Comprehensive Cancer Center
Tübingen-Stuttgart

Post ASH 2024 San Diego

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Update on diagnostics – Post ASH 2024

1. Education Program AML M&Ms: How to Integrate Mutations and MRD Data

2. Artificial Intelligence in Hematology: From generative AI to Ethics and Applications

3. #1538 Optical Genome Mapping As Standard-of-Care in Acute Leukemia: Diagnostic and Clinical Impacts 10 Months Post-Implementation

Latest Classifications for Acute Myeloid Leukemia and Myelodysplastic Syndromes

1. WHO 5th Edition

   Khoury JD, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*.

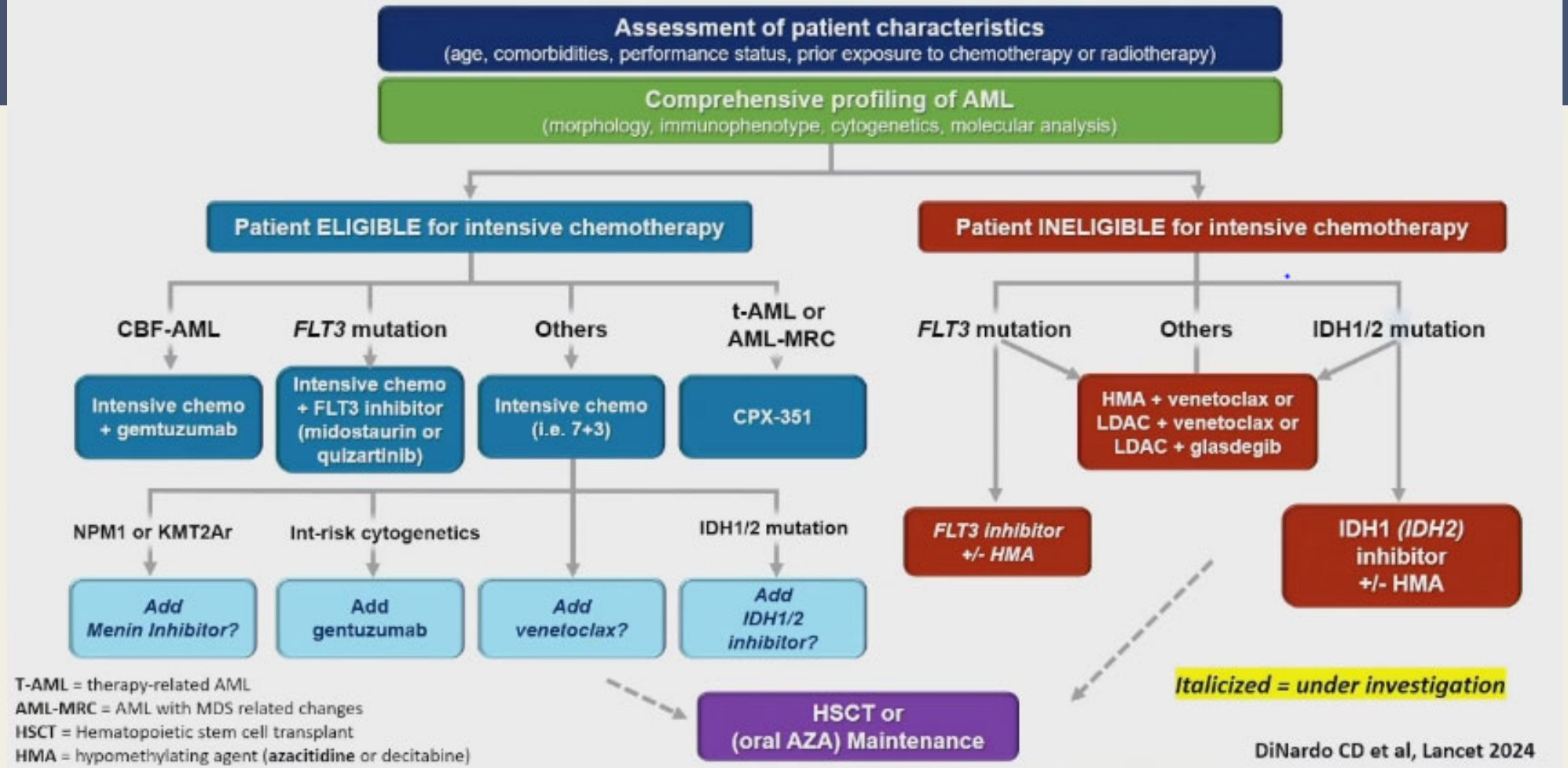
2. ICC 2022

   Arber DA et al. **I**nternational **C**onsensus **C**lassification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022

