blasts in PB and/or 10%-19% in BM and/or Auer rods are present

Changes in classification

Shared changes

	Peripheral blood	CMML subgroups
ICC 2022 WHO 2022	New monocyte Cutoff >0.5x10⁹/L (from >1.0x10⁹/L)	Elimination of CMML-0

Differences (new AML criteria)

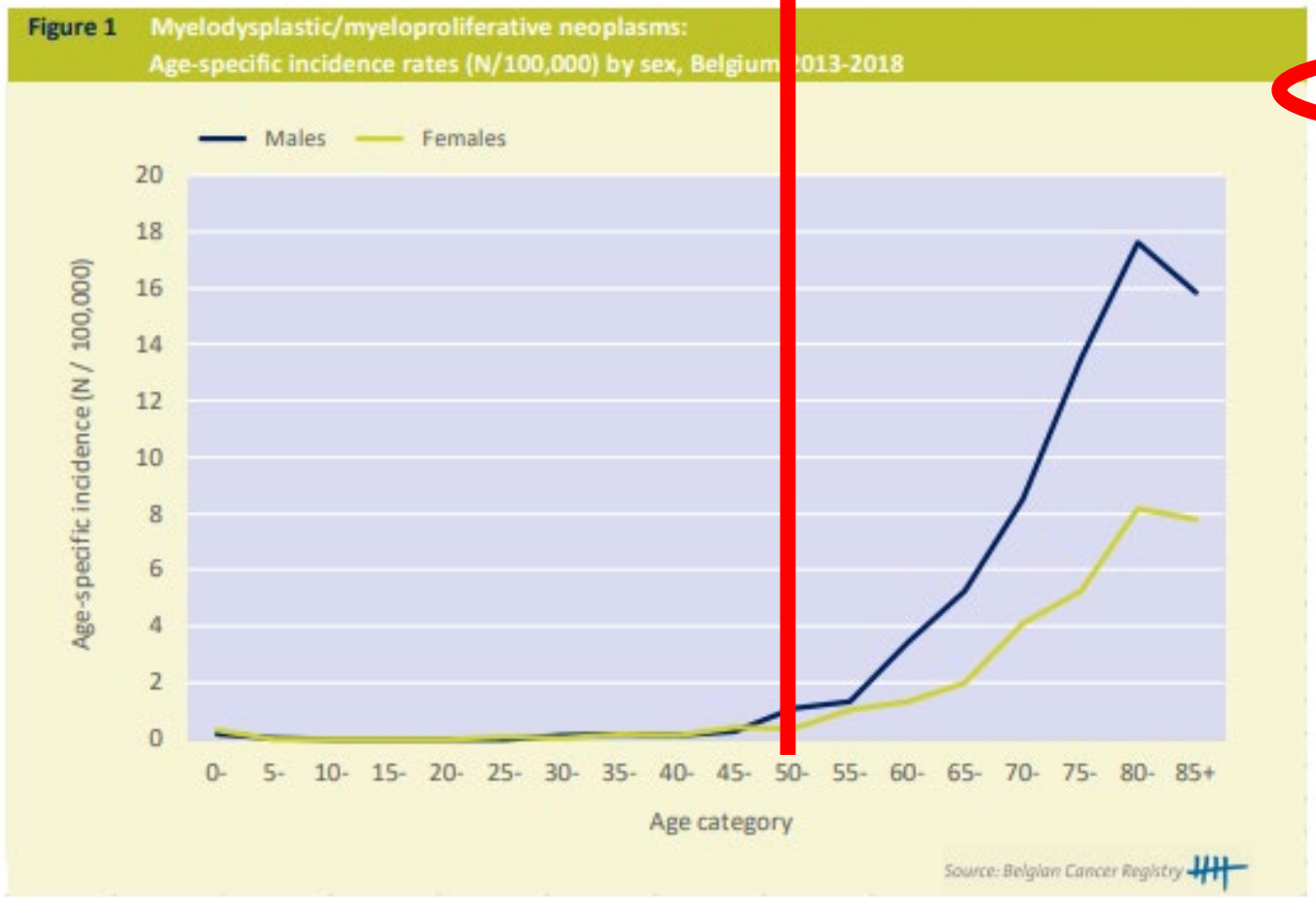
ICC 2022	≥10% blasts and AML-defining aberration
WHO 2022	AML-defining aberration

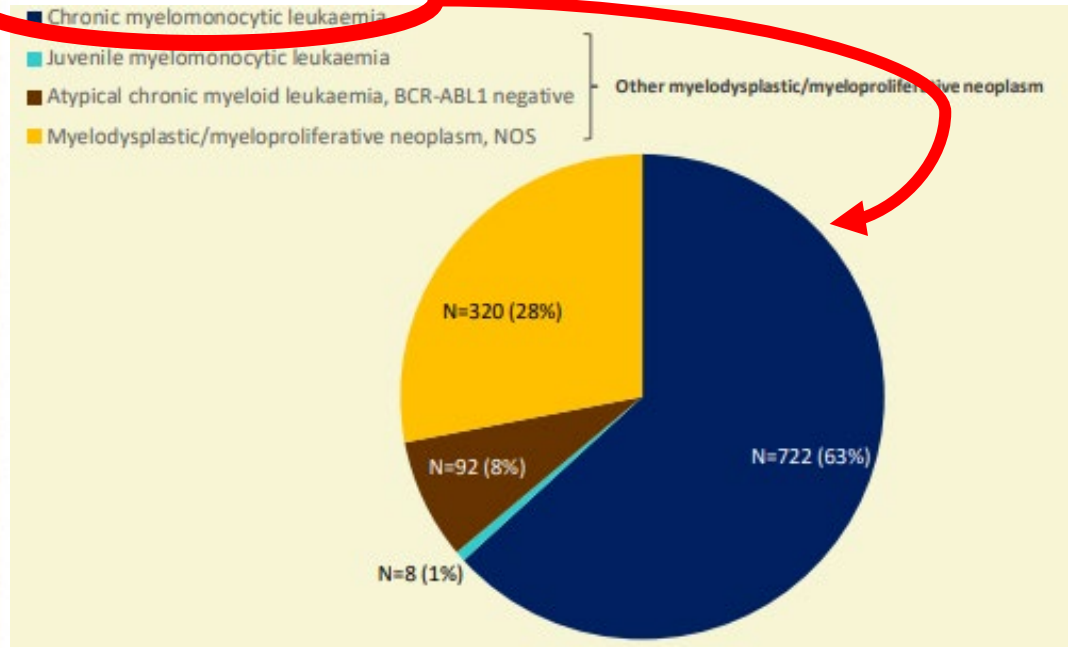
Differences (new CMML criteria)

	Peripheral blood	Bone marrow	Clonality	Flow cytometry
ICC 2022	Cytopenia	Age-adjusted hypercellularity and myeloid expansion	Variant allele frequency ≥10%	Aberrant surface marker expression
WHO 2022	No equivalent	Dysplasia ≥1 myeloid lineages (>10% of cells)	No reported variant allele frequency cutoff	Aberrant partitioning of peripheral blood monocytes

Baumgartner et al. Comparing malignant monocytosis across the updated WHO and ICC classifications of 2022. Blood. 2023 Dec 8:blood.2023021199. doi: 10.1182/blood.2023021199. Epub ahead of print. PMID: 38064663.

Epidemiology





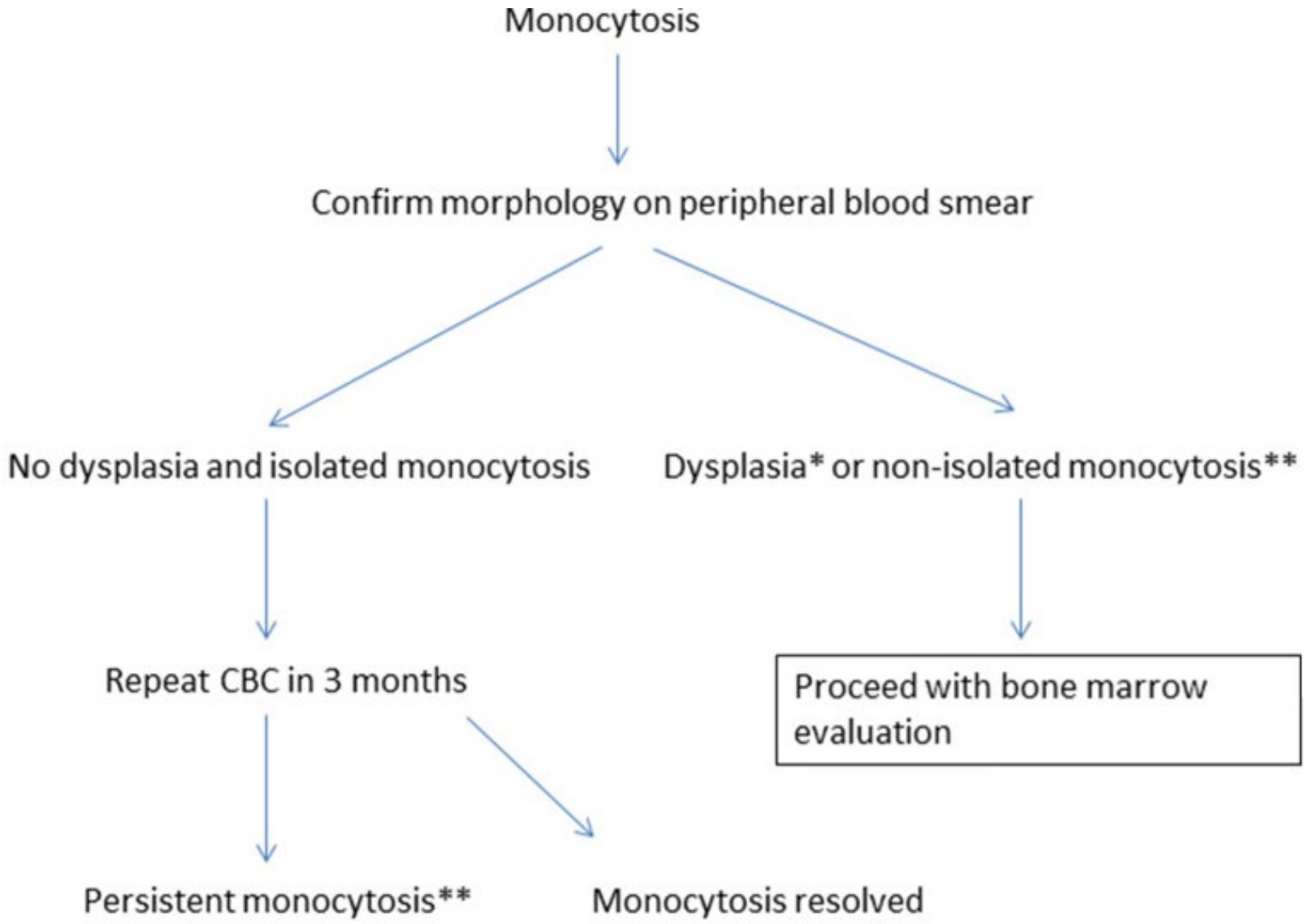
Monocytosis

Reactive

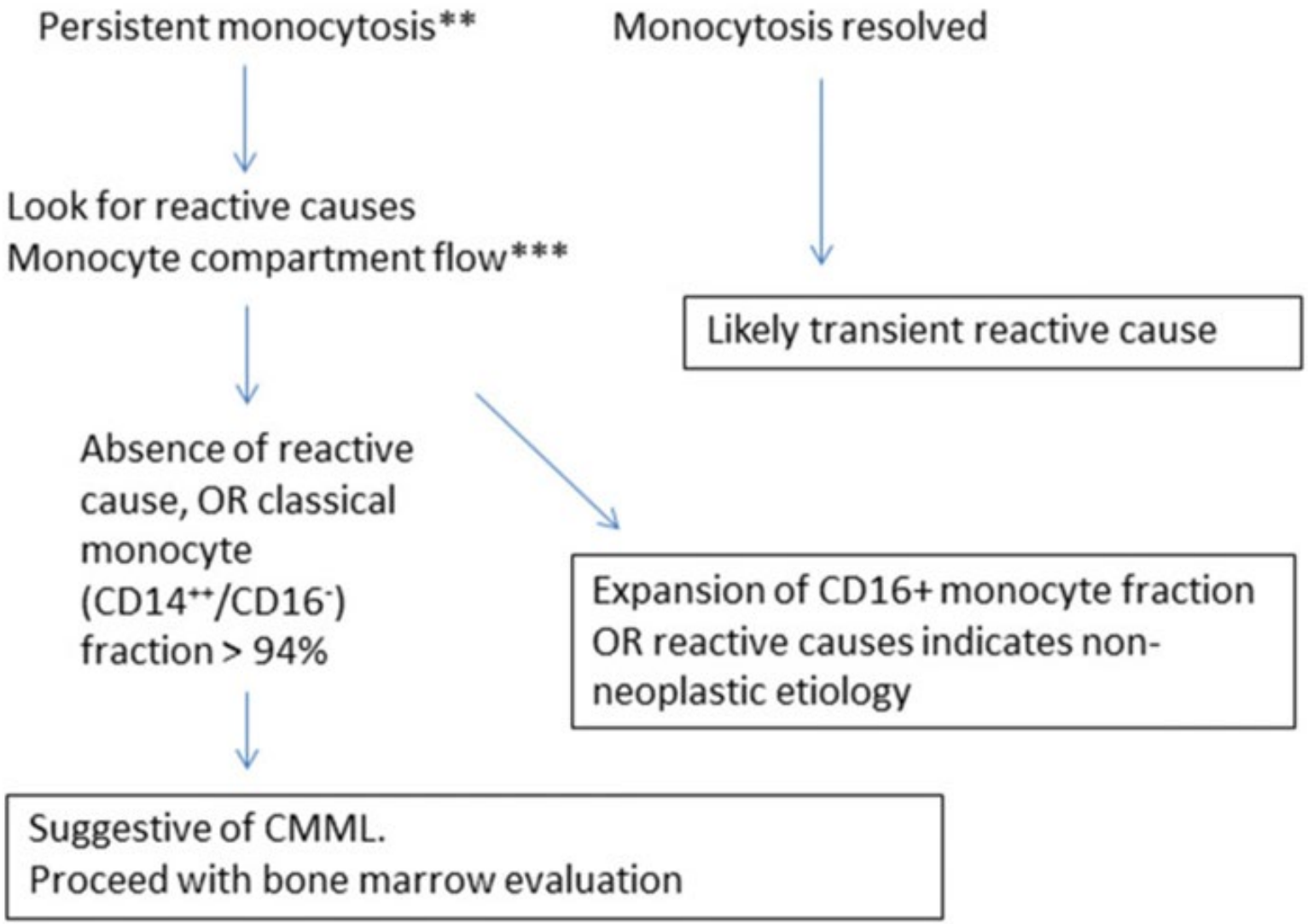
- Transient
  - Acute infections
  - Myocardial infarction
  - Bone marrow recovery
  - ....
- Persistent
  - Chronic infections
  - Rheumatological diseases
  - ....

Clonal

- Acute
  - Acute monocytic leukemia
  - Acute myelomonocytic leukemia
- Chronic
  - CMML
  - JMML
  - Neoplasm with recurrent rearrangements (PDGFRB, ...)
  - CML
  - MPN with monocytosis
  - ...



Mangaonkar et al. Differential Diagnosis and Workup of Monocytosis: A Systematic Approach to a Common Hematologic Finding. Curr Hematol Malig Rep. 2021 Jun;16(3):267-275..


Persistent monocytosis**
Monocytosis resolved
Look for reactive causes
Monocyte compartment flow***
Likely transient reactive cause
Absence of reactive cause, OR classical monocyte (CD14++/CD16-) fraction > 94%
Expansion of CD16+ monocyte fraction OR reactive causes indicates non-neoplastic etiology
Suggestive of CMML.
Proceed with bone marrow evaluation

BJH guidelines 2020

- Diagnostic criteria not adapted yet to the new classification
- Bone marrow aspirate should be assessed for monocytes, promonocytes and monoblasts

TABLE 1. Diagnostic criteria for CMML according to WHO.[3]

Persistent peripheral blood monocytosis (≥1000/μL), with monocytes accounting for ≥10% of the WBC count
Not meeting WHO criteria for *BCR-ABL1*-positive CML, PMF, PV, or ET†
No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
<20% blasts (including myeloblasts, monoblasts, and promonocytes) in the blood and BM
Dysplasia in 1 or more myeloid lineages ***or*** If myelodysplasia is absent or minimal, but all other criteria are met, and: • an acquired clonal cytogenetic or molecular genetic abnormality is present in hematopoietic cells‡ or • the monocytosis has persisted for ≥3 months and all other causes of monocytosis have been excluded

† A previous documented history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2*, *CALR*, or *MPL*) tend to support MPN with monocytosis rather than CMML.

‡ In the appropriate clinical context, mutations in genes often associated with CMML (e.g. *TET2*, *SRSF2*, *ASXL1* and *SETBP1*) support the diagnosis. However, some of these mutations can be age-related or present in other neoplasms; therefore, these genetic findings must be interpreted with caution.

Abbreviations: BM: bone marrow; CML: chronic myeloid leukaemia; ET: essential thrombocythemia; MPN: myeloproliferative neoplasms; PMF: primary myelofibrosis; PV: polycythemia vera; WBC: white blood cell.

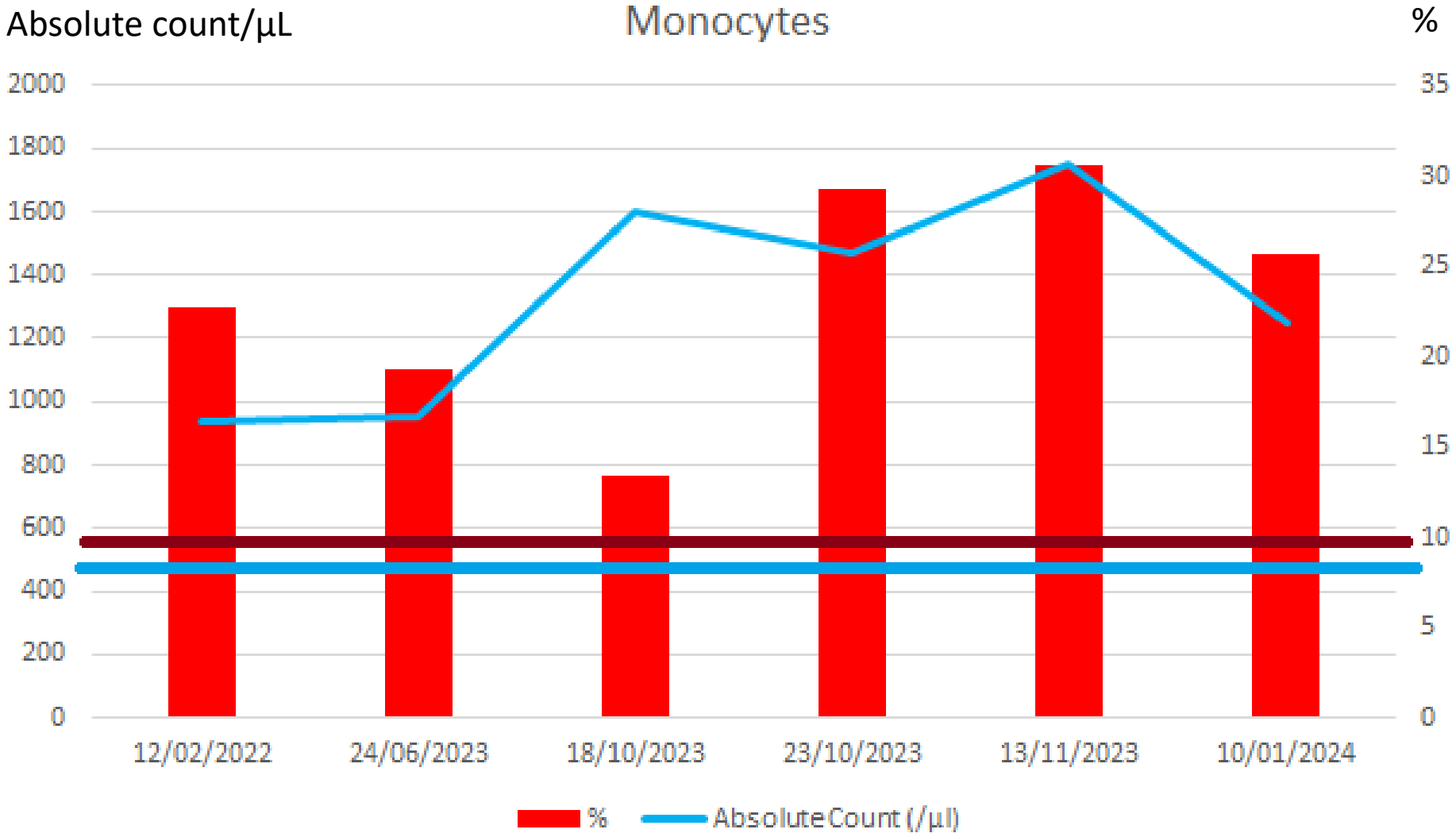
Beckers et al. Belgian guidelines for diagnosis and treatment of chronic myelomonocytic leukaemia (BELG J HEMATOL 2020;12(2):66-76)

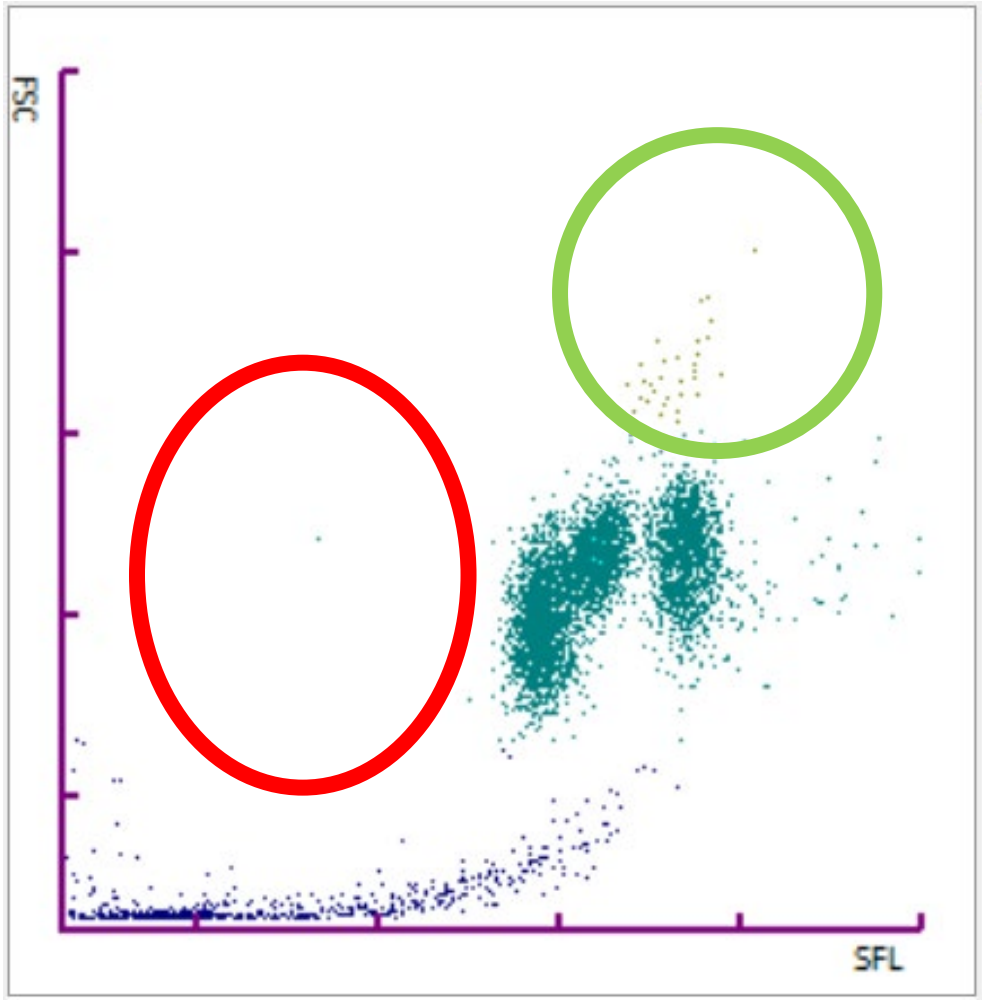
Recommendations

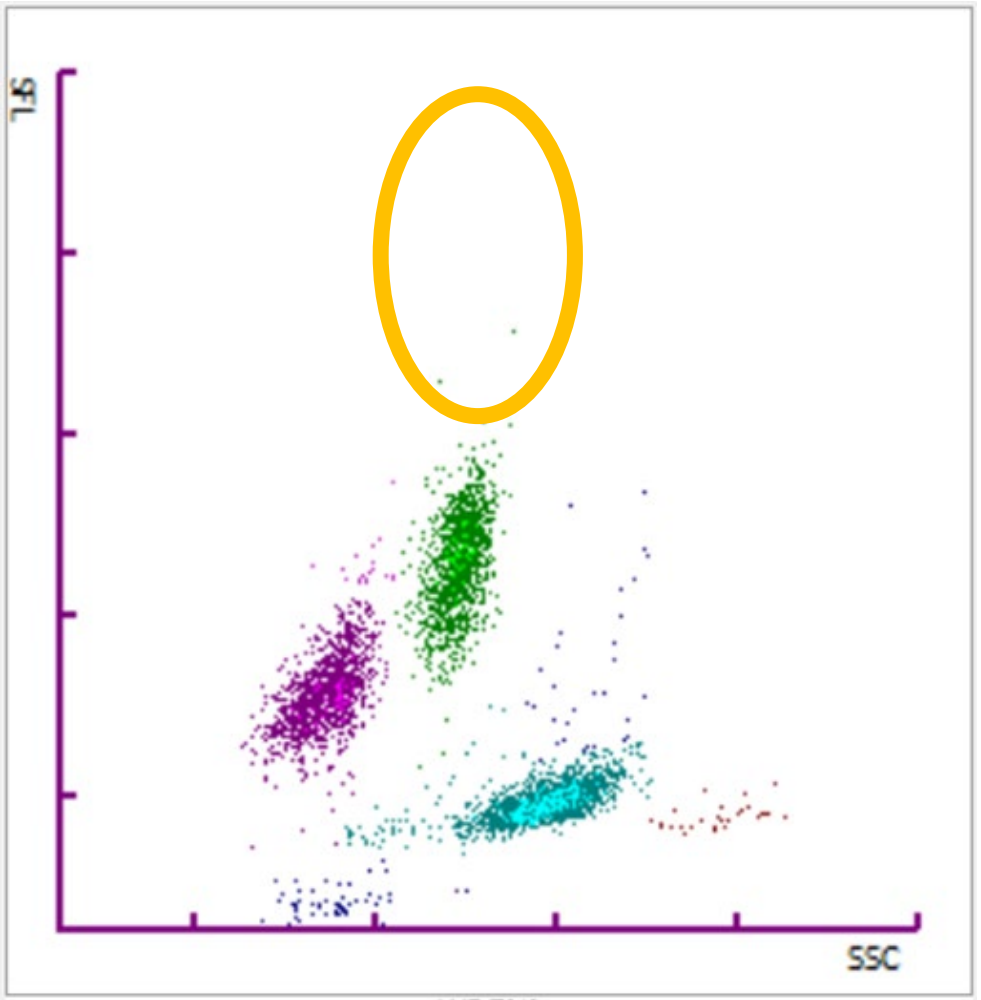
- Complete blood count including peripheral blood smear
- Bone marrow aspirate
- Bone marrow biopsy
- Cytogenetic analysis (at least twenty mitoses) of preferably bone marrow is mandatory in the diagnostic work-up of CMML
- Mutational analysis, using a conventional myeloid panel should also be included