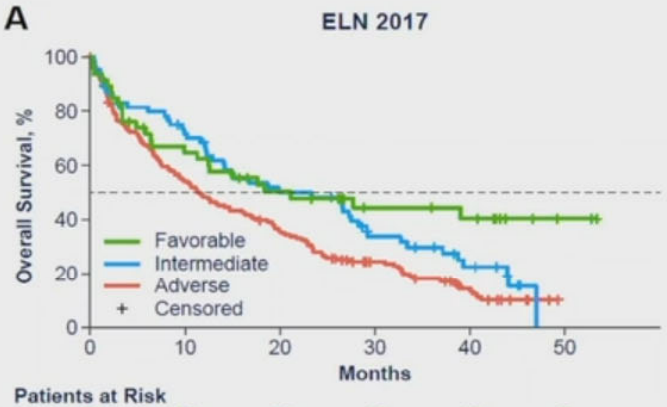
3. ELN 2022

   Hartmut Döhner, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022

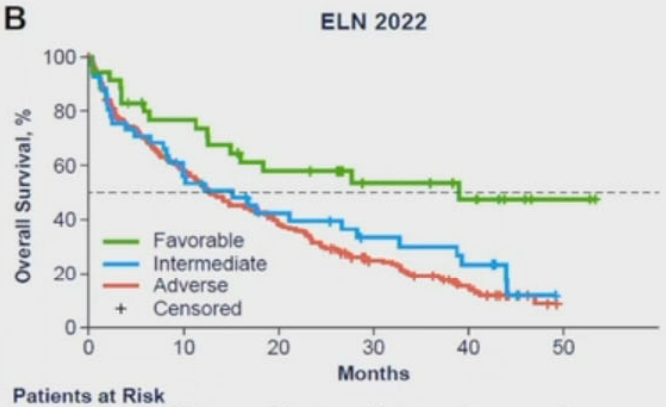
Evolving diagnostic and treatment paradigm for Newly Dx AML



Neither ELN 2017 nor 2022 discriminate optimally for patients receiving HMA+VEN therapies



ELN 2017	n	Events	Median OS, months (95% CI)
Favorable	46	25	21.1 (9.9, NR)
Intermediate	65	48	23.3 (12.9, 28.3)
Adverse	168	141	11.5 (8.9, 16.2)

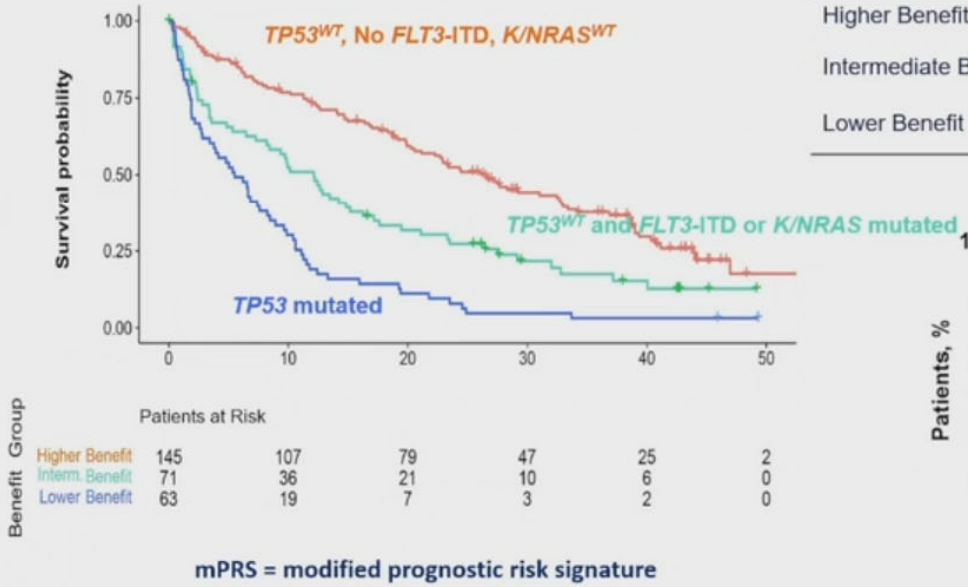


ELN 2022	n	Events	Median OS, months (95% CI)
Favorable	35	16	39.0 (12.5, NR)
Intermediate	41	31	15.2 (7.9, 28.3)
Adverse	203	167	12.7 (10.4, 17.6)