Case 1

- 87y woman
- Medical History:
  - Partial colectomy
  - Hysterectomy
  - Age related macula degeneration
- Admitted for a femur fracture and osteoporosis


Absolute count/µL
Monocytes
%
2000
1800
1600
1400
1200
1000
800
600
400
200
0
35
30
25
20
15
10
5
0
12/02/2022
24/06/2023
18/10/2023
23/10/2023
13/11/2023
10/01/2024
%
Absolute Count (/µl)





WBC 4740/µL

38,6% neutrophils

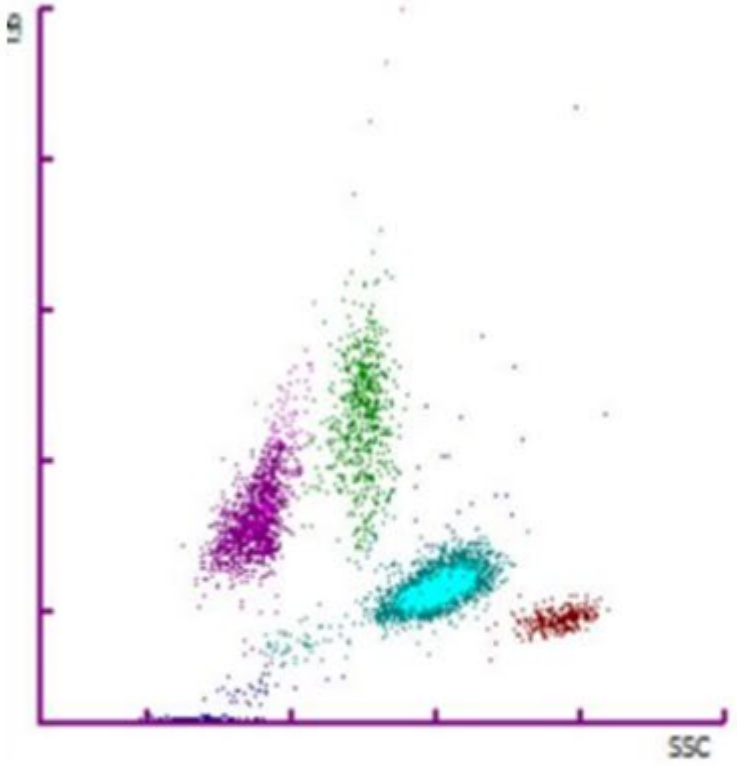
29,6% lymphocytes

29,8% monocytes

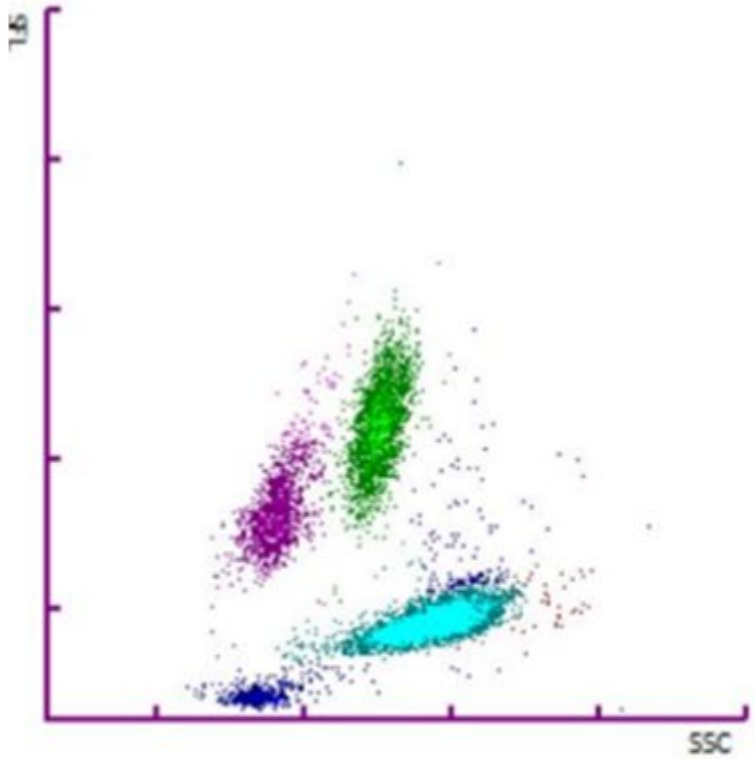
0,6% eosinophils

0,8% basophils

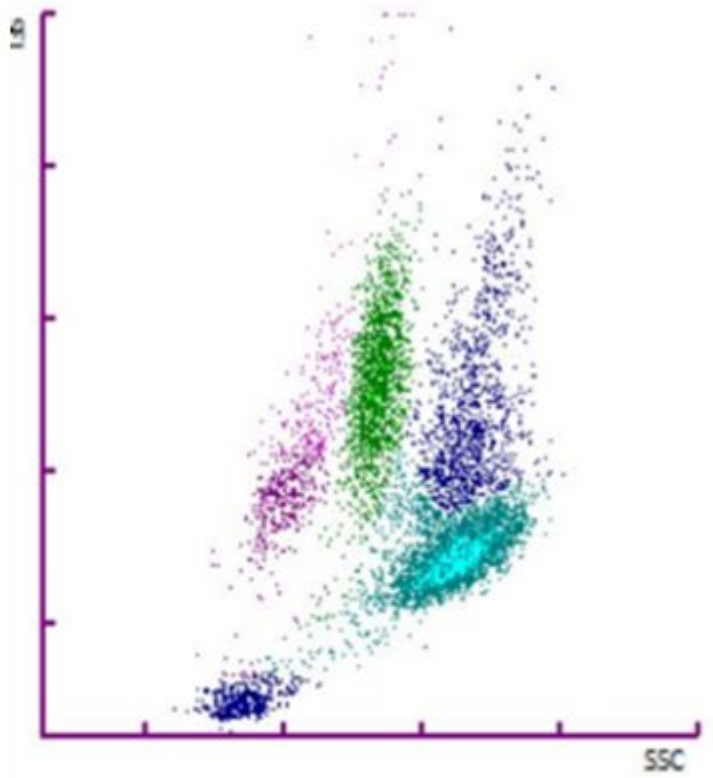
No nRBCs



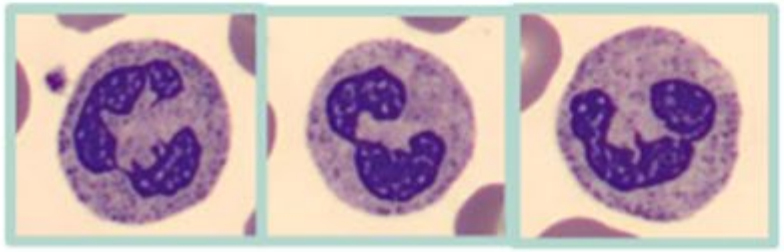
Normal

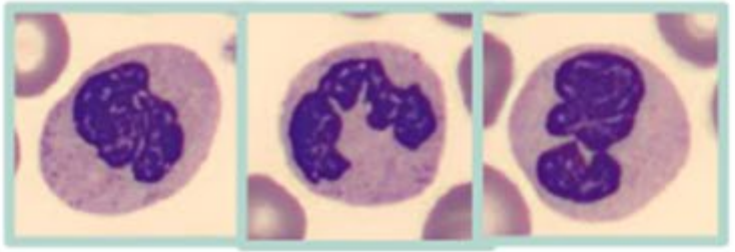


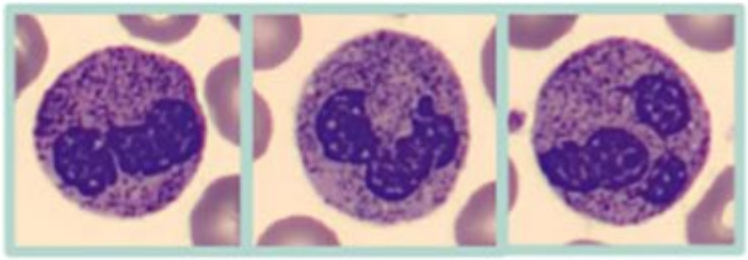
CMML



Reactive



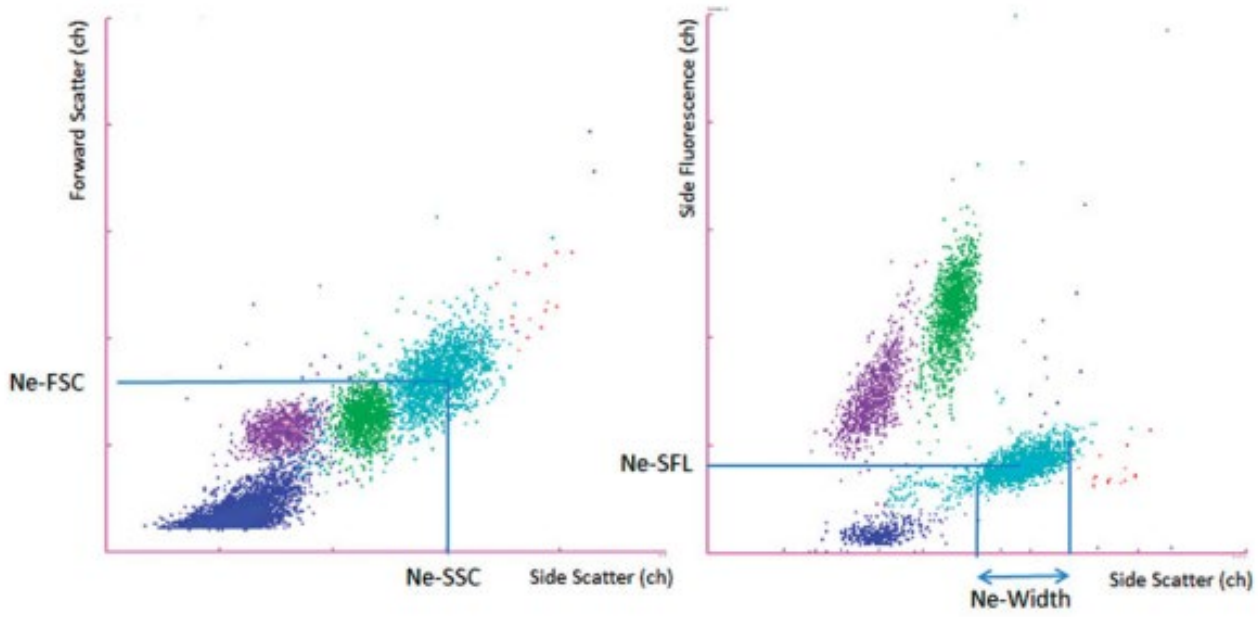




Mono-dysplasia score

- Calculation based on
  - Monocyte count
  - Neutrophil count/Monocyte cound
  - NE-WX

  - Positive if > 0,160
  - Sensitivity: 92,3%
  - Specificity: 93,6%



$$\text{Ne-WX} = \frac{\text{Ne-Width}}{\text{Ne-SSC}} \times 100$$

$$\frac{1}{1+e^{-(-11{,}623+0{,}026*Ne-WX-1{,}385*\frac{Ne}{Mo}+2{,}714*AbsMono)}}$$

Schillinger F et al. (2018): A new approach for diagnosing chronic myelomonocytic leukemia using structural parameters of Sysmex XN analyzers in routine laboratory practice. Scand J Clin Lab Invest. 78(3)

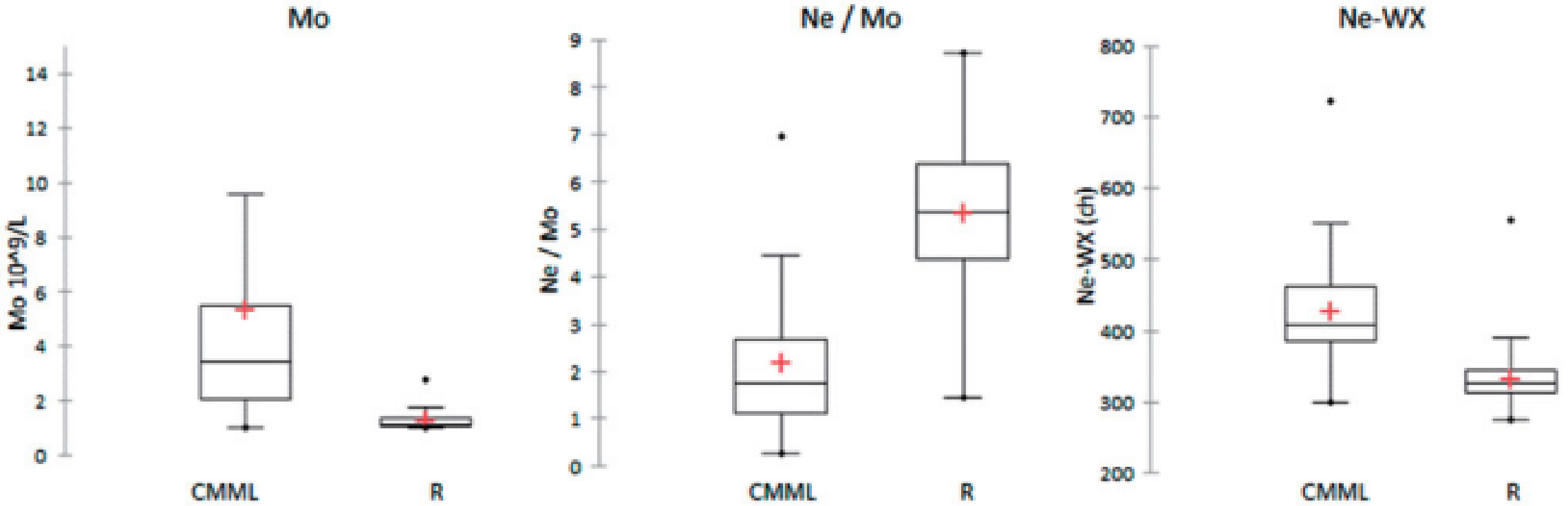
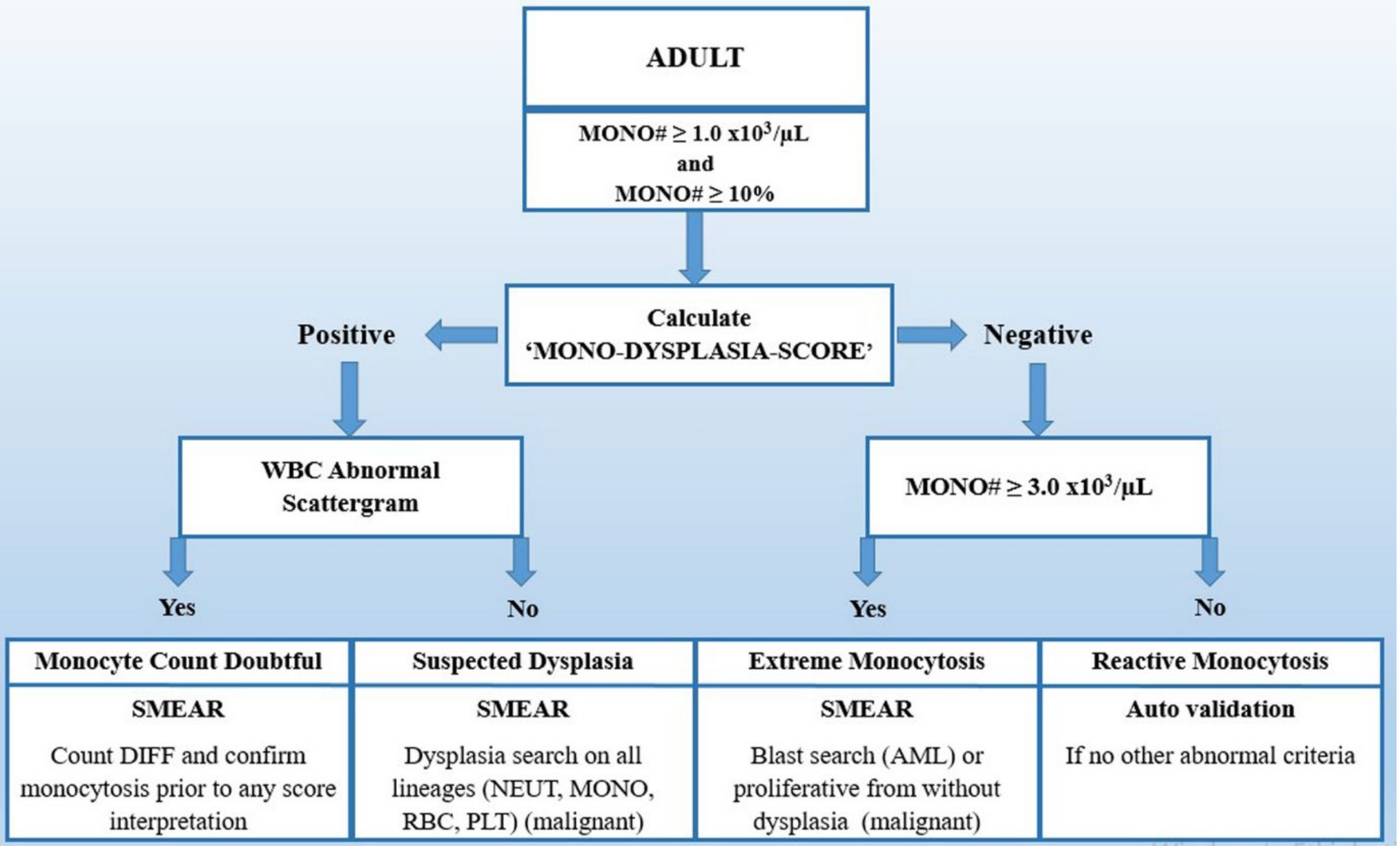


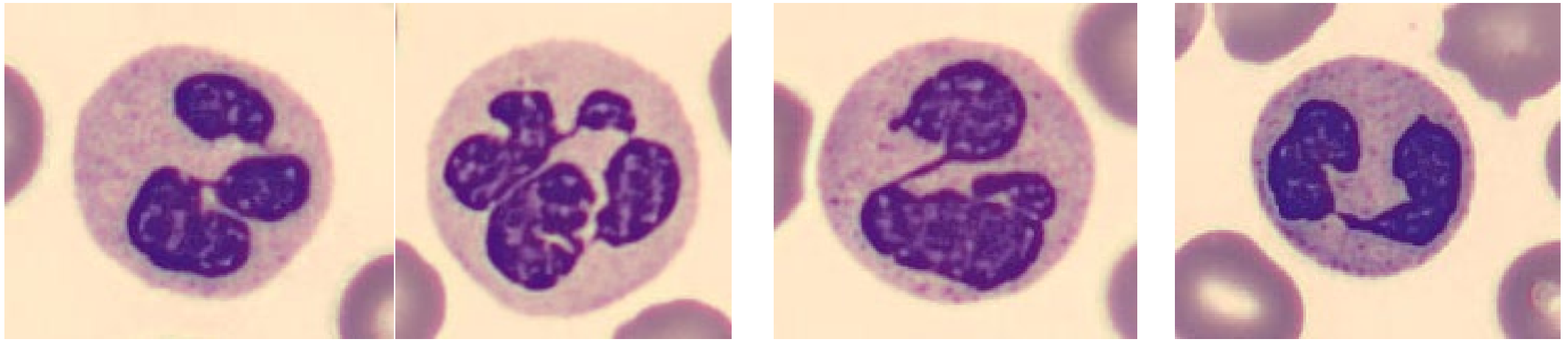
Figure 2. Box-plots of the three most discriminant variables between CMML and reactive monocytosis. R:reactive monocytosis; Mo:monocyte blood count; Ne/Mo: neutrophil/monocyte ratio, Ne-WX:dispersion parameter of neutrophils on the *X* axis.



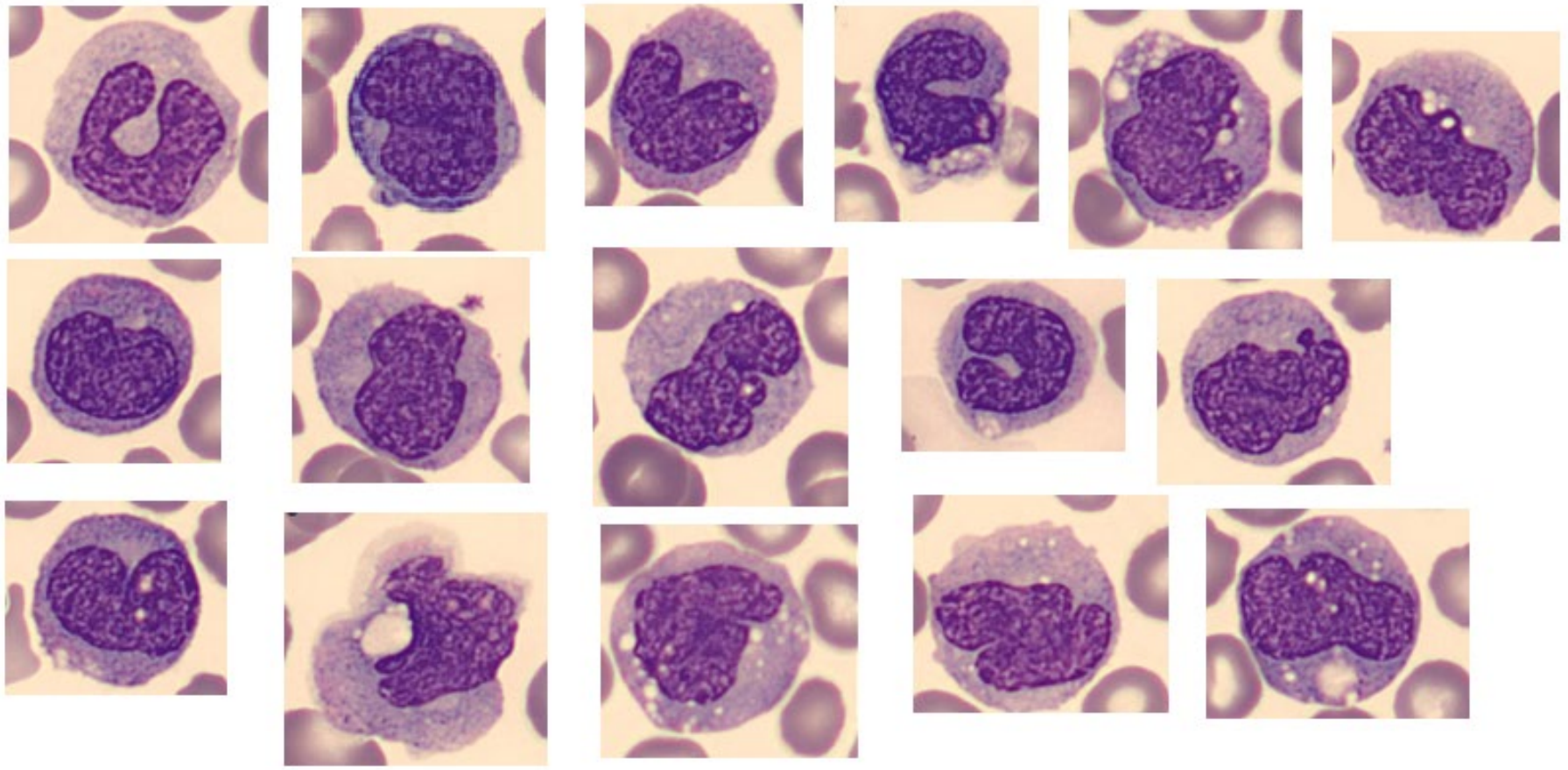
Monocyte Count Doubtful	Suspected Dysplasia	Extreme Monocytosis	Reactive Monocytosis
SMEAR	**SMEAR**	**SMEAR**	**Auto validation**
Count DIFF and confirm monocytosis prior to any score interpretation	Dysplasia search on all lineages (NEUT, MONO, RBC, PLT) (malignant)	Blast search (AML) or proliferative from without dysplasia (malignant)	If no other abnormal criteria

Kocaturk et al. A new approach for diagnosing hematological malignancies using monocytosis workflow optimization and abnormal lymphocyte/blast flag of Sysmex XN series of blood count analyzers. Int J Lab Hematol. 2020 Dec;42(6):744-749.

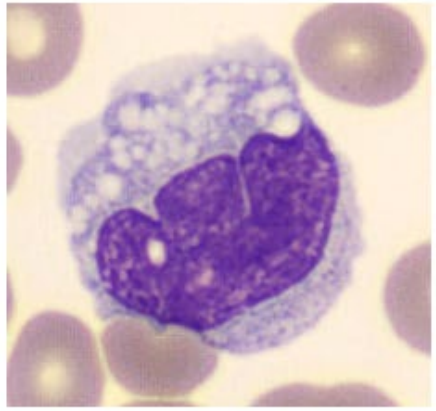
Neutrophils

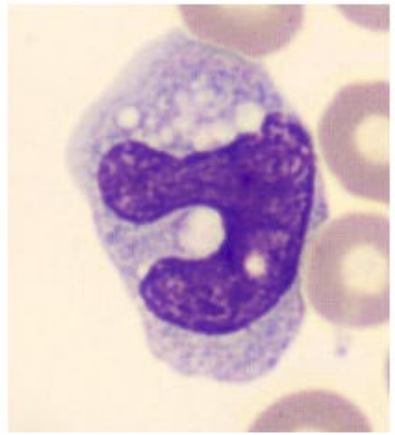


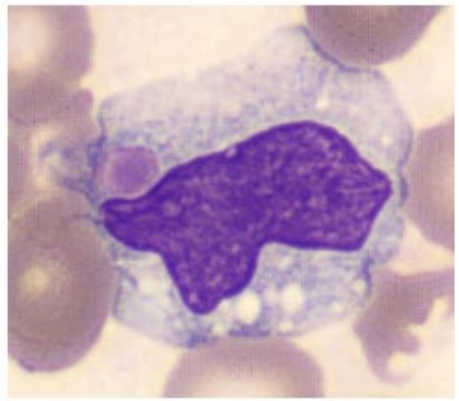
Monocytes



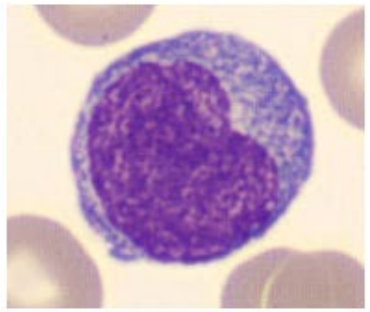
Mature monocyte

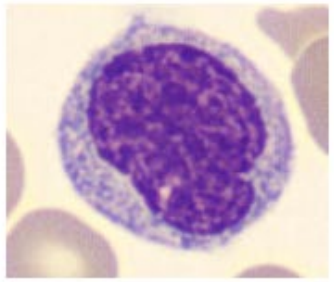


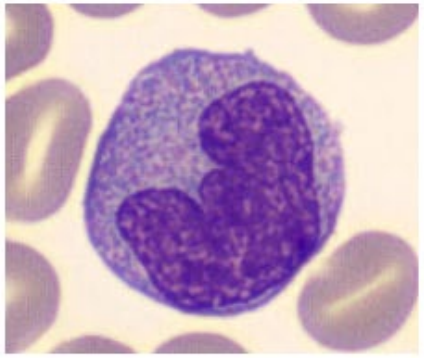




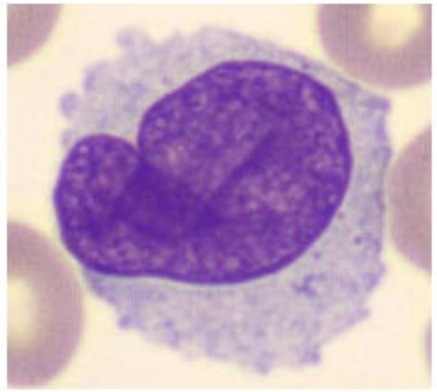
Immature monocyte

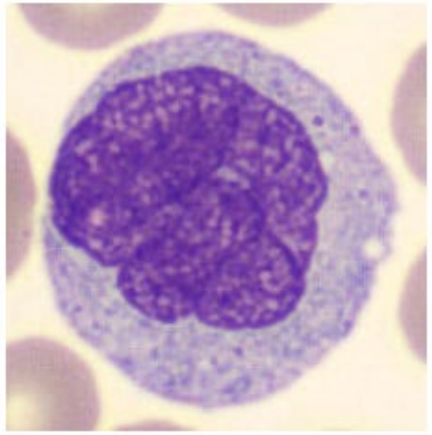


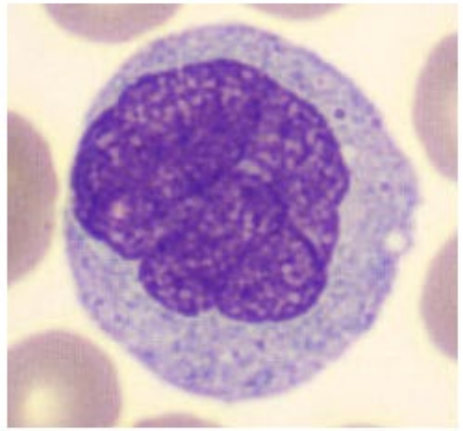




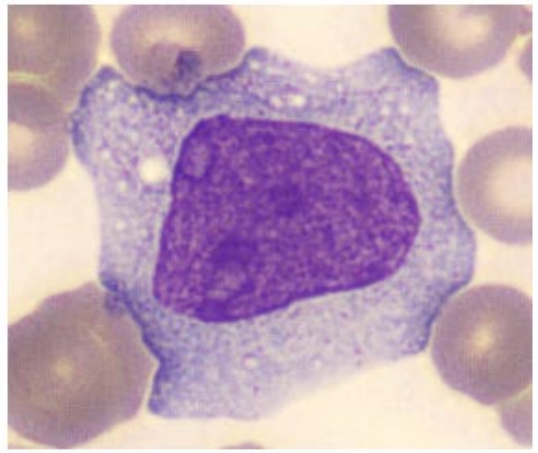
Promonocyte

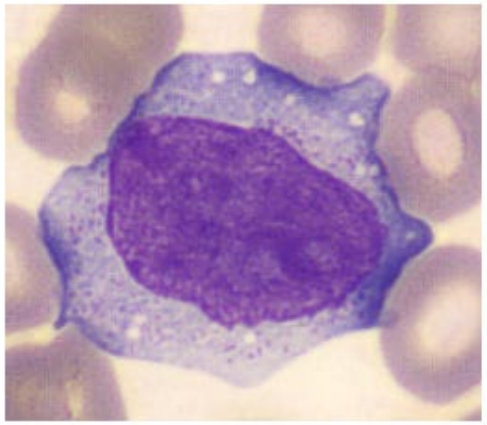


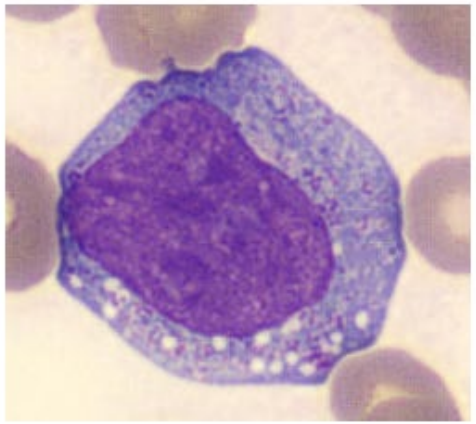




Monoblast







Cellwiki.net

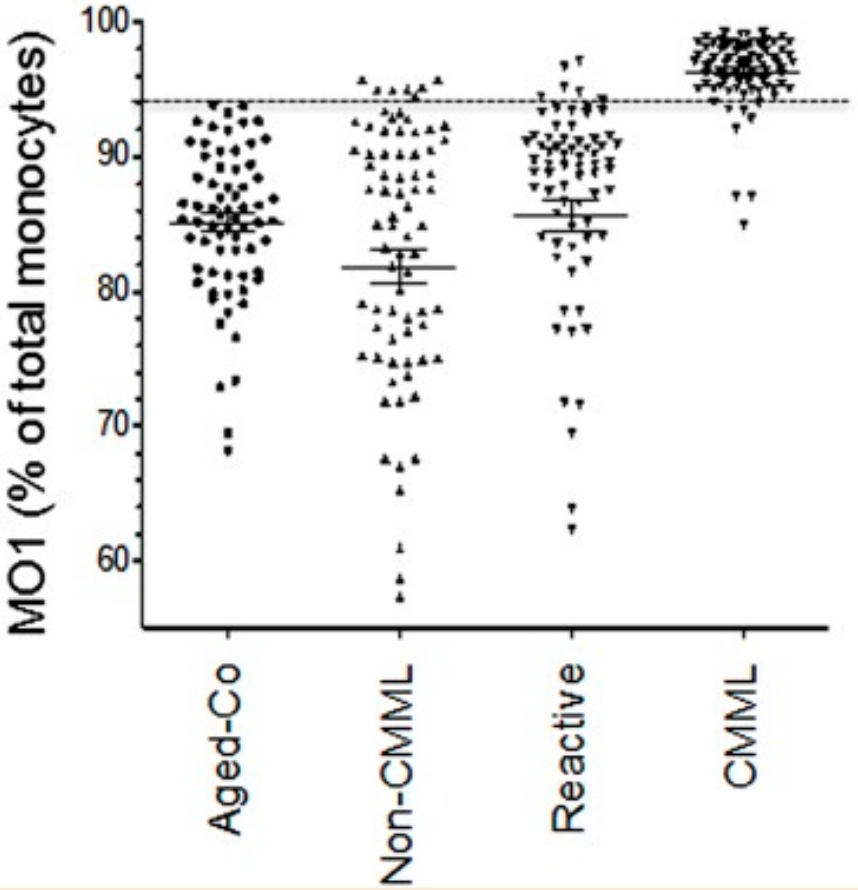
Flow cytometry

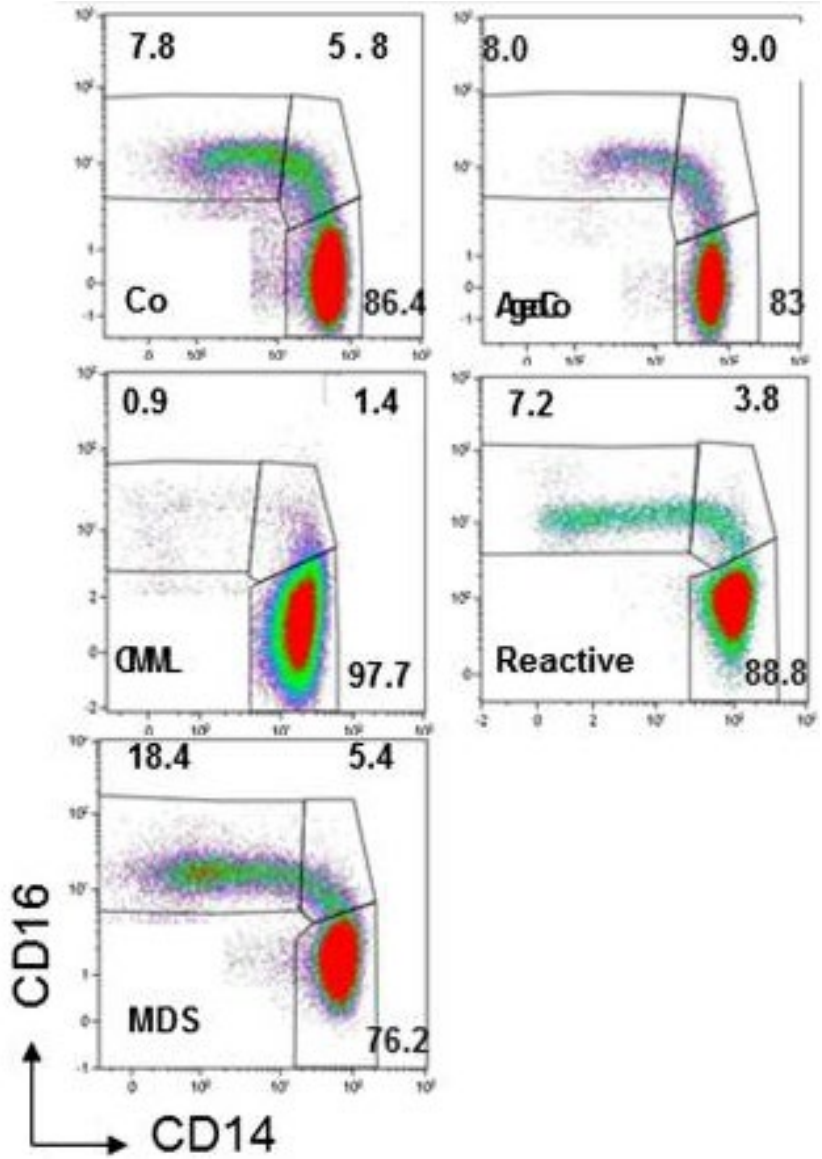
- Monocyten subsetanalysis
  - cMo CD14++ CD16-
  - iMo CD14++ CD16+
  - ncMo CD14 low/neg CD16++

- Sensitivity 90,6-91,9%, specificity 94,1-95,1%
- CMML based on old WHO 2016 criteria

Selimoglu-Buet D, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukaemia. Blood. 2015; 125(23):3618-26.

Flowcytometry





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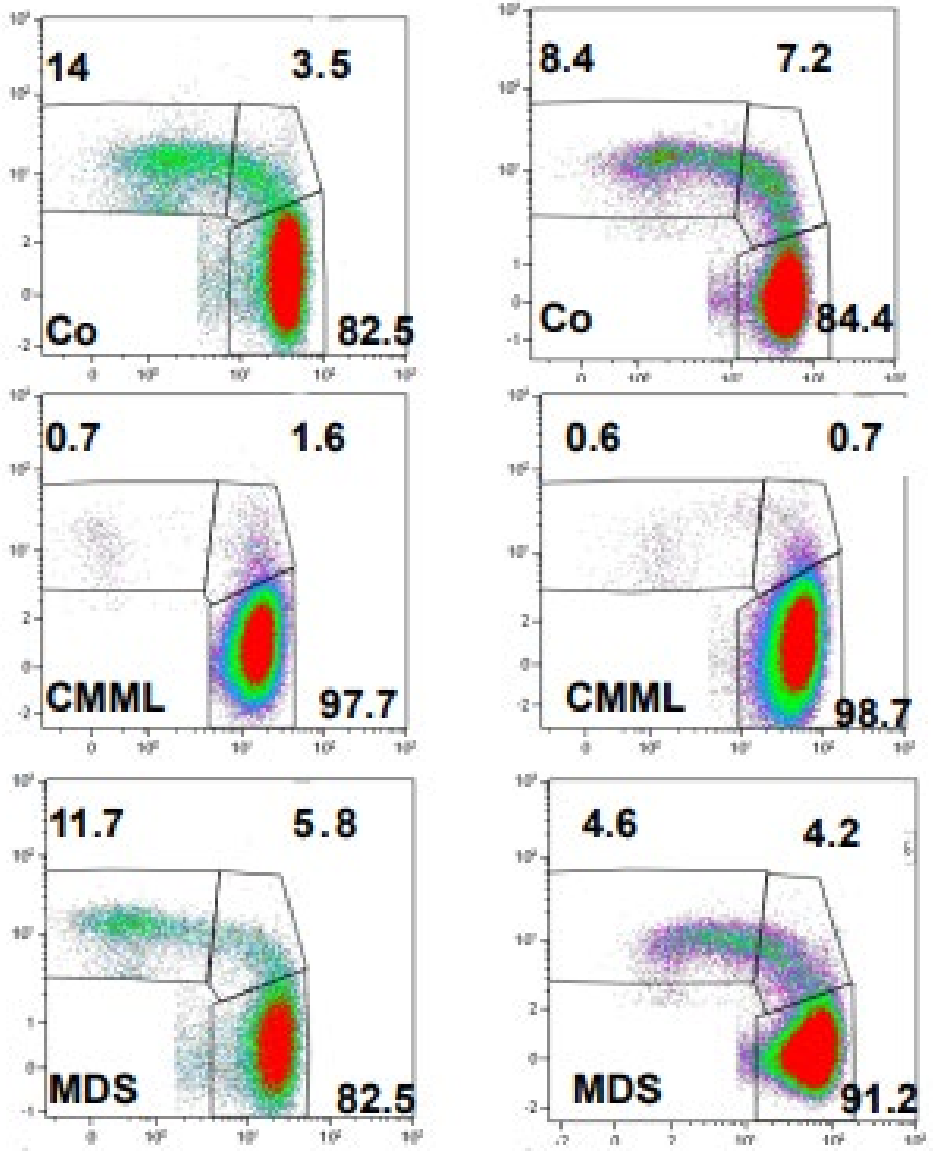