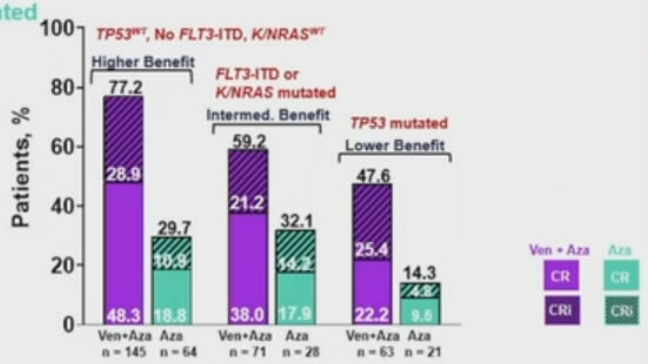
Dohner H et al, Blood 2024

Patients receiving Ven+Aza are **better characterized** by three molecularly-defined subgroups

"mPRS Score"



Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	**26.51** (20.24, 32.69)
Intermediate Benefit	71	57	**12.12** (7.26 – 15.15)
Lower Benefit	63	61	**5.52** (2.79 – 7.59)



mPRS = modified prognostic risk signature

Dohner H et al, Blood 2024

Latest Classifications for Acute Myeloid Leukemia and Myelodysplastic Syndromes

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3. ELN 2022	Hartmut Döhner, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022
4. ELN 2024 LIT	Hartmut Döhner, et al. Döhner H, DiNardo CD, Appelbaum FR, et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. *Blood* 2024

Risk Classifications Updated to Reflect Intended Therapy

	ELN 2022, Döhner et al, *Blood*, 2022	**ELN 2024 LIT**, Döhner et al, *Blood*, 2024
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* • **Mutated *NPM1*** without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖	• **Mutated *NPM1*** (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH1*∗ (*TP53*^{wt}) • Mutated *DDX41*†, • Other cytogenetic and/or molecular abnormalities‡ (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	• Mutated *NPM1* with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse	• Other cytogenetic and molecular abnormalities‡ (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* • Mutated *TP53*	• **Mutated *TP53***

This classification does not apply to patients who have received prior treatment with an HMA or who have progressed from MPN.

† consider germline testing

∗if treated with Aza/Ivosidenib

‡For many cytogenetic and molecular abnormalities, single or as coaberrations, no data are currently available; they are tentatively categorized as favorable and intermediate-risk depending on the absence or presence of activating signaling gene mutations.

ELN 2024 Less Intensive

Favorable-risk group	Median OS, months	Reference
Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39	4
Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37	4
Mutated *IDH1*∗ (*TP53*^{wt})	29	6,17
Mutated *DDX41*	>24	3,13
AML with MR gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23	4
Intermediate-risk group		
AML with MR gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13	4
Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12	4
Adverse-risk group		
Mutated *TP53*	5-8	3,4,7,10,14-16

4 Döhner, et al. Genetic risk stratification and outcomes among treatment-naive patients with AML treated with venetoclax and azacitidine. *Blood*. 2024

6 Montesinos, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia . *N Engl J Med.* 2022

3 Jahn, et al. Clinical impact of the genomic landscape and leukemogenic trajectories in non-intensively treated elderly acute myeloid leukemia patients. Leukemia. 2023