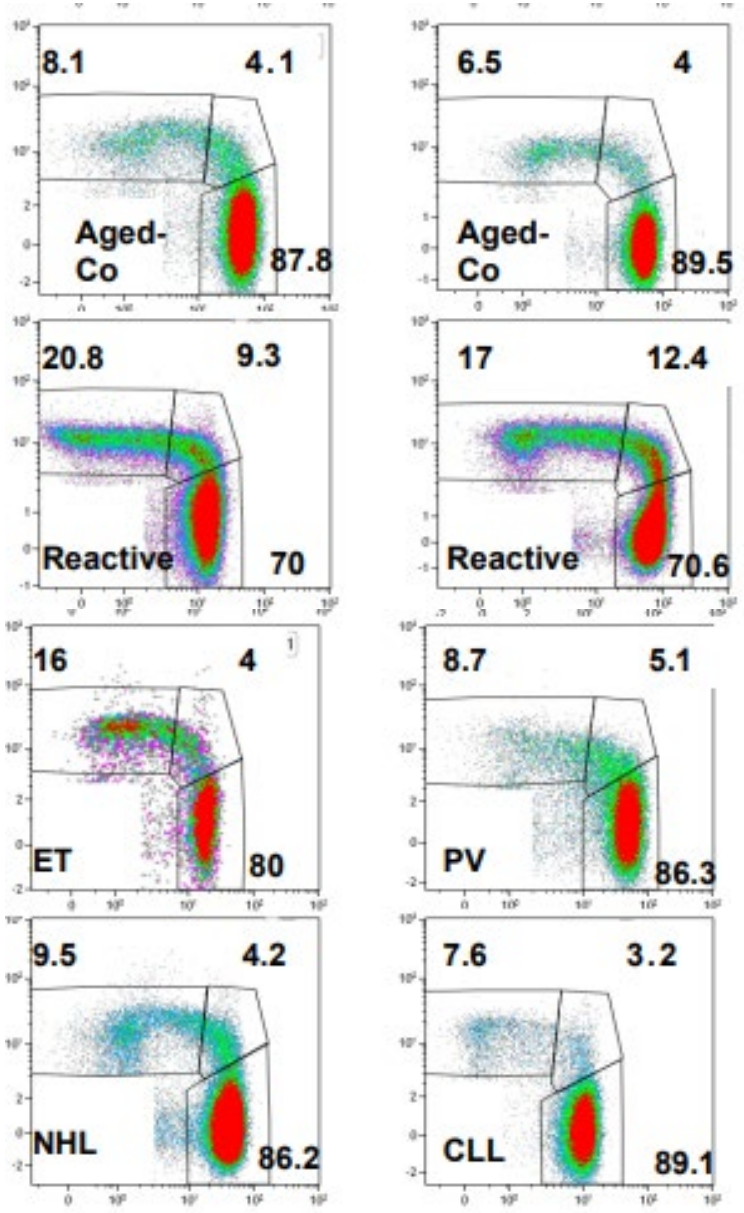

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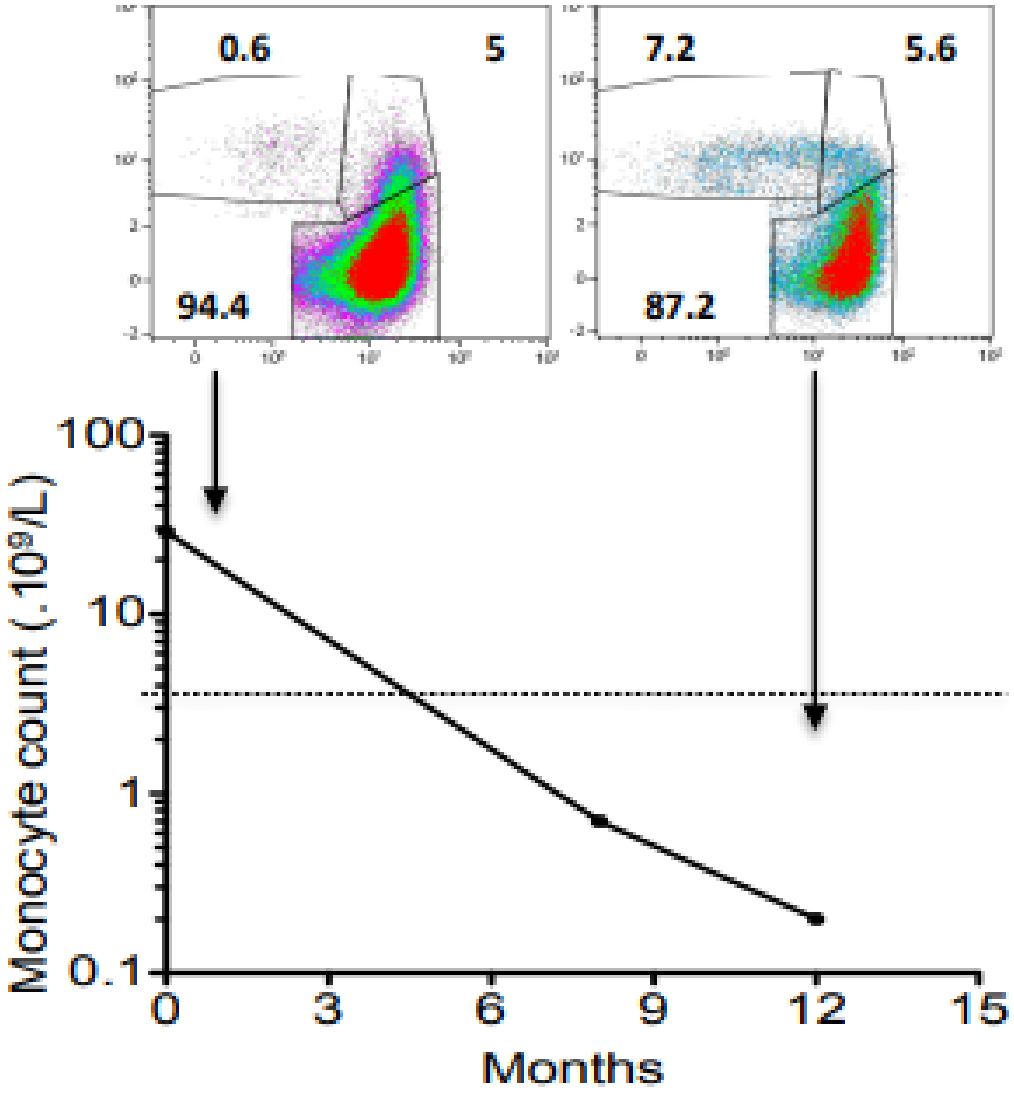
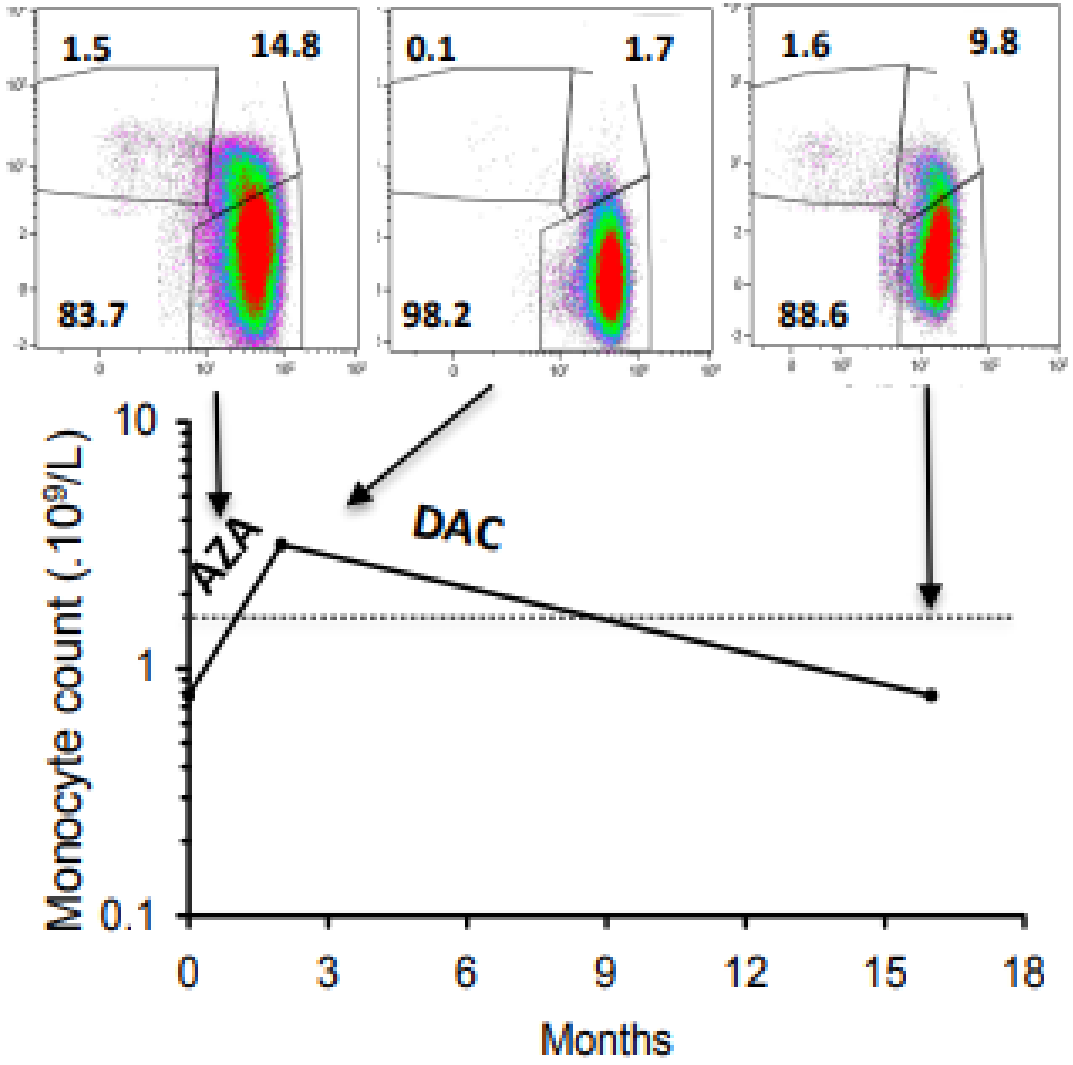
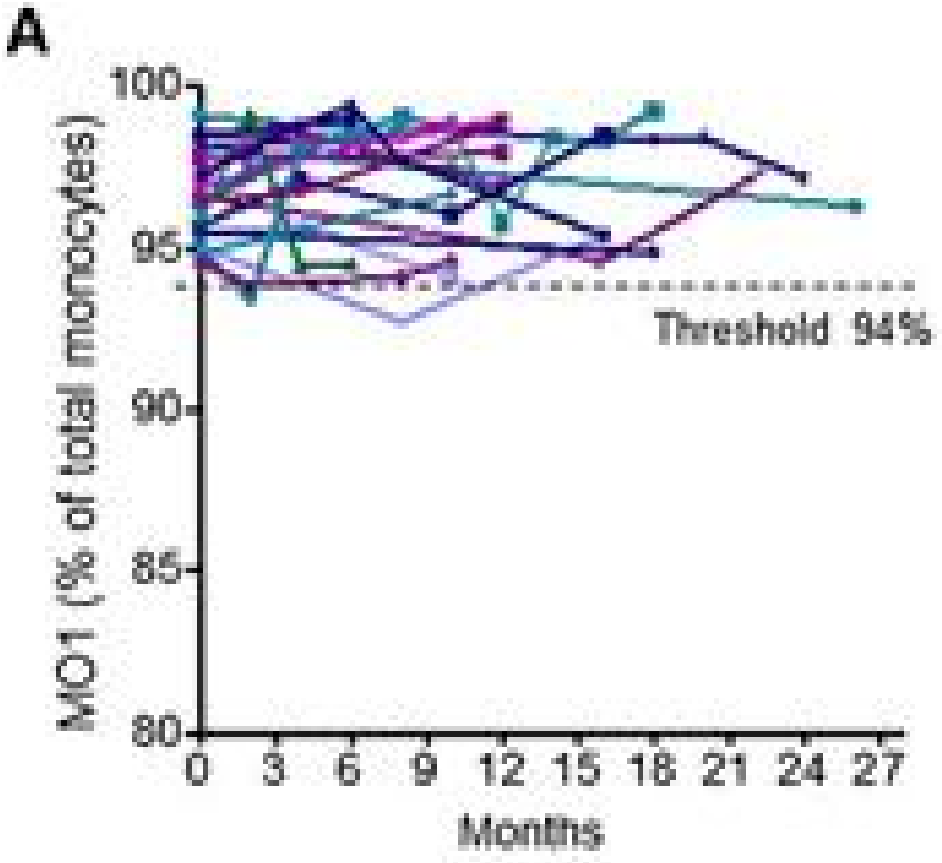
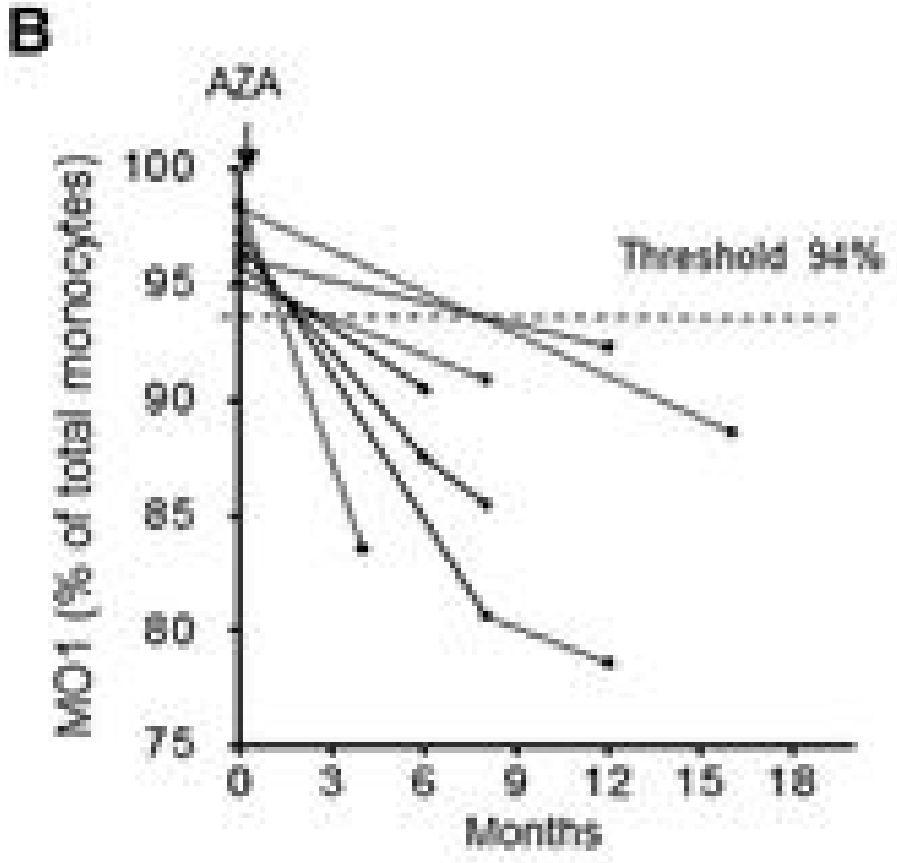
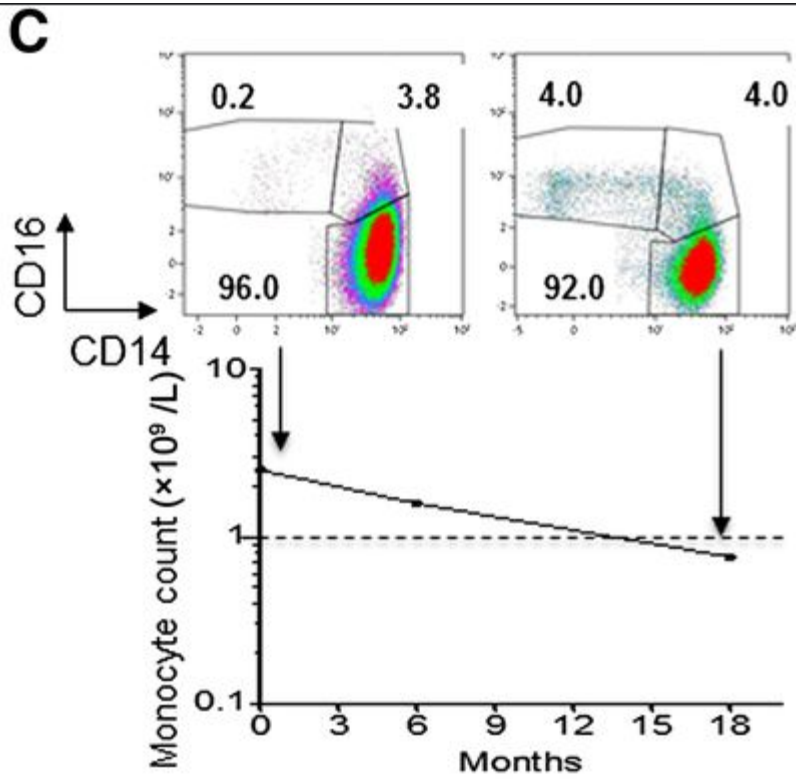


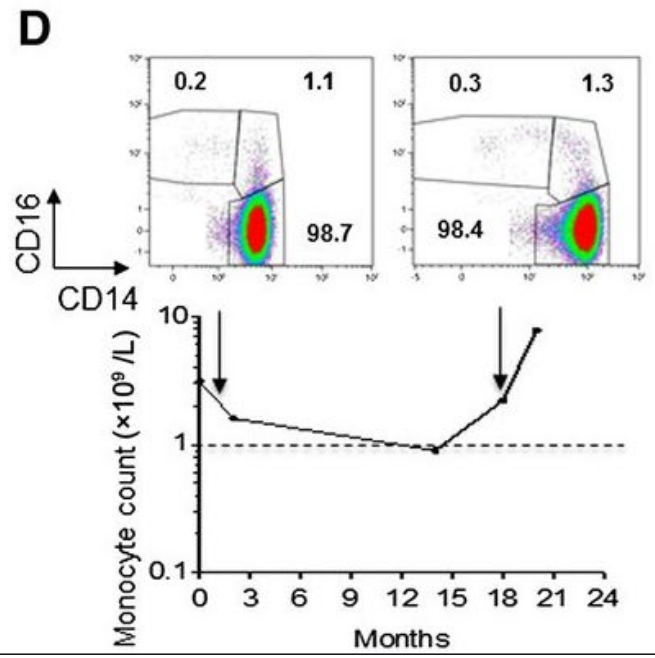


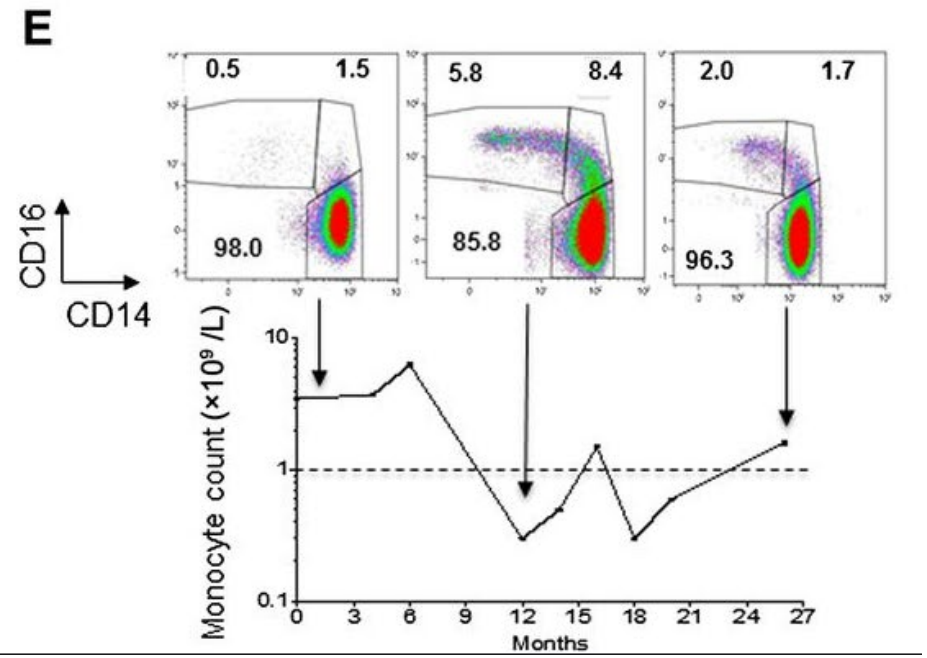
Selimoglu-Buet D, et al. Characteristic repartition of monocyte subsets as a diagnostic signature of chronic myelomonocytic leukaemia. Blood. 2015; 125(23):3618-26.

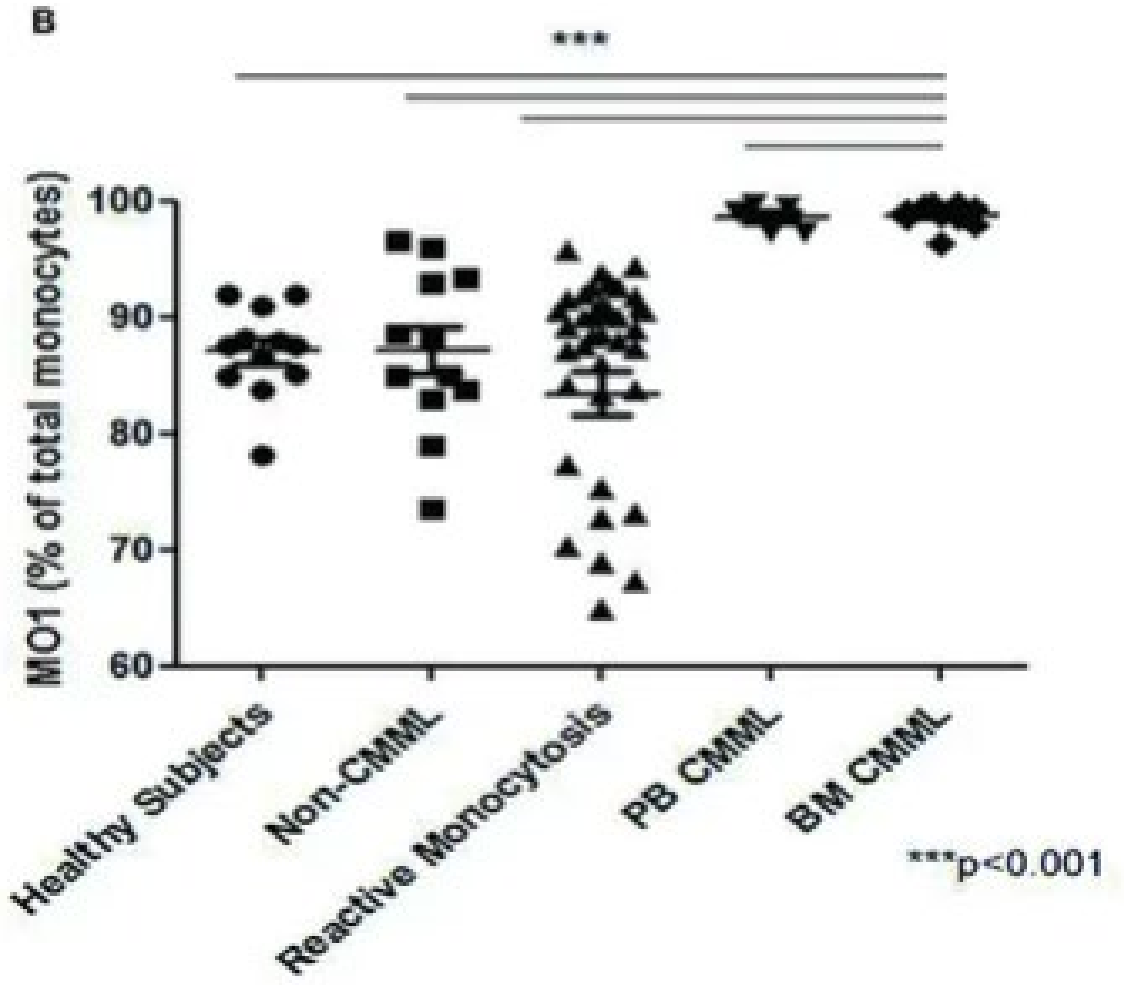

A
MO1 (% of total monocytes)
100
95
90
85
80
Threshold 94%
0 3 6 9 12 15 18 21 24 27
Months


B
AZA
MO1 (% of total monocytes)
100
95
90
85
80
75
Threshold 94%
0 3 6 9 12 15 18
Months

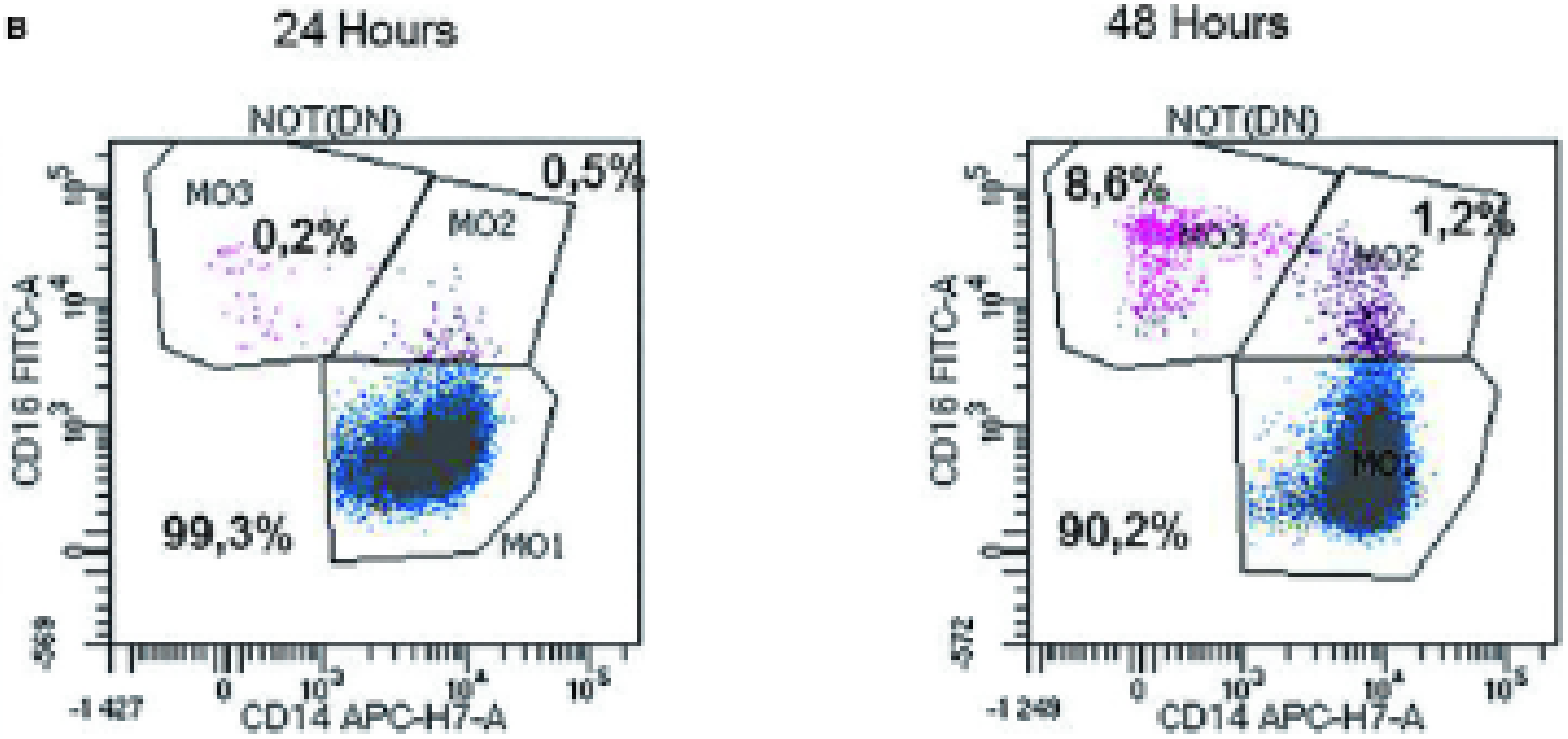

C
0.2
3.8
96.0
4.0
4.0
92.0
CD16
CD14
Monocyte count (×10⁹ /L)
10
1
0.1
0 3 6 9 12 15 18
Months


D
0.2
1.1
98.7
0.3
1.3
98.4
CD16
CD14
Monocyte count (×10⁹ /L)
10
1
0.1
0 3 6 9 12 15 18 21 24
Months

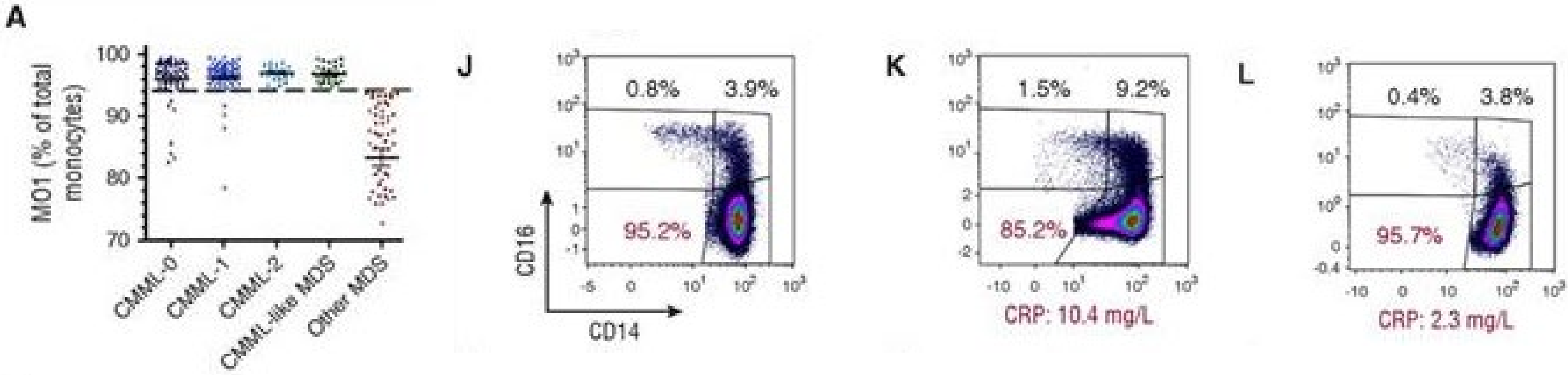

E
0.5
1.5
98.0
5.8
8.4
85.8
2.0
1.7
96.3
CD16
CD14
Monocyte count (×10⁹ /L)
10
1
0.1
0 3 6 9 12 15 18 21 24 27
Months



Picot et al. Evaluation by Flow Cytometry of Mature Monocyte Subpopulations for the Diagnosis and Follow-Up of Chronic Myelomonocytic Leukemia. Front Oncol. 2018 Apr 12;8:109.



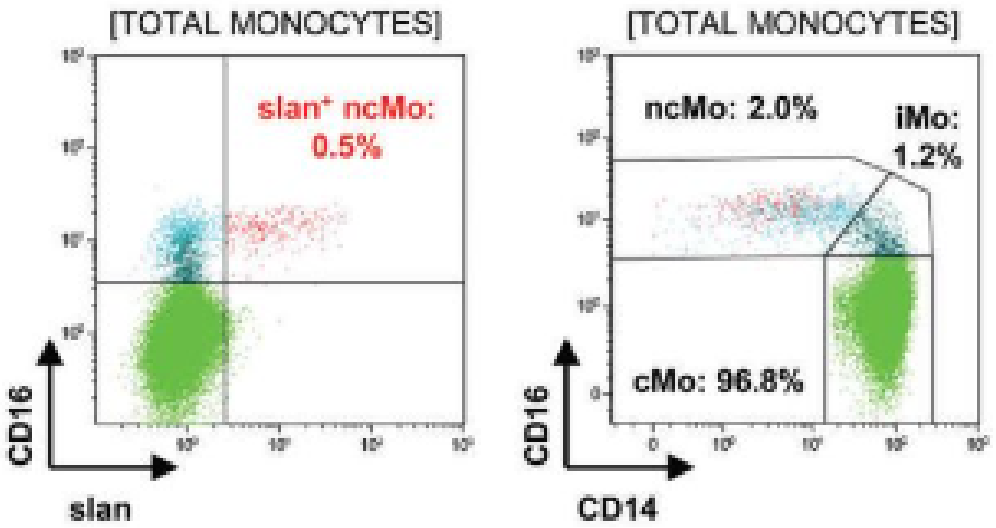
Picot et al. Evaluation by Flow Cytometry of Mature Monocyte Subpopulations for the Diagnosis and Follow-Up of Chronic Myelomonocytic Leukemia. Front Oncol. 2018 Apr 12;8:109.



Selimoglu-Buet et al. Accumulation of classical monocytes defines a subgroup of MDS that frequently evolves into CMML. Blood. 2017 Aug 10;130(6):832-835.

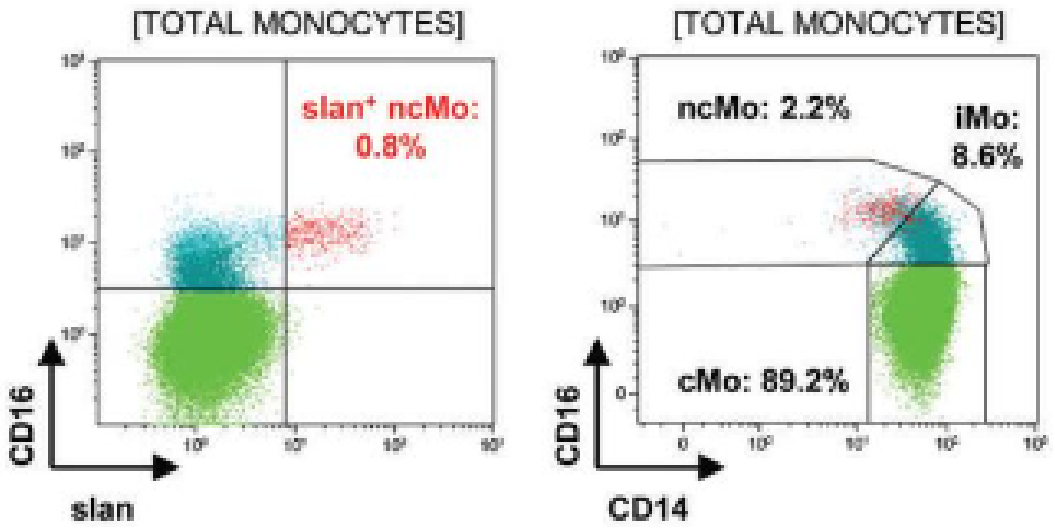
A

Example of typical CMML



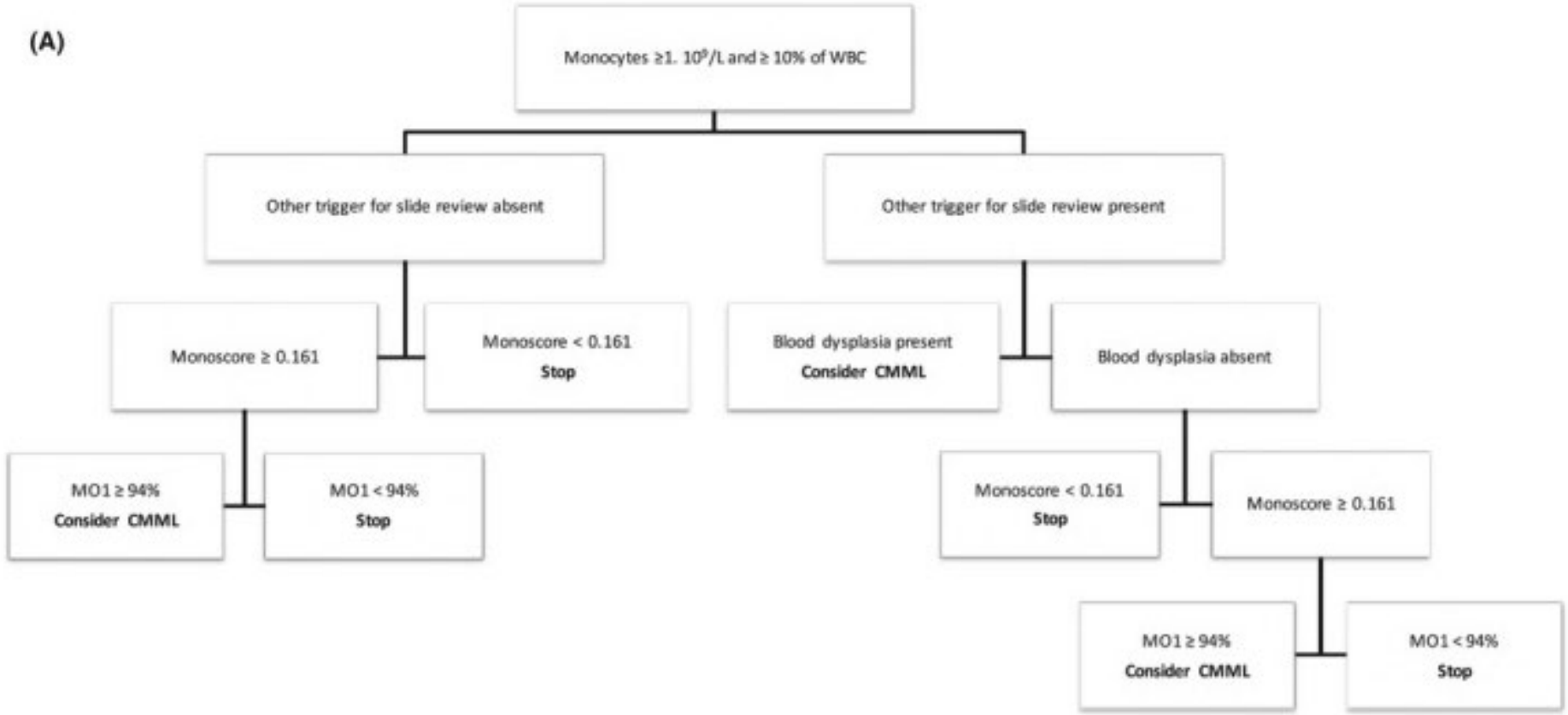
B

Example of inflammatory CMML



Tarfi et al. Disappearance of slan-positive non-classical monocytes for diagnosis of chronic myelomonocytic leukemia with associated inflammatory state. Haematologica. 2019;105:e147–e152.

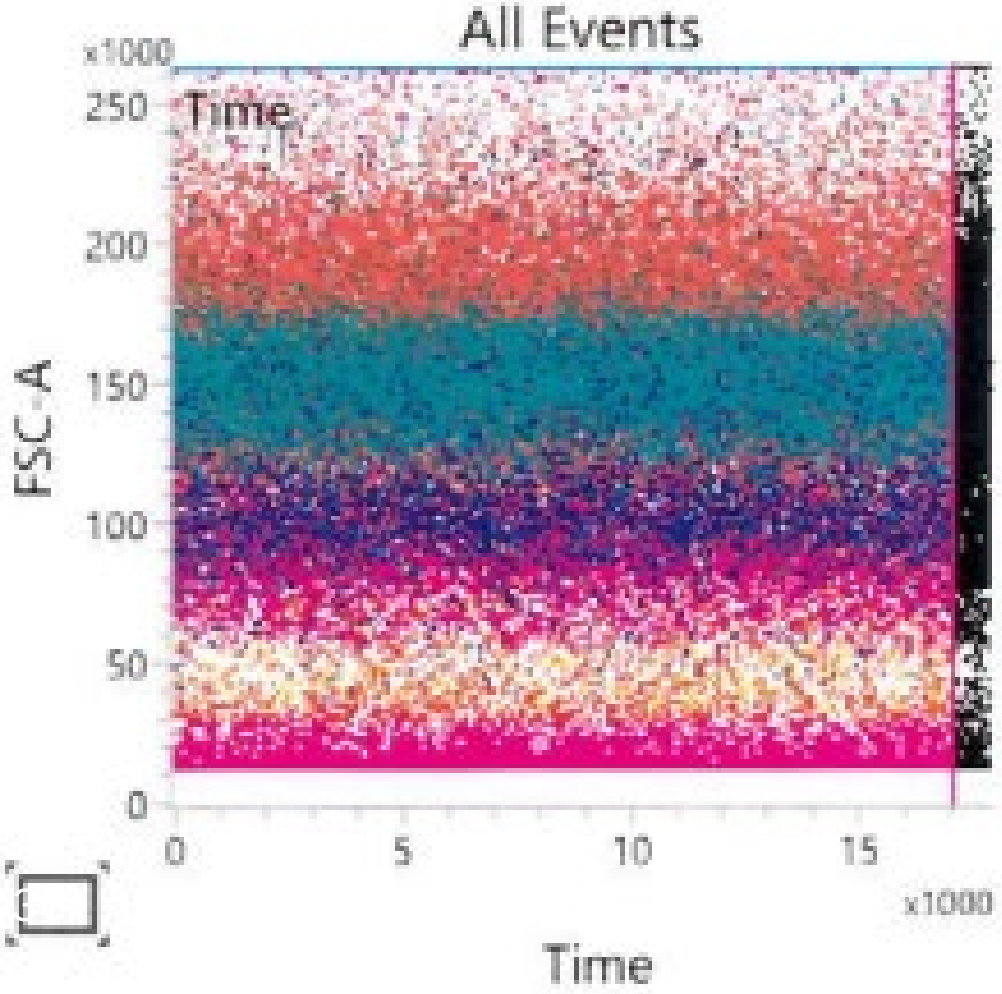
Approach mono-dysplasia + flow

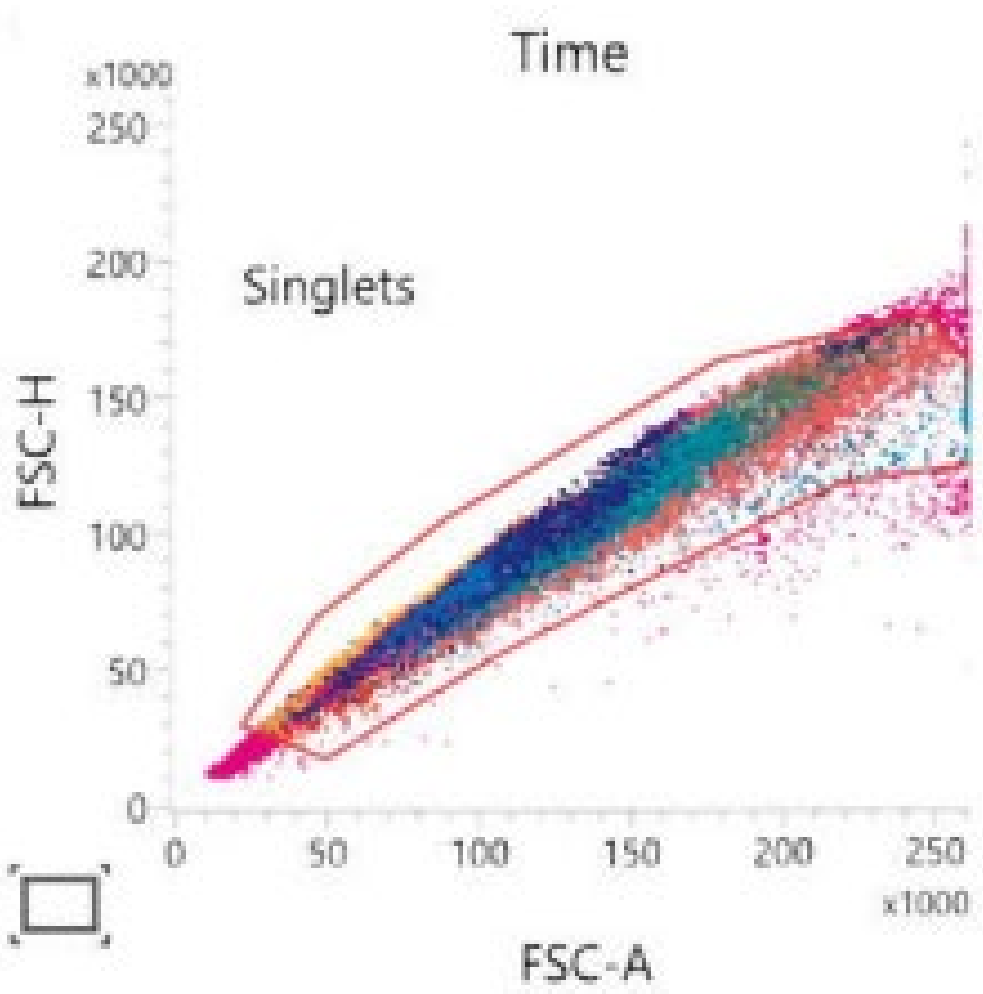


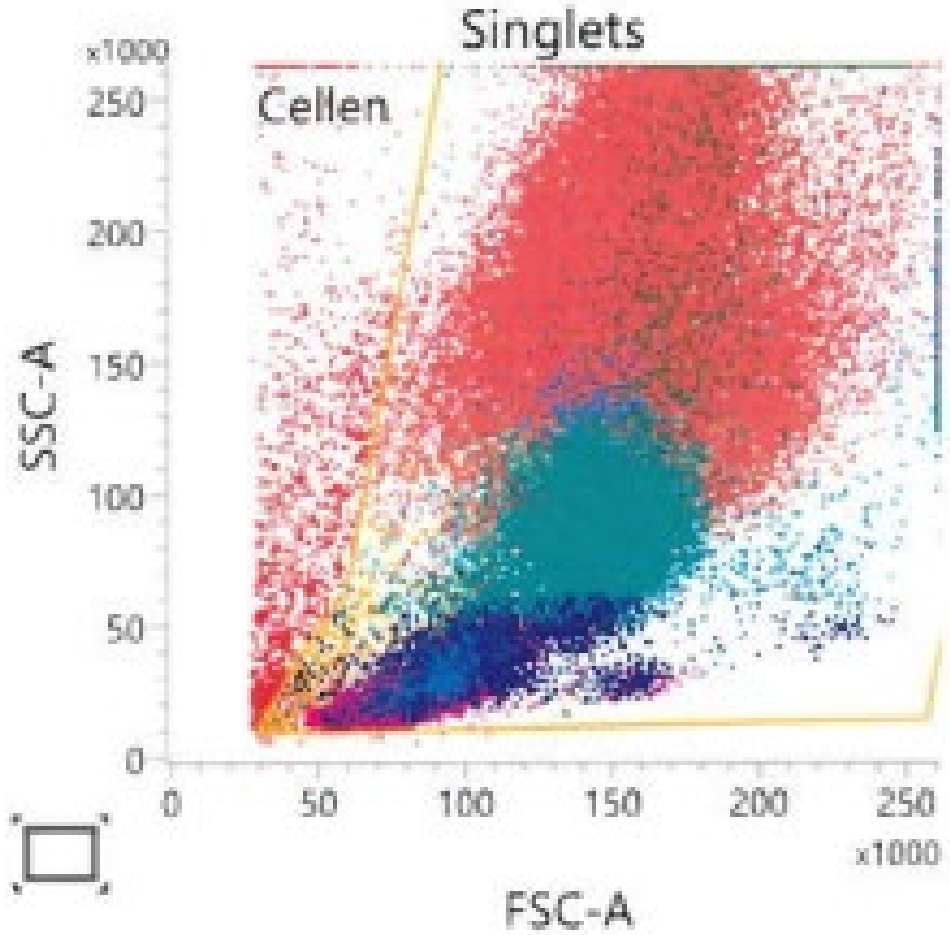
Zhu et al. A hierarchical approach in the diagnostic workflow of chronic myelomonocytic leukemia: Pivotal role of the "Mono-dysplasia-score" combined with flow cytometric quantification of monocyte subsets. Int J Lab Hematol. 2019 Dec;41(6):782-790.