Evolving Classifications and more to come

FAB-Classification 1976

FAB-Classification update 1989

NCCN v1.2025

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 1997

WHO Classification 2001

WHO Classification 2008

Revised 4th WHO Classification 2017

5th WHO Classification 2022

ELN 2010

ELN 2017

ELN 2022

ELN 2024 less intensive

ICC 2022

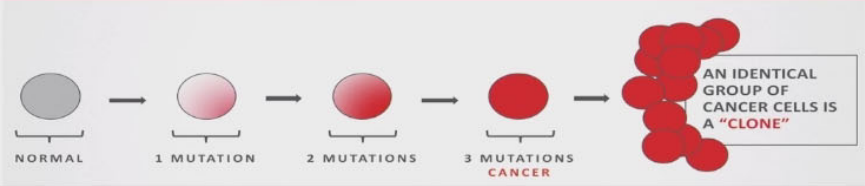
Choosing the right MRD assay

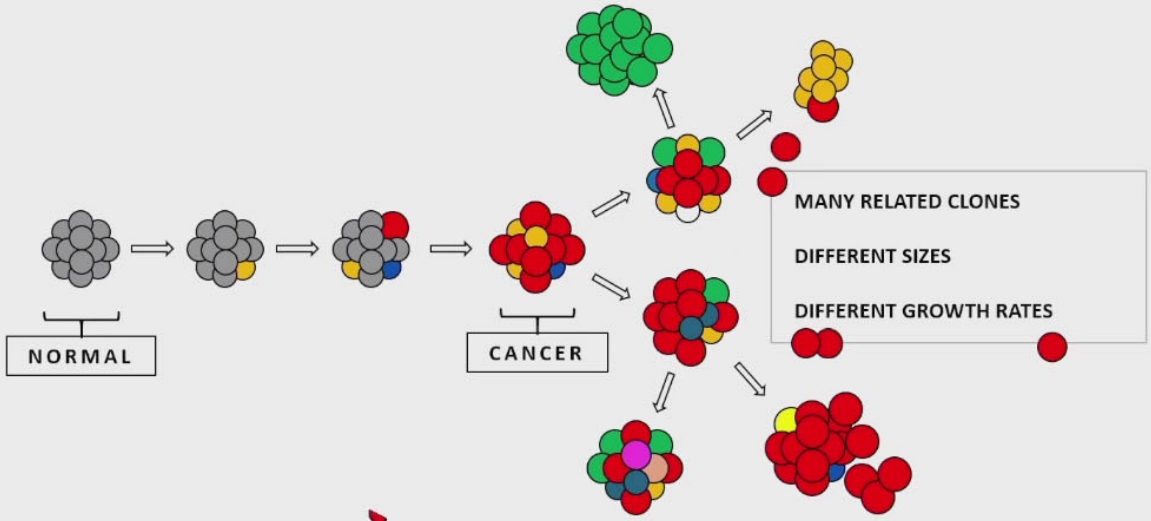
ELN risk group	Genetic subgroup	MRD assay in non-transplanted patients	MRD assay after alloHCT
Favorable	NPM1 mut	qPCR	qPCR
	RUNX1/RUNXT1 or CBFB/MYH11	qPCR	qPCR
	CEBPA bZIP inframe	MFC #1570	Not established
Intermediate	FLT3-ITD NPM1wt	FLT3-NGS or MFC	FLT3-NGS or MFC
	FLT3-ITD NPM1mut	qPCR + FLT3-NGS	qPCR (FLT3-NGS)
	MLLT3::KMT2A	MFC or qPCR	qPCR (MFC, NGS)
	Other	MFC	MFC (or NGS)
Adverse	Fusion genes	qPCR or MFC	qPCR or MFC (or NGS)
	-5 or del(5q); -7; -17/abn(17p)	MFC	MFC (or NGS)
	Complex karyotype	MFC	MFC (or NGS)
	Myelodysplasia-related gene mutations	MFC	MFC (or NGS)
	TP53	MFC	MFC (or NGS)

American Society *of* Hematology

Heuser M&M 2024

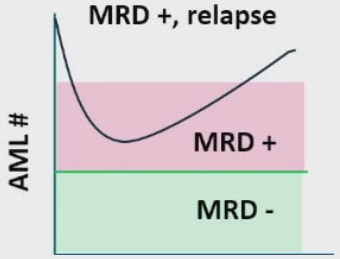
Cancer often has many clones-making of the cancer ecosystem

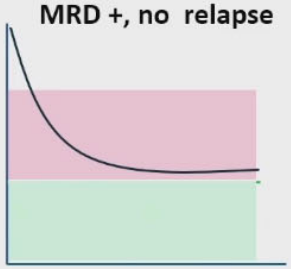




Four possible states of MRD and relapse

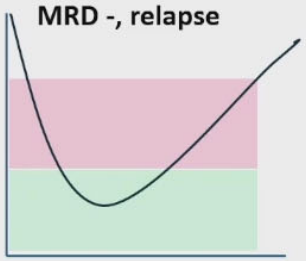
- This makes sense
- Persistent clone?
- New clone?