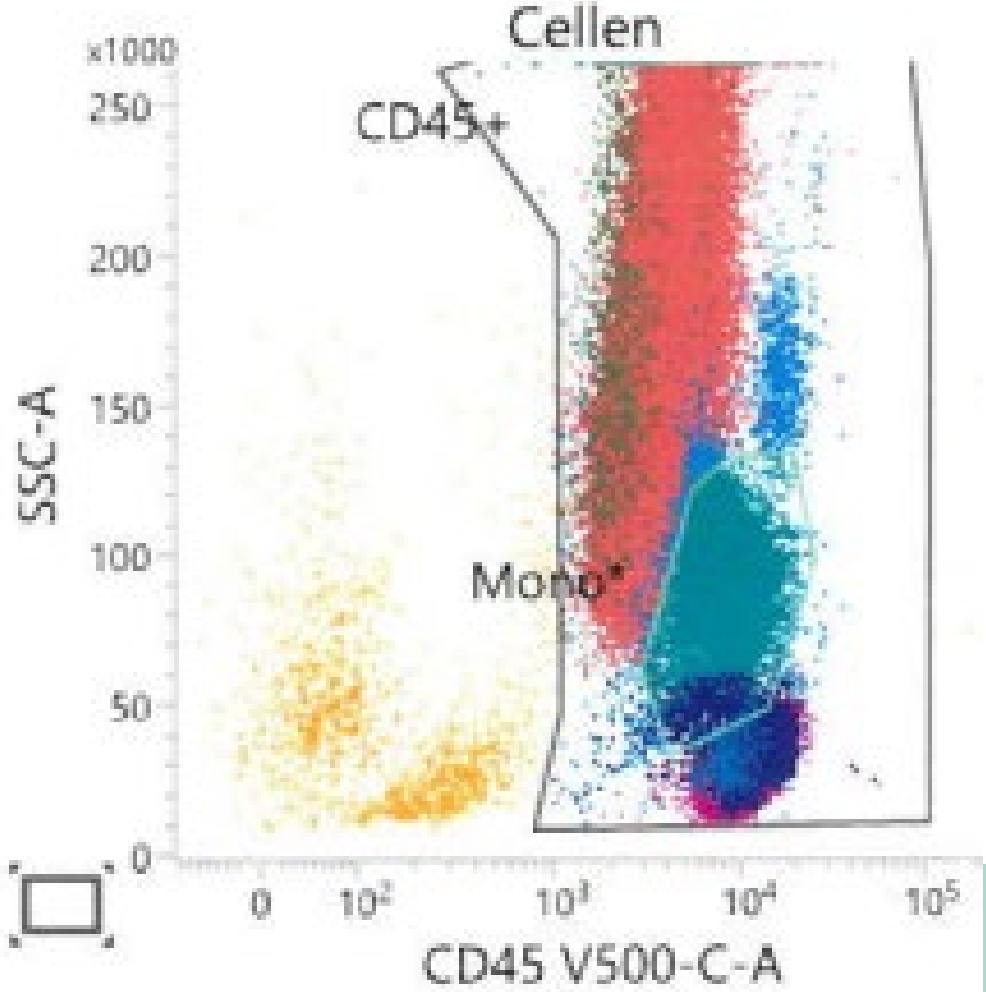
Jessa Ziekenhuis

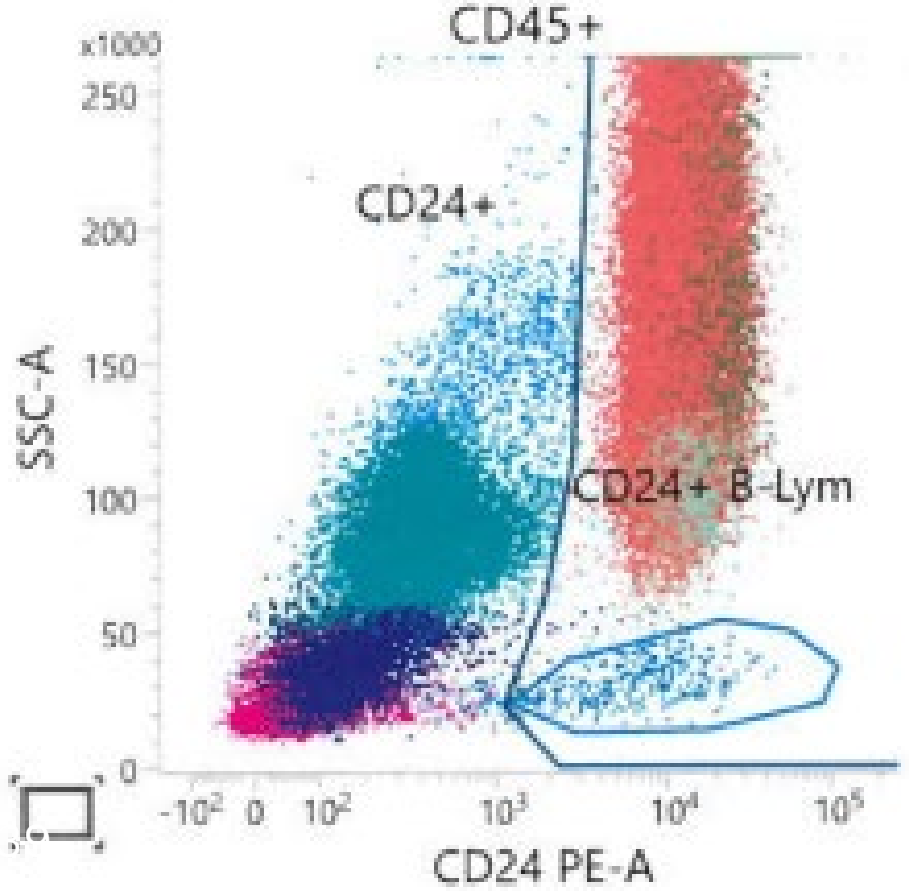
Flow cytometry blood

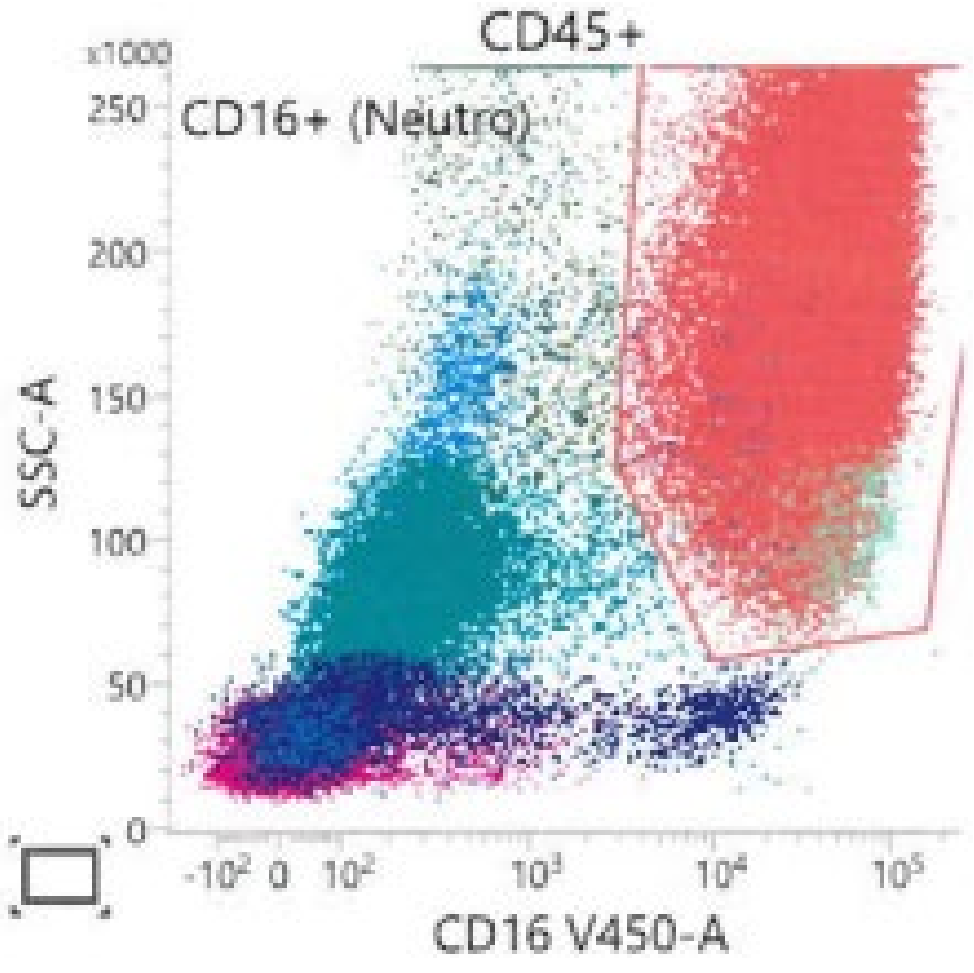


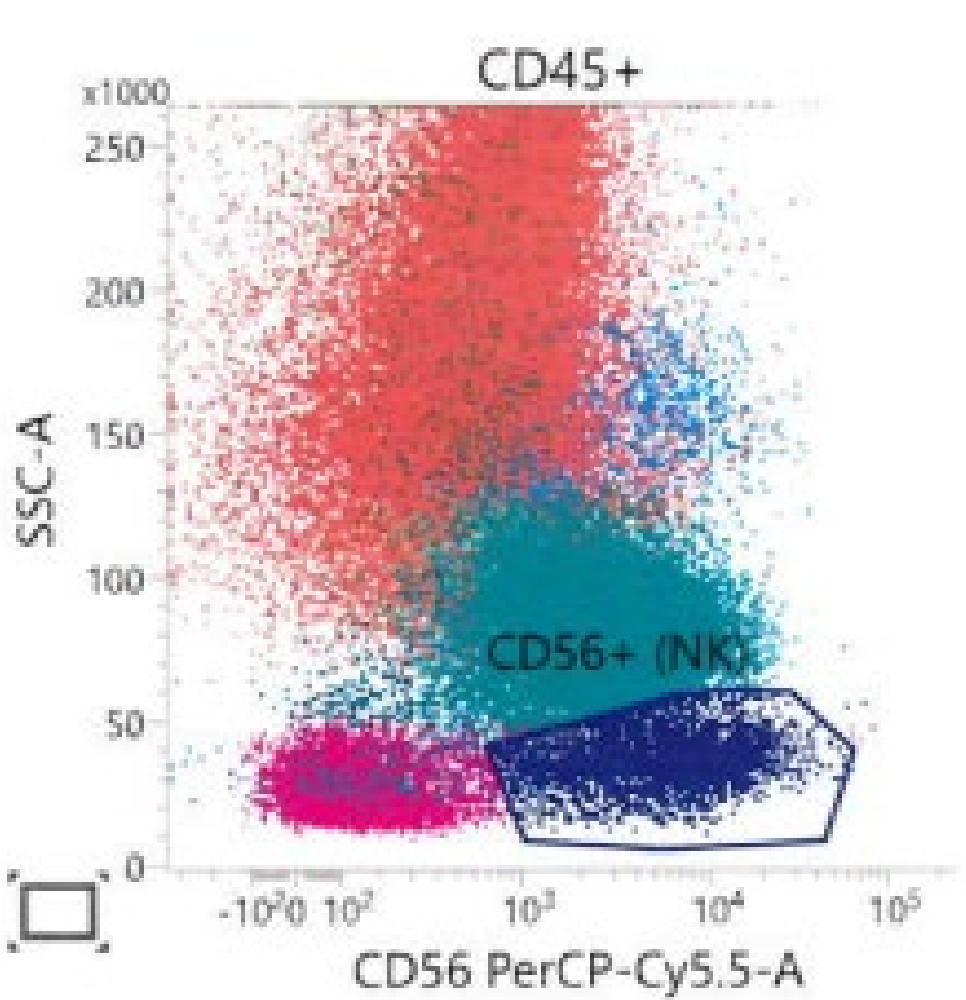


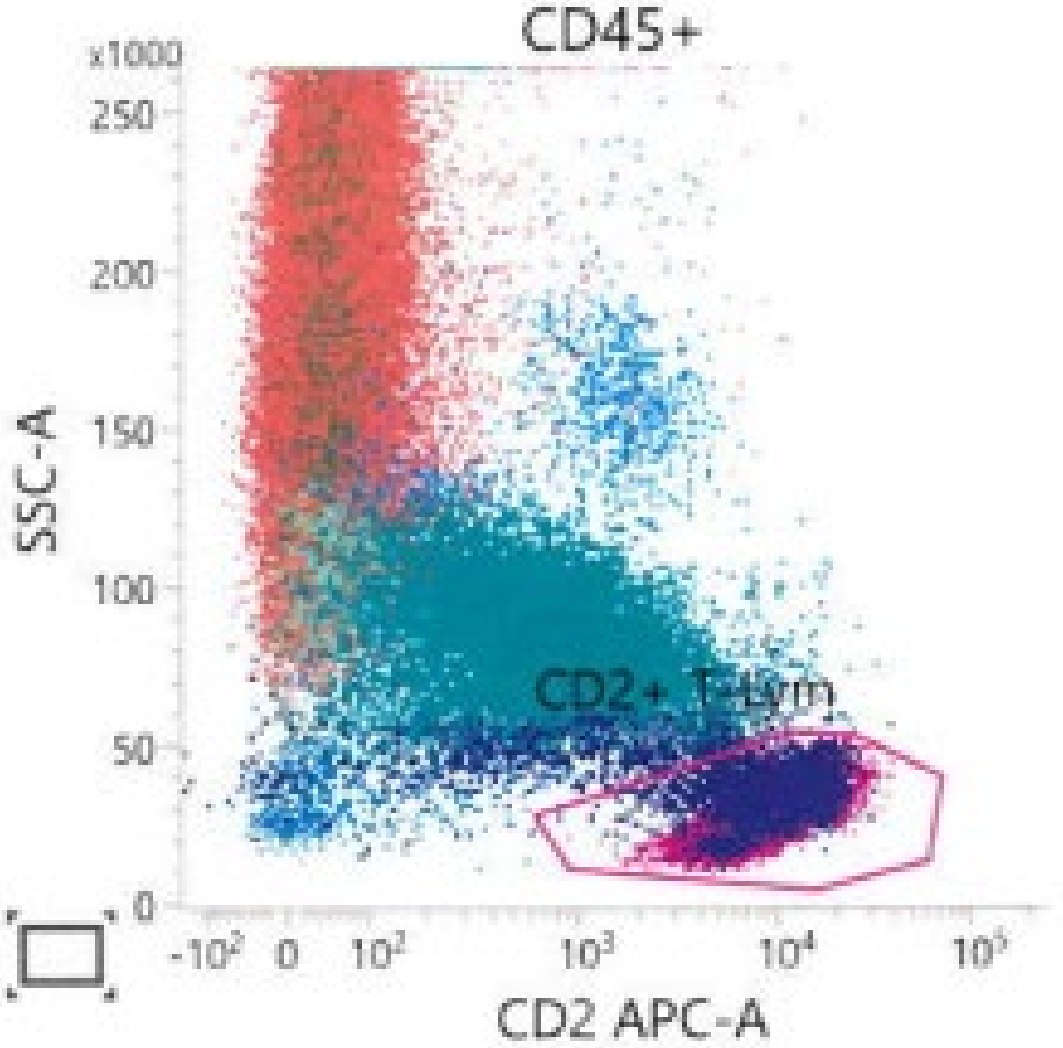

Singlets
Cellen
x1000
250
200
150
100
50
0
SSC-A
0
50
100
150
200
250
x1000
FSC-A

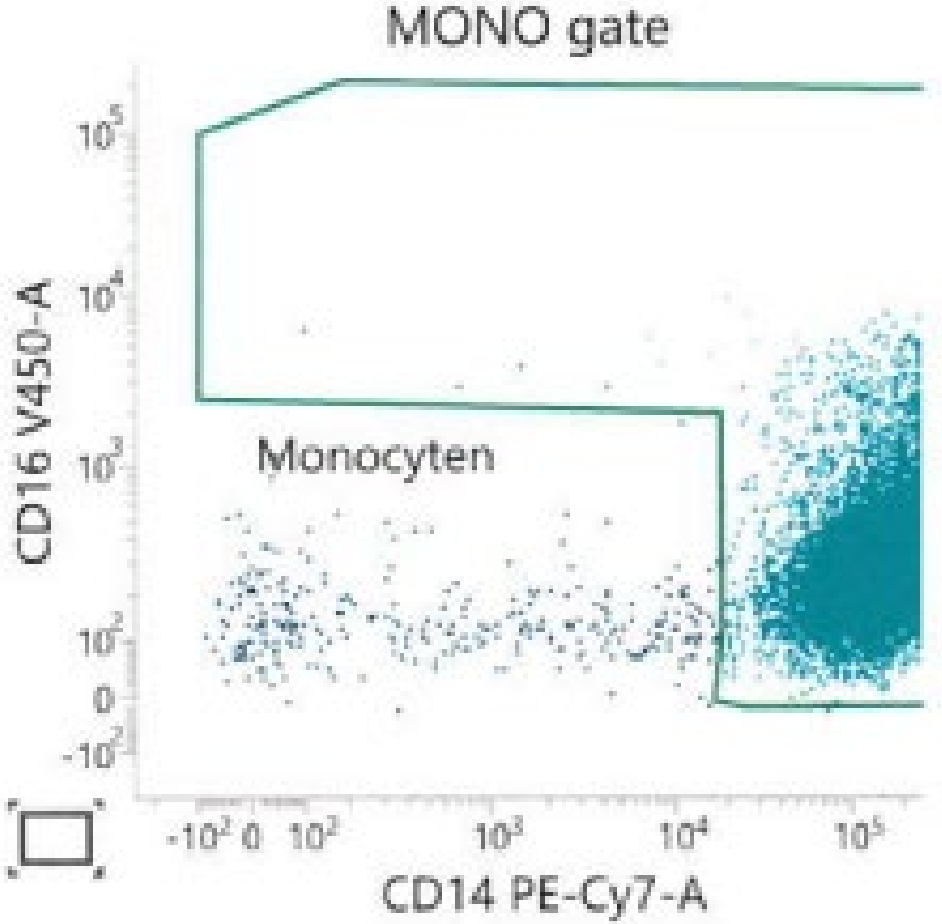

Cellen
CD45+
Mono*
x1000
250
200
150
100
50
0
SSC-A
0
10^2
10^3
10^4
10^5
CD45 V500-C-A

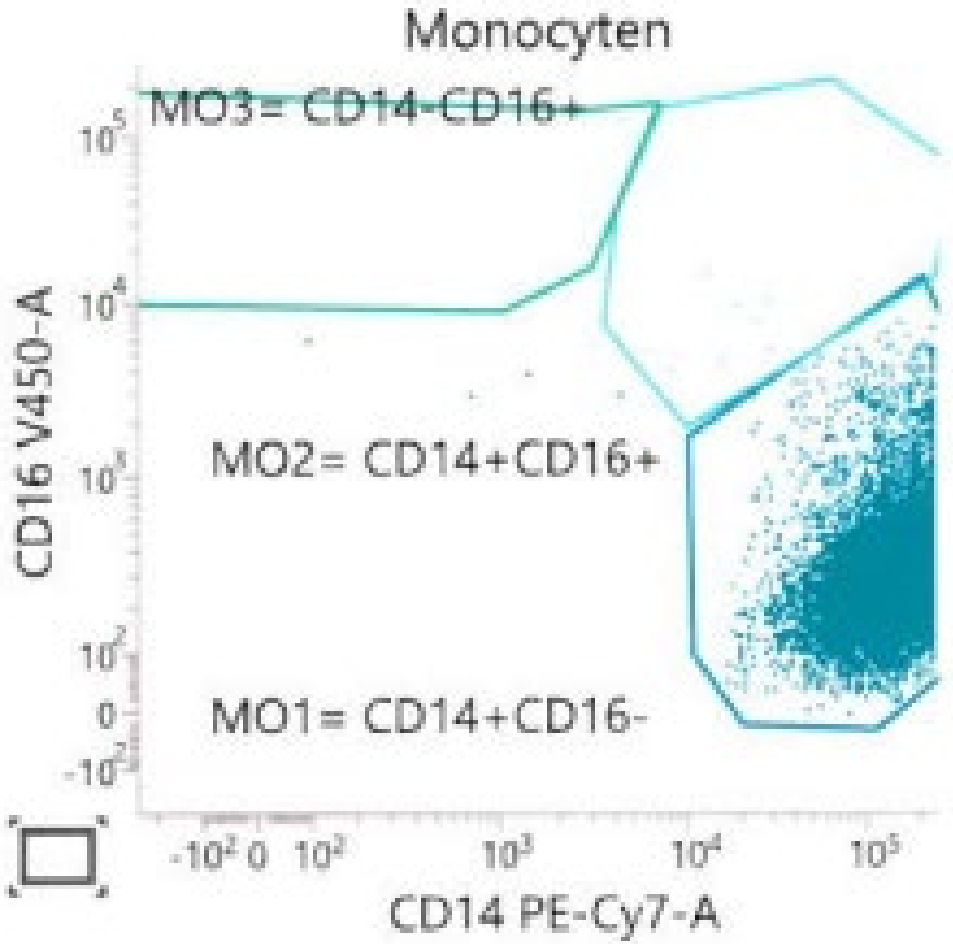

CD45+
CD24+
CD24+ B-Lym
SSC-A
x1000
250
200
150
100
50
0
-10² 0 10² 10³ 10⁴ 10⁵
CD24 PE-A

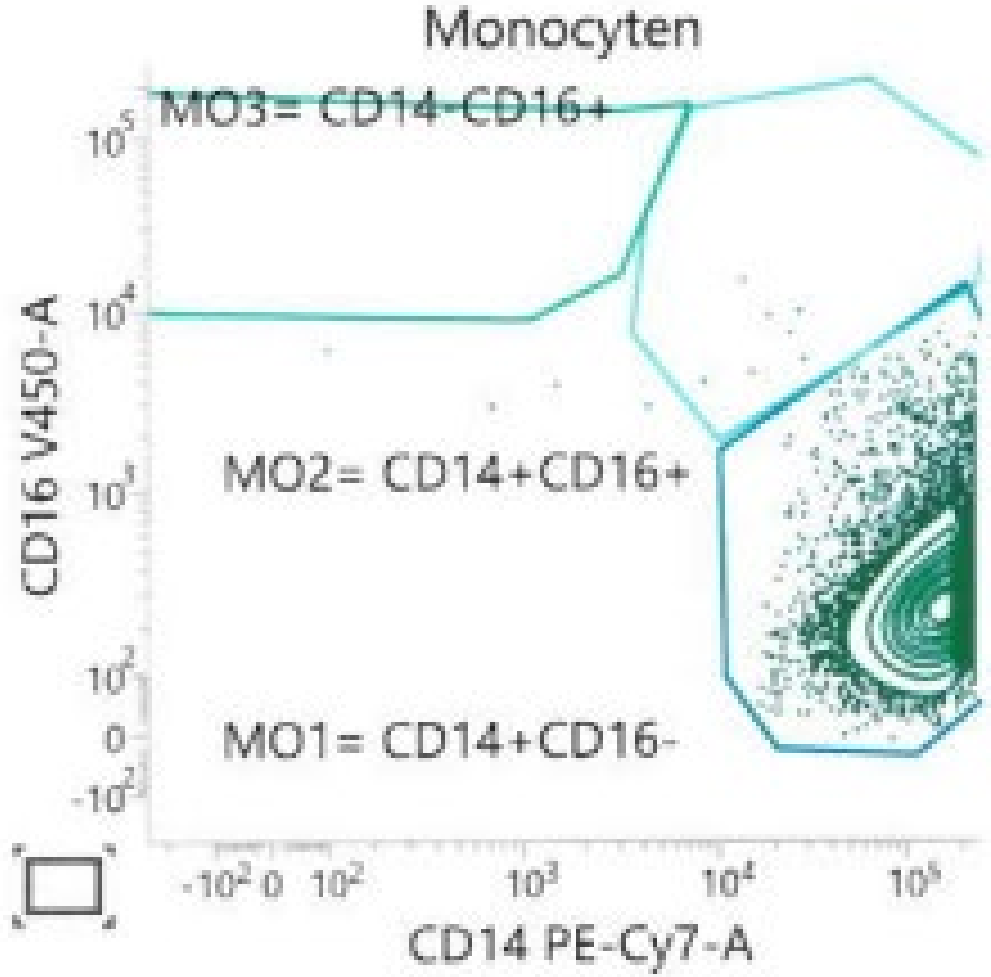

CD45+
CD16+ (Neutro)
SSC-A
x1000
250
200
150
100
50
0
-10² 0 10² 10³ 10⁴ 10⁵
CD16 V450-A


CD45+
x1000
250
200
150
100
50
0
SSC-A
CD56+ (NK)
-10²0 10² 10³ 10⁴ 10⁵
CD56 PerCP-Cy5.5-A


CD45+
x1000
250
200
150
100
50
0
SSC-A
CD2+ T-lym
-10² 0 10² 10³ 10⁴ 10⁵
CD2 APC-A


MONO gate
Monocyten
CD16 V450-A
CD14 PE-Cy7-A


Monocyten
MO3= CD14-CD16+
MO2= CD14+CD16+
MO1= CD14+CD16-
CD16 V450-A
CD14 PE-Cy7-A

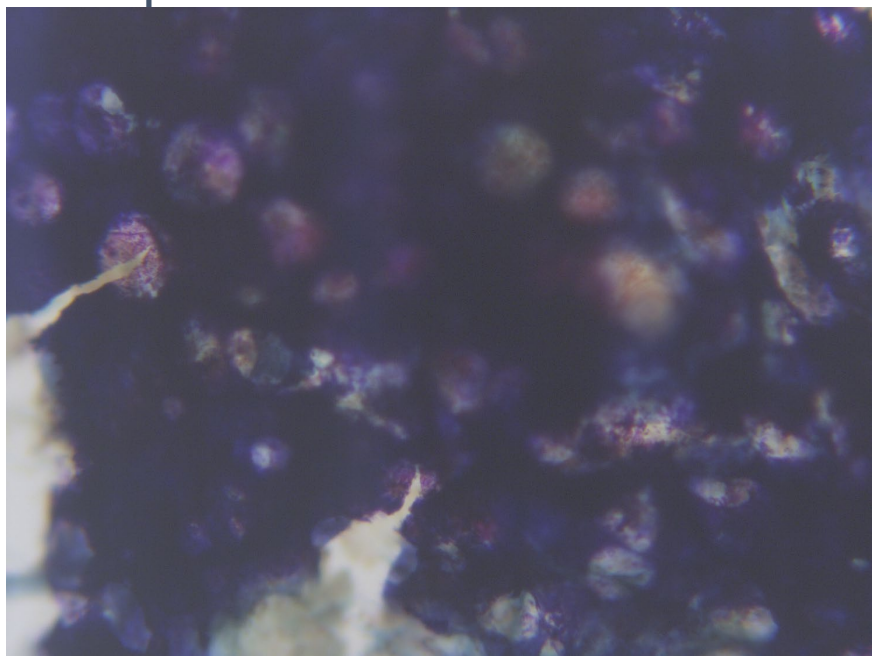


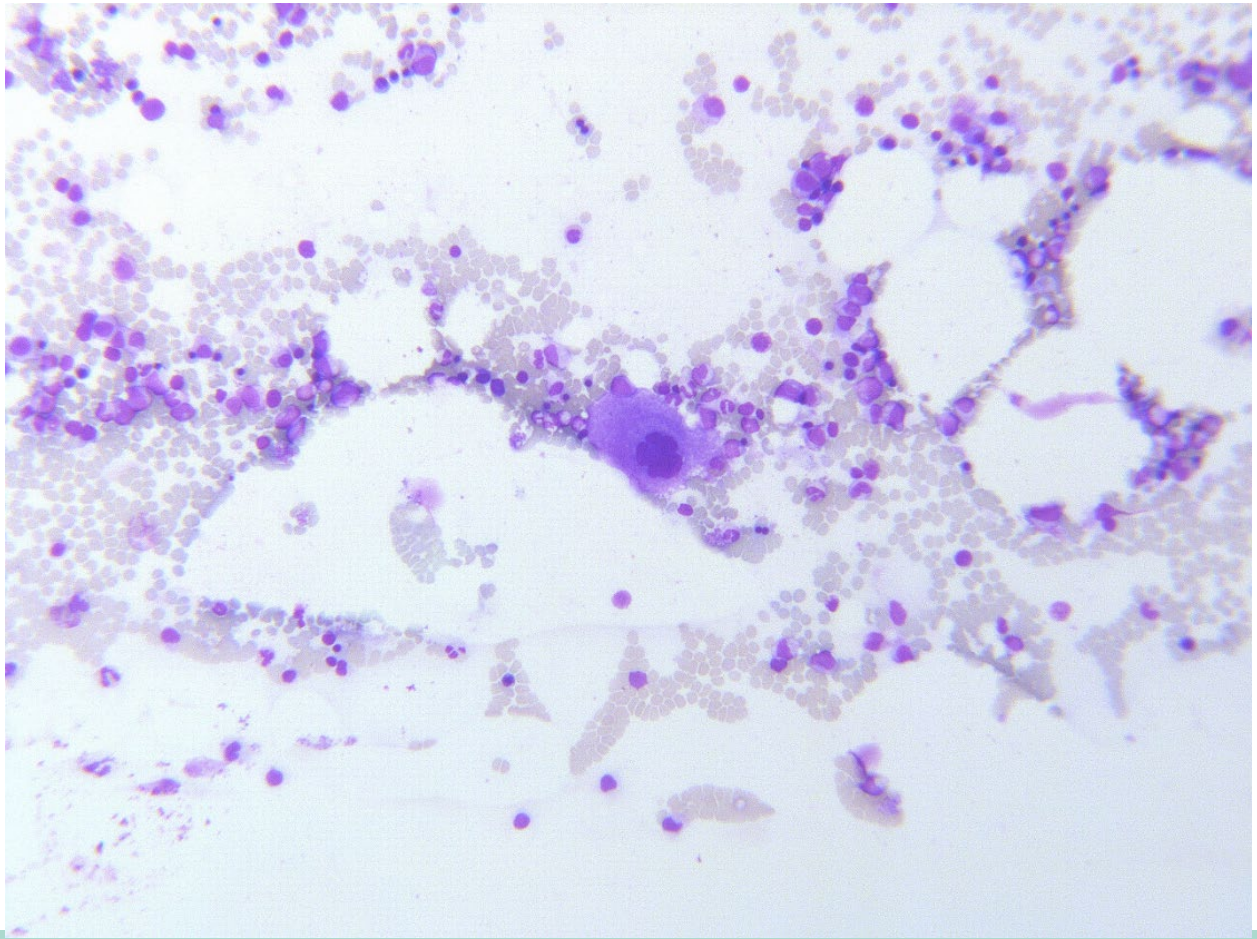
Statistics

MO1 (CD14+CD16-):	99.9 %
MO2 (CD14+CD16+):	0.1 %
MO3 (CD14-CD16+):	0.0 %
CD2+ (T-Lym):	12.5 % WBC
CD14+ Mono:	18.6 % WBC
CD16+ (Neutro):	64.5 % WBC
CD24+ (B-Lym):	0.3 % WBC
CD56+ (NK):	4.1 % WBC