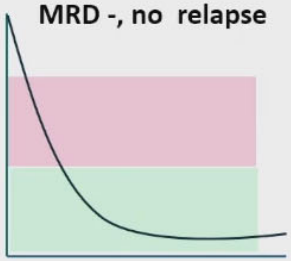




- Some clones more" tolerable?"
- Persistence of "CHIP" mutations?
- Mutation in lymphoid lineage?
- GVL?

- Need a better test?
- Clonal evolution and loss of markers?
- New clone?

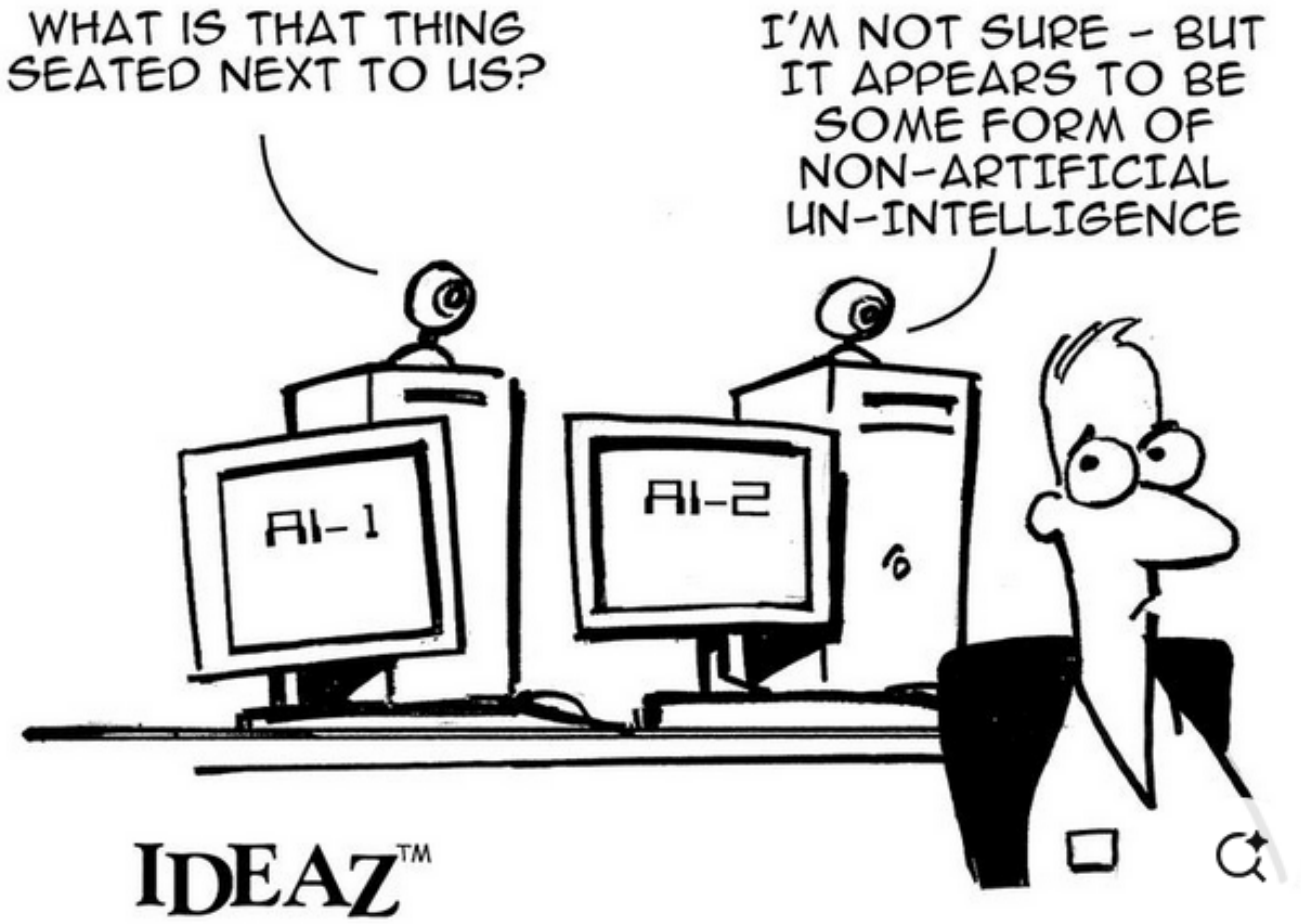




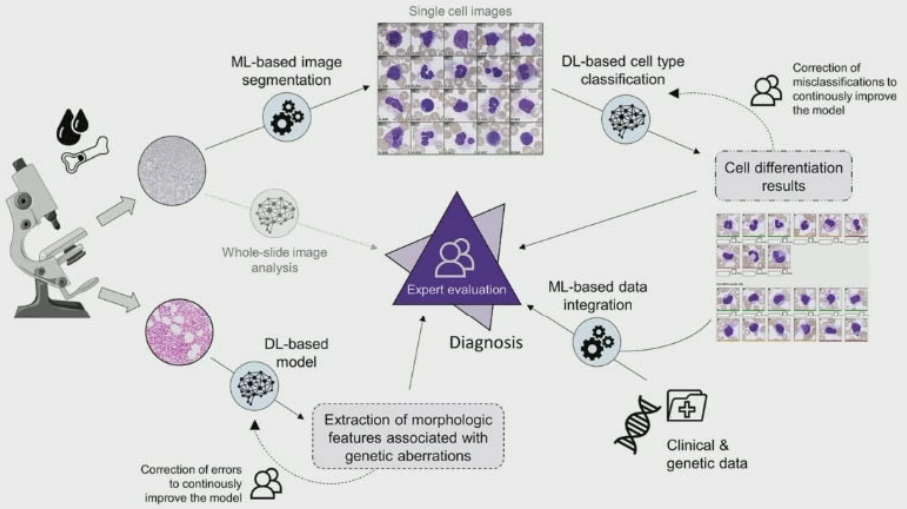
- This makes sense

AML #

TIME


WHAT IS THAT THING SEATED NEXT TO US?
I'M NOT SURE - BUT IT APPEARS TO BE SOME FORM OF NON-ARTIFICIAL UN-INTELLIGENCE
AI-1
AI-2
IDEAZ™

Applications in Cytomorphology



Important questions:
What is the intended use? Augment or replace humans?
High relevance for required accuracy of output

Walter W. et al. Blood Reviews 2022

Reproduce current diagnostic approach
cell (pre)classification reviewed by an expert to optimize the diagnostic workflow

Identify new features for disease classification
e.g. to distinguish *SF3B1*-mutant MDS from other MDS using cyto-morphology and blood counts alone

Guilherme de Almeida J. et al., Nature Communications 2023

Automated karyotyping

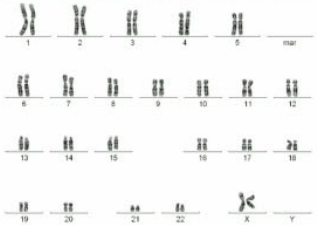
Normal karyotype

Experienced technician

AI-based model

MLL data

Next steps – Identification of chromosome aberrations



24 normal chromosomes

t(9;22), t(15;17), t(11;14), der(1;7)

7 aberrant chromosomes

Majority decision on class normal, t(9;22), t(15;17) or der(1;7) for each case based on metaphase classification of at least 5 metaphases