Bonemarrow aspirate

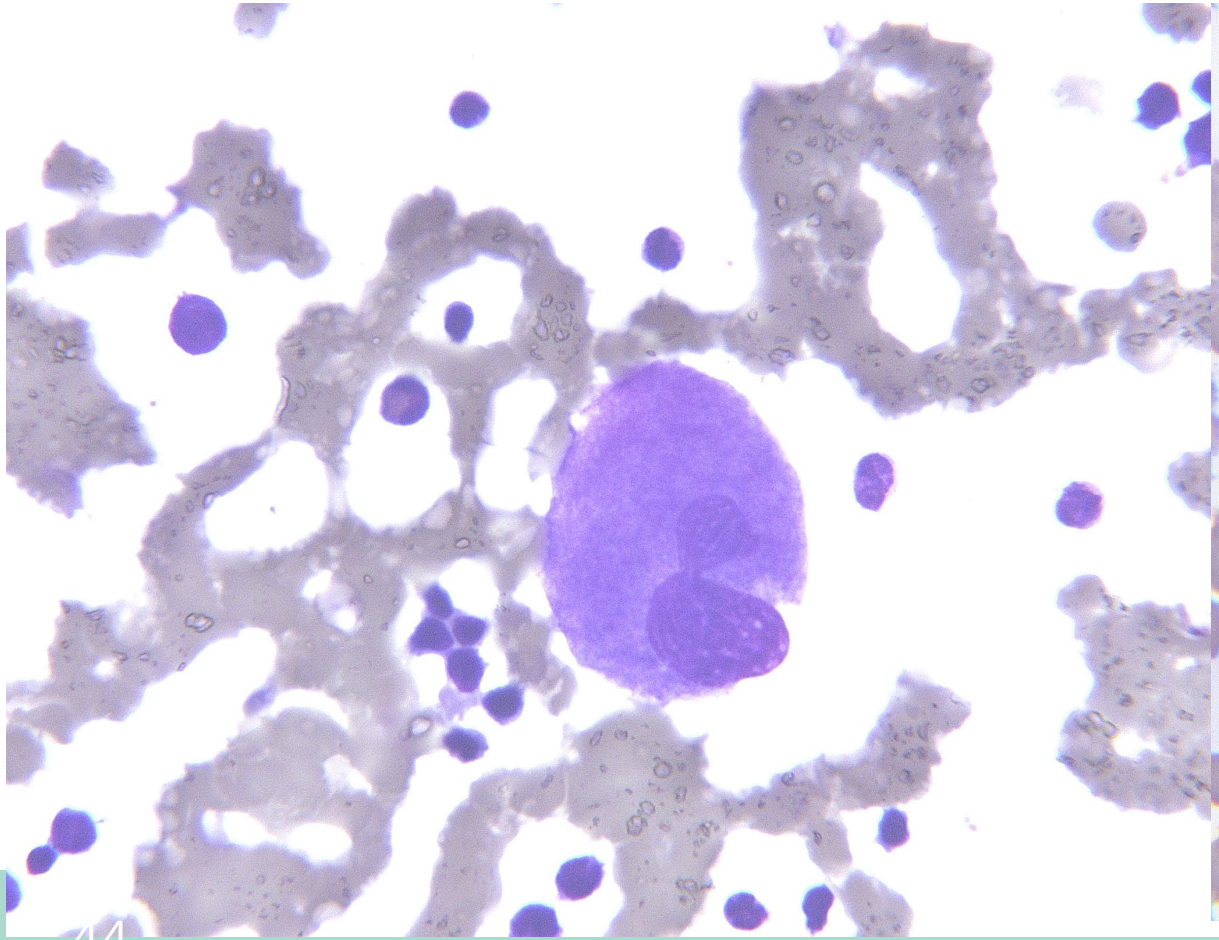
10x spicule

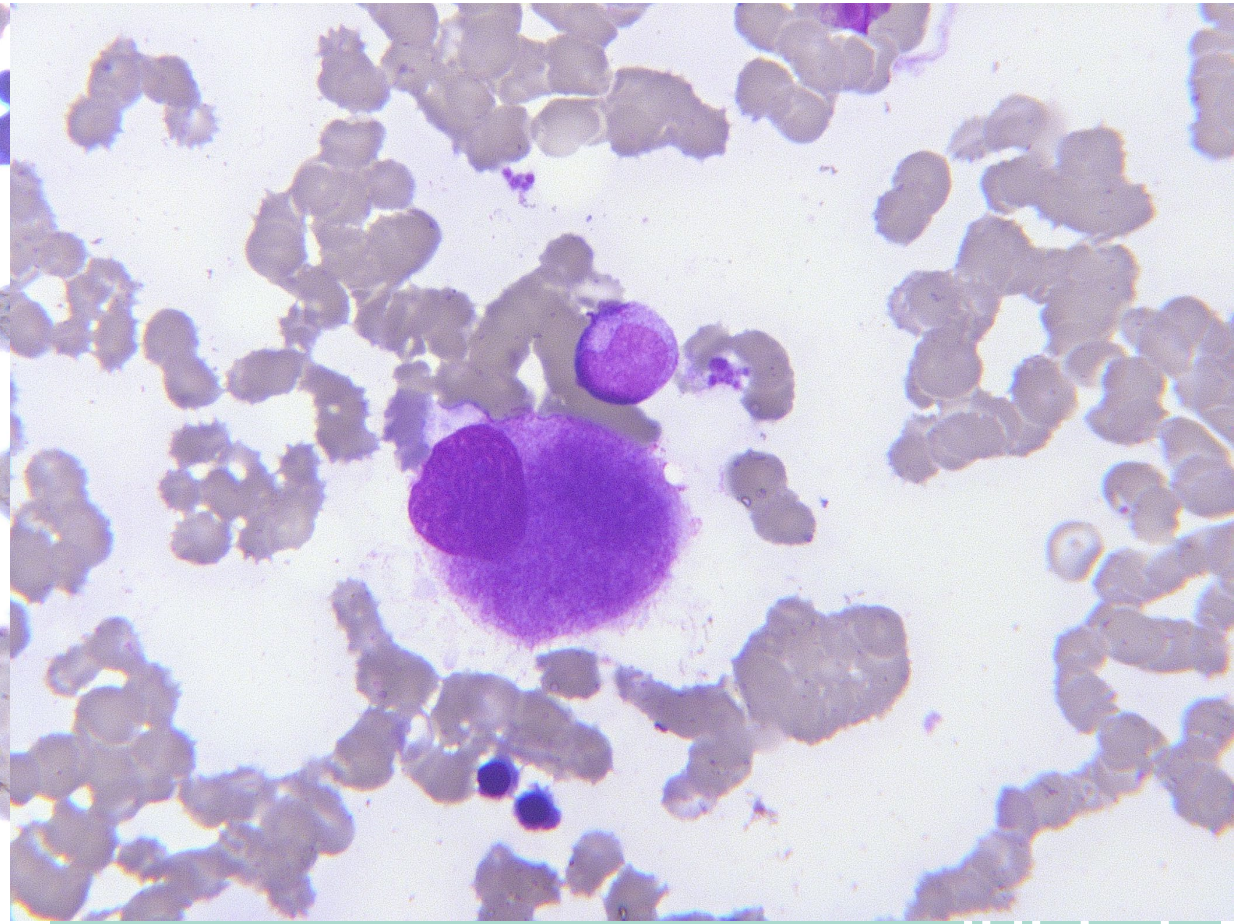




Key abnormalities

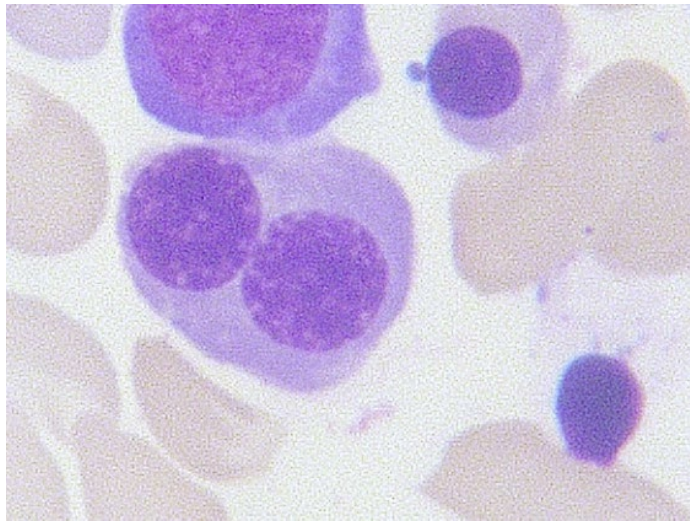
Megakaryocytic

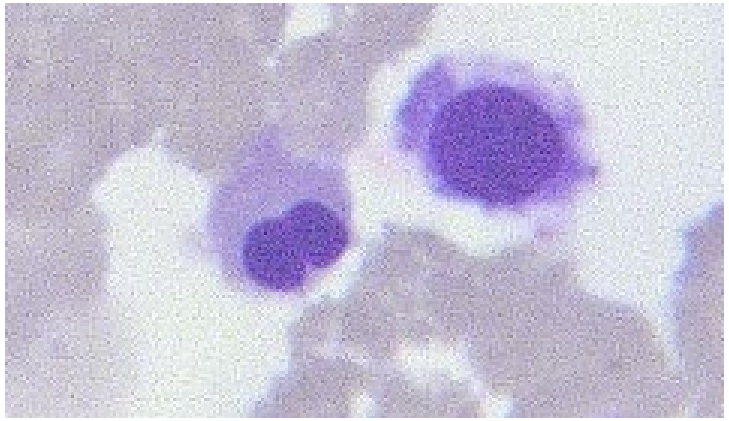




Key abnormalities

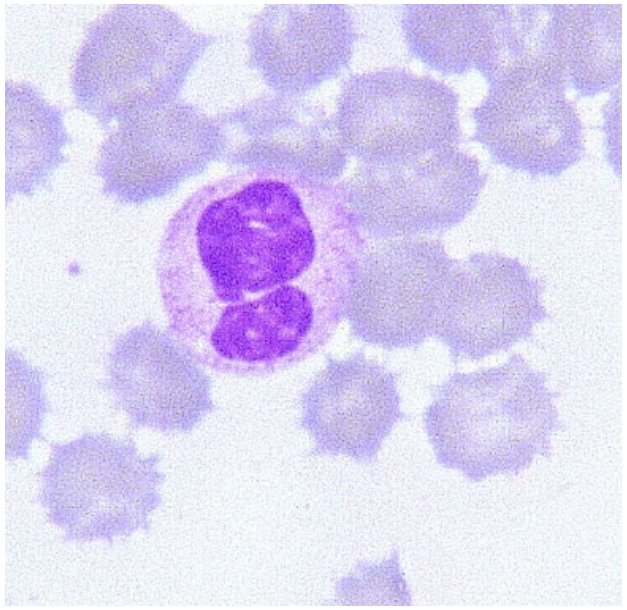
Erythroid

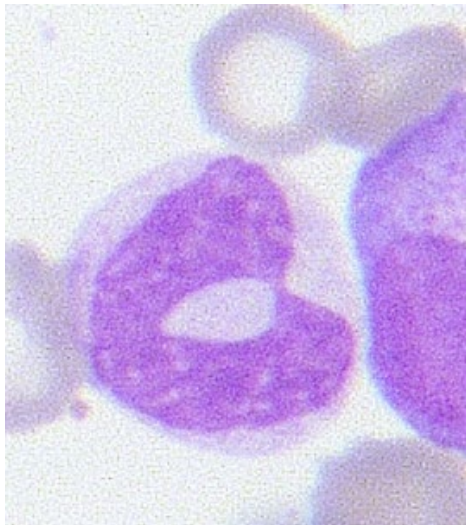




Key abnormalities

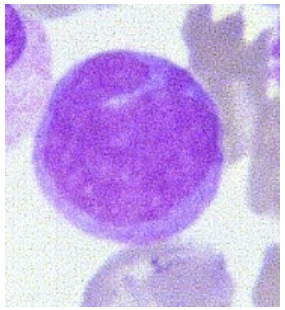
Myeloid

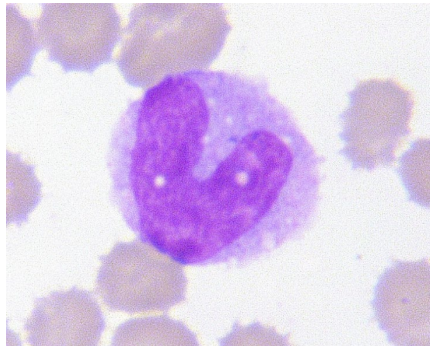


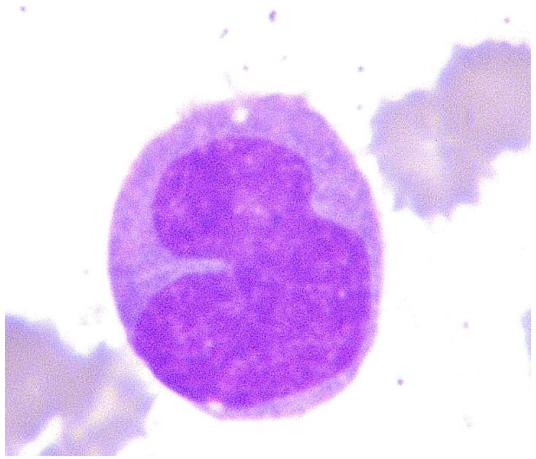


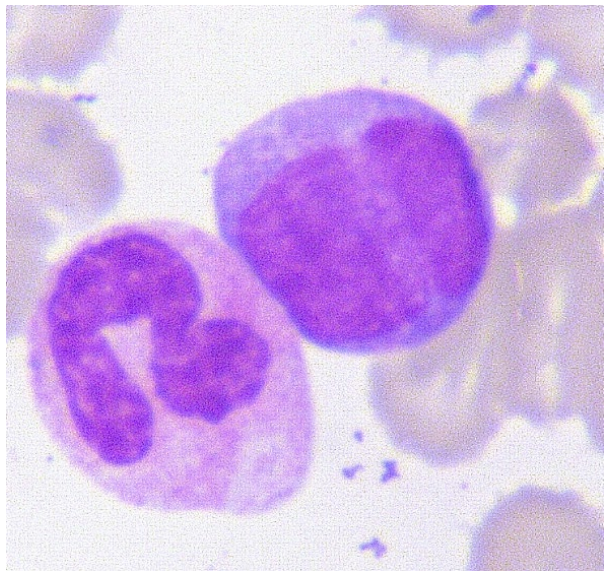
Key abnormalities

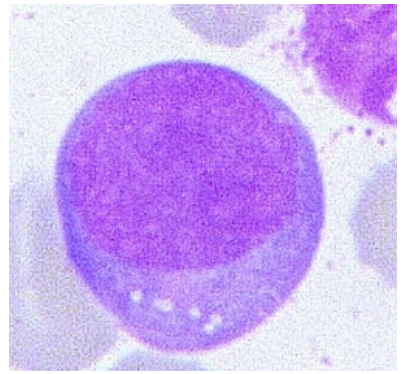
Monocytic

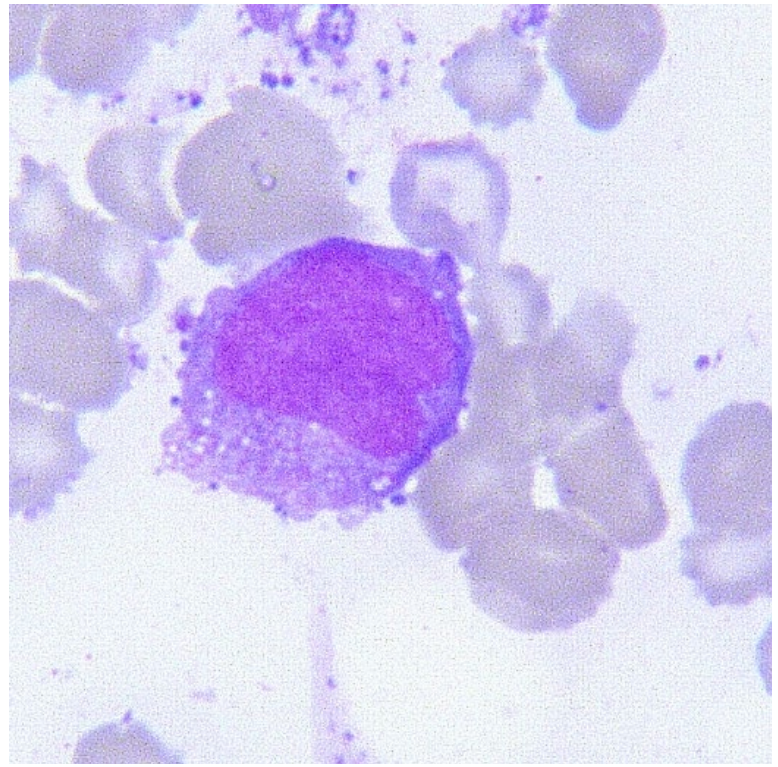












Conclusion cytology

- Mild hypogranulation and seldom nuclear abnormality of myeloid cells
- Seldom erythroid nuclear abnormality
- Seldom mono- and bilobed megakaryocytes

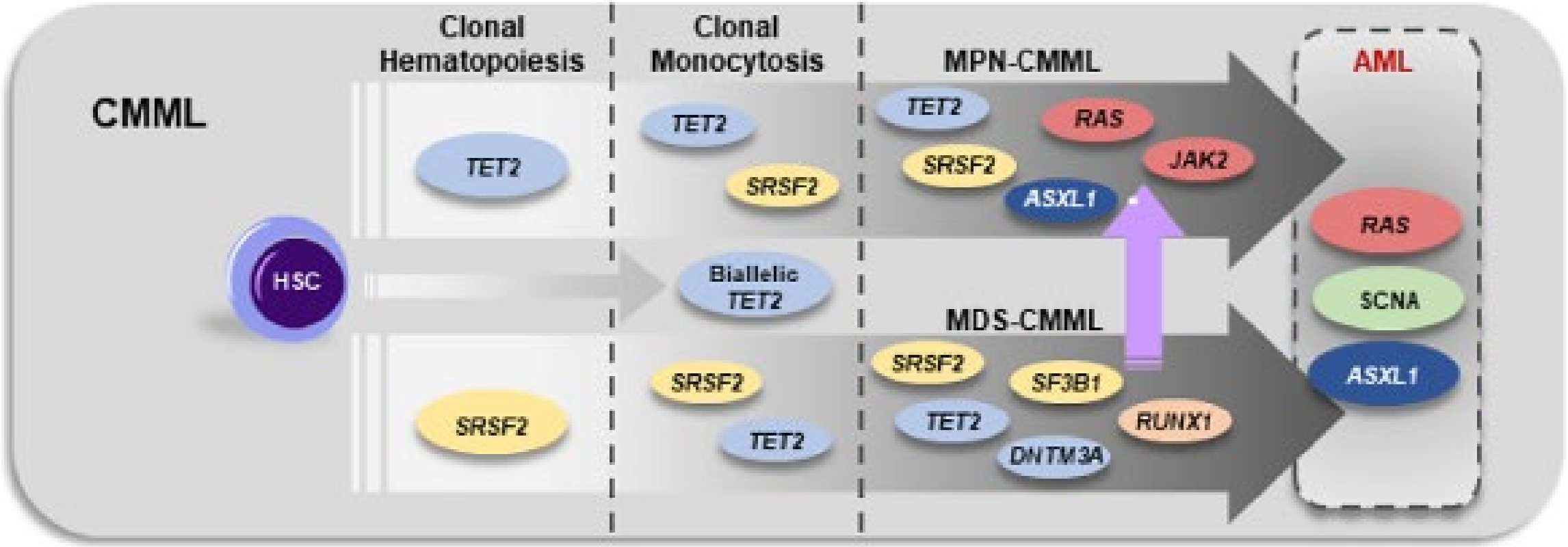
= Dysplasia in the 3 lineages

- Normal blast count (2,6%) (ref <2,9%)
- Elevated monocyte count (9,4%) (ref <5,2%)

Cytogenetics

- 20-30% of the patients have an abnormality
- Frequent abnormalities include:
  - Trisomy 8
  - Loss of Y chromosome
- Not disease specific

Molecular origin of CMML

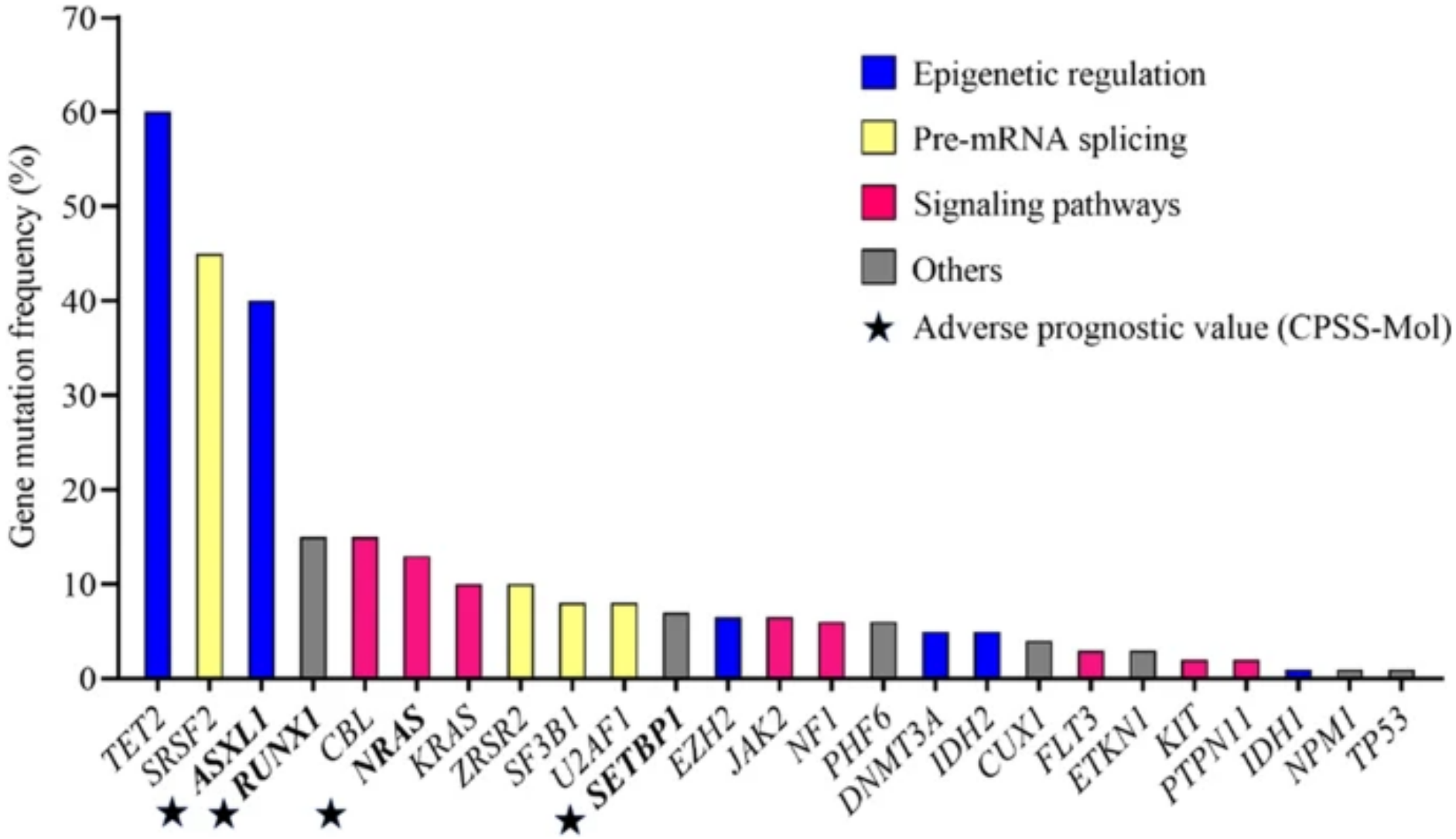


Chan et al. Chronic myelomonocytic leukemia diagnosis and management. Leukemia. 2021 Jun;35(6):1552-1562.

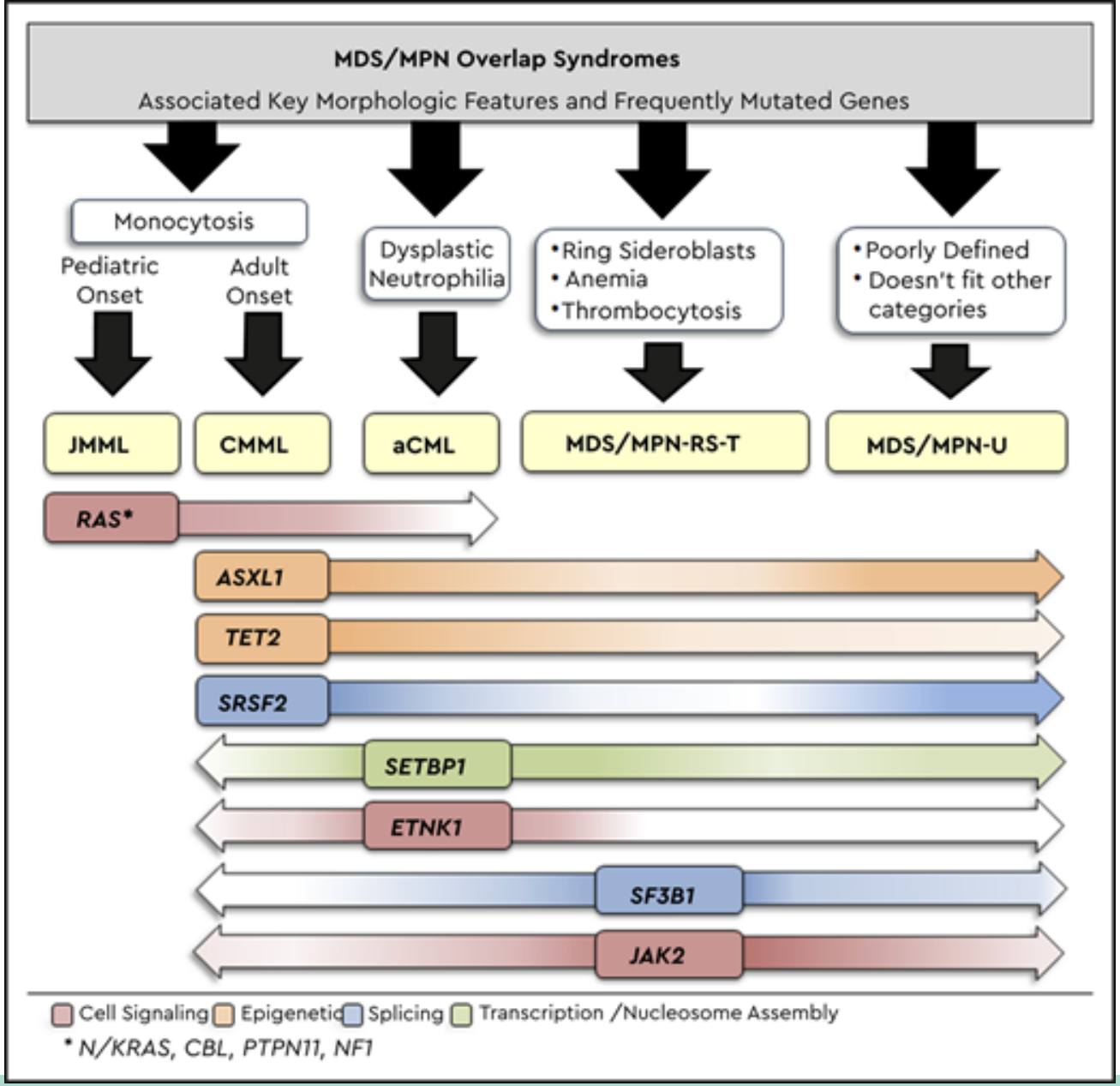
Most frequently affected molecular genes

- Epigenetic regulation
  - TET2, ASXL1
- Spliceosome
  - SRSF2
- Signal transduction
  - RAS pathway

Fig. 2: Recurrent gene mutations in CMML.



Chan et al. Chronic myelomonocytic leukemia diagnosis and management. Leukemia. 2021 Jun;35(6):1552-1562.



Patnaik et al. Myelodysplastic syndrome/myeloproliferative neoplasm overlap syndromes: a focused review. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):460-464..

Molecular approach

- BCR-ABL P190 P210
- NGS myeloid panel DNA
- NGS myeloid panel RNA

NGS

AmpliSeq for Illumina Myeloid Panel (74 genes) on the Miseq

- DNA-NGS panel for all (suspected) myeloid samples
- Plus RNA-NGS panel for AML and (suspected) MPN with eosinophilia

Hotspot gene (23)									
ABL1	*BRAF*	*CBL*	*CSF3R*	*DNMT3A*	*FLT3*	*GATA2*	*HRAS*	*IDH1*	*IDH2*
JAK2	*KIT*	*KRAS*	*MPL*	*MYD88*	*NPM1*	*NRAS*	*PTPN11*	*SETBP1*	*SF3B1*
SRSF2	*U2AF1*	*WT1*							
Full genes (17)									
ASXL1	*BCOR*	*CALR*	*CEBPA*	*ETV6*	*EZH2*	*IKZF1*	*NF1*	*PHF6*	*PRPF8*
RB1	*RUNX1*	*SH2B3*	*STAG2*	*TET2*	*TP53*	*ZRSR2*			
Fusion driver genes (29)									
ABL1	*ALK*	*BCL2*	*BRAF*	*CCND1*	*CREBBP*	*EGFR*	*ETV6*	*FGFR1*	*FGFR2*
FUS	*HMGA2*	*JAK2*	*KMT2A (MLL)*	*MECOM*	*MET*	*MLLT10*	*MLLT3*	*MYBL1*	*MYH11*
NTRK3	*NUP214*	*PDGFRA*	*PDGFRB*	*RARA*	*RBM15*	*RUNX1*	*TCF3*	*TFE3*	
Expression genes (5)					**Expression control genes (5)**				
BAALC	*MECOM*	*MYC*	*SMC1A*	*WT1*	*EIF2B1*	*FBXW2*	*PSMB2*	*PUM1*	*TRIM27*

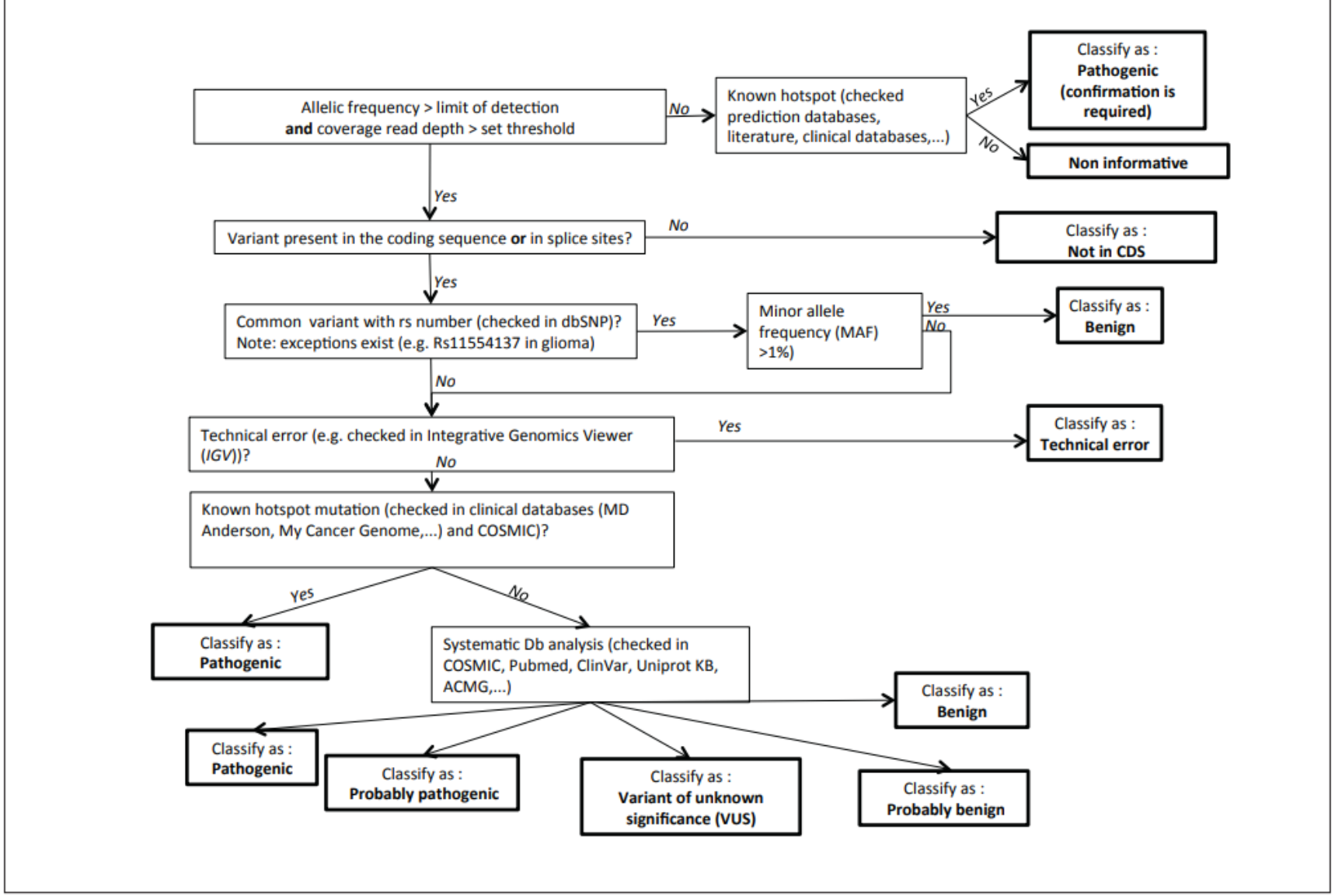


FIGURE 2 Biological classification of variants. Modified with permission from Froyen et al., 2016.

- 0 Pathogenic variants
- 2 Probably pathogenic variants

TET2	c.4097G>A;p.(Arg1366His)	(R1366H)	43%
TET2	c.294_297del;p.(Ser99Asnfs*13)	(S99Nfs*)	41%

Case 2

APD

- 73 years old man
- History: 1995 Car accident talusfracture
- 1997 Psychotic depression
- Bilateral pneumonia 2005
- Umbilical hernia reapir 2010
- Arthroscopic evaluation right shoulder
- Lumbalgia

- Leukocytosis with myelomonocytic formula
- -> bone marrow evaluation

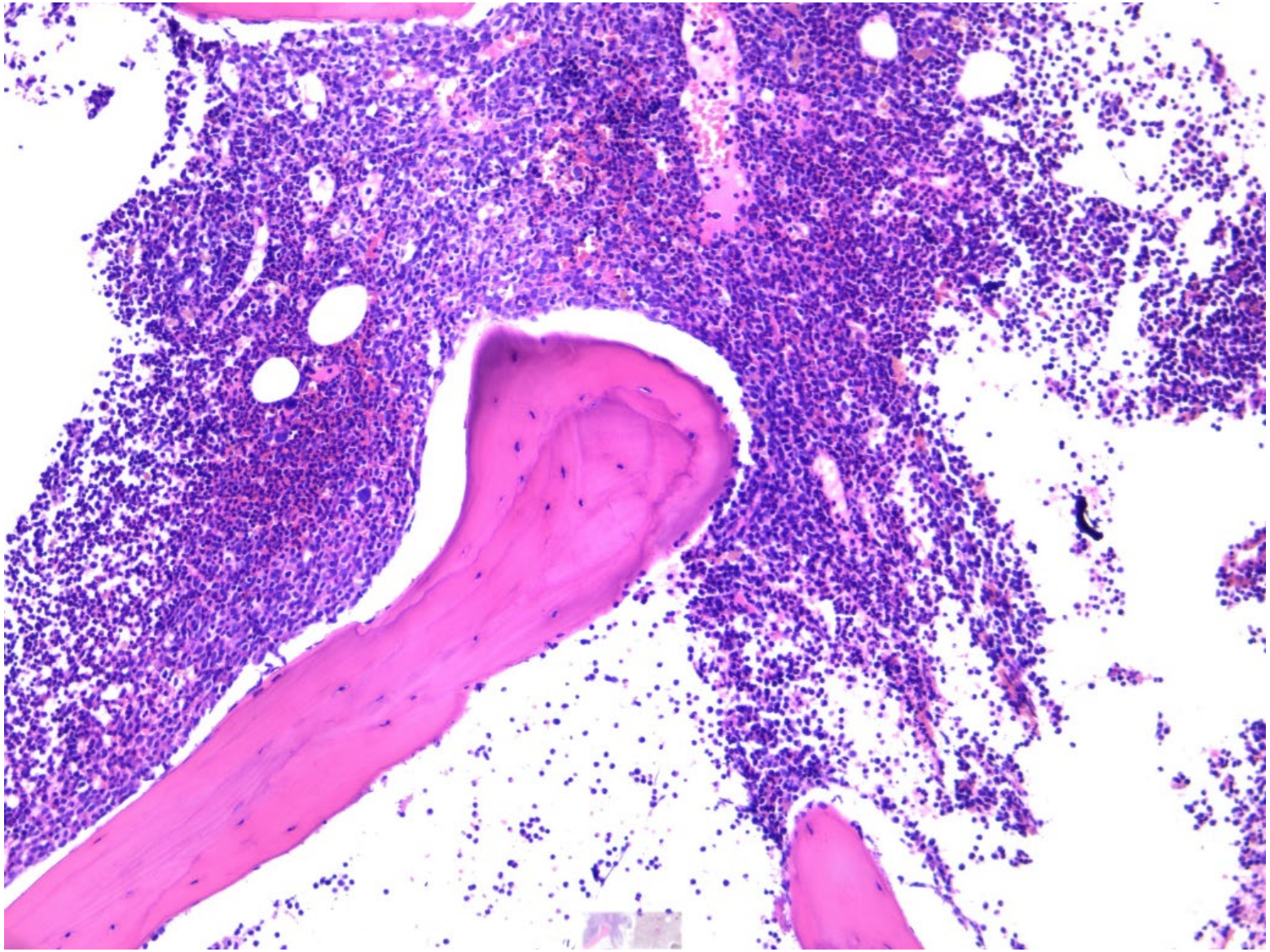
Peripheral blood

- WBC 12600

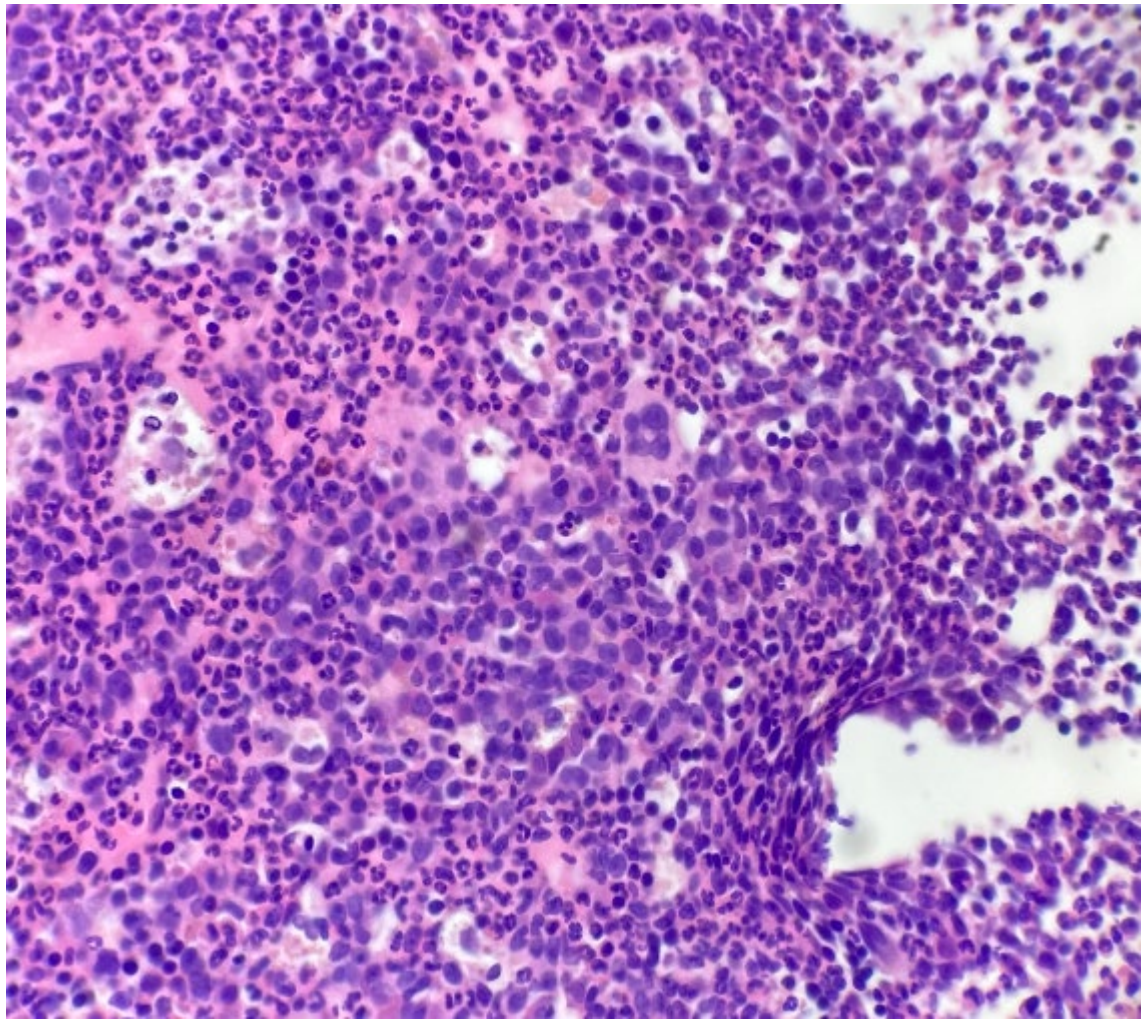
WBC differentiatie microscopie				
Myelocyten %	*	1.9	%	<= 0.0
Metamyelocyten %	*	8.6	%	<= 1.0
Neutrofielen %		59.6	%	50.0 - 70.0
Neutrofielen aantal		7.5	10**9/L	1.5 - 7.5
Eosinofielen %	*	0.0	%	1.0 - 6.0
Eosinofielen aantal		0.0	10**9/L	<= 0.5
Basofielen %		1.0	%	0.0 - 1.0
Basofielen aantal		0.1	10**9/L	<= 0.2
Lymfocyten %	*	10.6	%	20.0 - 45.0
Lymfocyten aantal		1.3	10**9/L	1.0 - 3.5
Monocyten %	*	18.3	%	5.0 - 12.0
Monocyten aantal	*	2.3	10**9/L	0.1 - 1.0

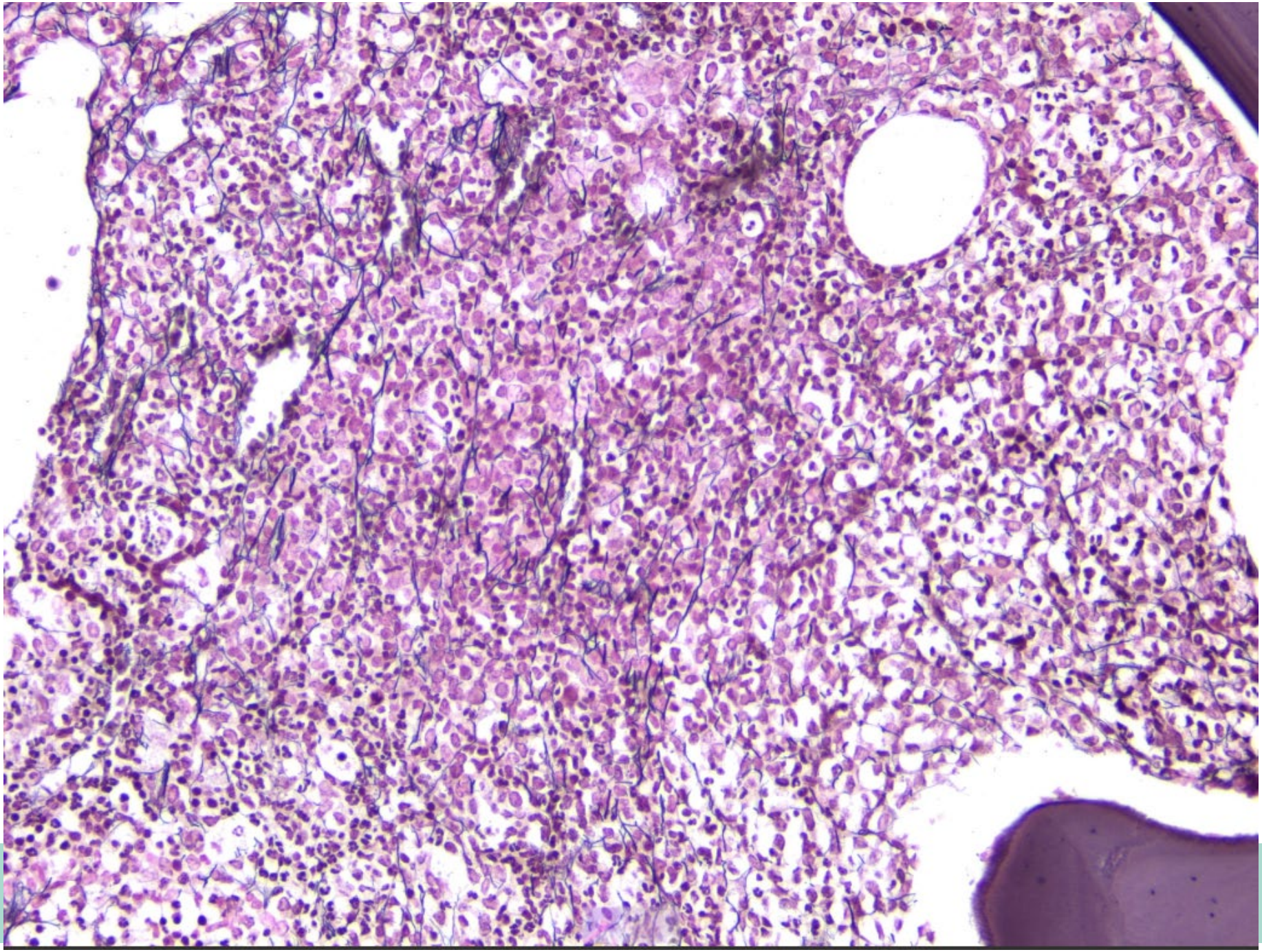
APD

- Hypercellular for age



Courtesy of Dr. T. Steelandt





APD conclusion

- Hypercellular for age
- Proliferation of myeloid lineage
- No specific abnormalities in erythroid and megakaryocytic lineage
- Grade 1 fibrosis (MF-1)

Aspirate conclusion

- Mild hypogranulation and nuclear abnormalities in myeloid lineage
- Normal erythroid lineage
- Seldom monolobar megakaryocytes

- Normal blast count (0,8%) (ref <2,9%)
- Monocytosis (12,8%) (ref <5,4%)

Molecular results

- 1 Pathogenic variants
- 3 Probably pathogenic variants

SRSF2c.284C>A;p.(Pro95His) (P95H)54%
TET2c.4393C>T;p.(Arg1465*) (R1465*)51%
TET2c.3594_3594+1insTTAA;p.(Val1199Leufs*9) (V1199Lfs*)47%
ASXL1c.1762C>T;p.(Gln588*) (Q588*)45%

Prognosis

TABLE 5. Prognostic scoring systems for CMML.

Score	GFM[21]	Mayo[13]	CPSS[44]	MADPS[45]	CPSS-Mol[46]
Clinical features	Age >65	No	RBC-TD	No	RBC-TD
Morphology	WBC >15000/µl; Anaemia; Platelets <100000/µl	Increased AMC >10000/µl; Presence of circulating IMC; Hb <10 g/dl; Platelets <100000/µl	WBC; Blasts %	Hb <12 g/dl; Circulating IMC; ALC >2500/µl; BM blasts >10%	WBC ≥13000/µl BM blasts ≥5%
Cytogenetics	No	No	Yes	Yes	Yes
Molecular analysis	*ASXL1*	No	No	No	Yes
Risk groups	3	3	4	4	4
Median OS (months)	14-60	10-32	5-72	5-26	18- > 144
External validation	Yes	Yes	Yes	No	Yes

CPSS-Mol part A

TABLE 6. CPSS-Mol risk score.[46] **A.** Calculation of the cytogenetic risk.

	Spanish cytogenetic risk[1]	*ASXL1*	*NRAS*	*RUNX1*	*SETBP1*
0	low	unmutated	unmutated	unmutated	unmutated
1	intermediate	mutated	mutated	-	mutated
2	high	-	-	mutated	-

Cytogenetic risk score	
0	low
1	int-1
2	int-2
≥3	high

[1]Spanish cytogenetic risk:
low: normal, -Y
intermediate: other
high: trisomy 8, chromosome 7 abnormalities, complex karyotype.

CPSS-Mol part B

B. Calculation CPPS-Mol.

	0	1	2	3
CPSS genetics	low	int-1	int-2	high
BM blasts	<5%	≥5%	–	–
Leukocyte count	<13000/µl	≥13000/µl	–	–
Transfusion dependence	no	Yes	–	–

CPSS-Mol score	Risk	med OS (mo)
0	low	NR
1	int-1	68
2-3	int-2	30
≥4	high	17

Summary

- Important changes in diagnostic criteria
- Implementation of peripheral blood flow cytometry
- Role of molecular diagnostics

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