Cases with ≥5 metaphases

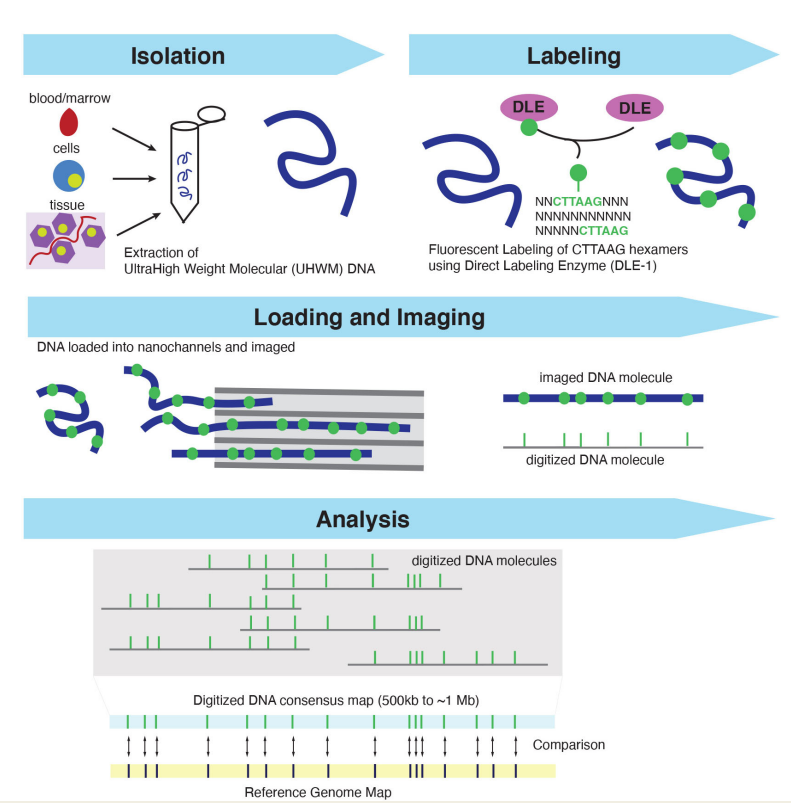
Aberration	N Cases	Rank 1	Rank 1 [%]	Rank 2	Rank 2 [%]
Normal	113	112	99.1	1	0.9
der(1;7)	167	166	99.4	1	0.6
t(9;22)	120	119	99.2	1	0.8
t(11;14)	130	130	100.0	0	0.0
t(15;17)	143	136	95.1	7	4.9

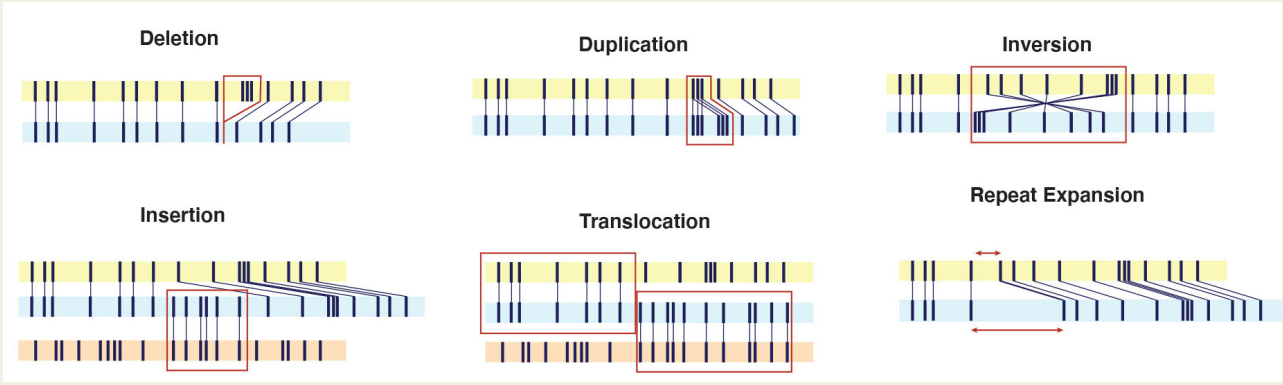
MLL data

- Testing of classifier on high number of metaphases with various karyotypes
- Determination of optimal parameters for routine diagnostics
- Training of further common aberrant chromosome classes

New Method Edging Towards Routine Diagnostics ? – Optical Genome Mapping

Optical Genome Mapping -





Brody et al, College of American Pathologists

OPTICAL GENOME MAPPING (OGM) AS STANDARD OF CARE FOR ACUTE LEUKEMIA DIAGNOSIS: DIAGNOSTIC AND CLINICAL IMPACTS 10 MONTHS POST-IMPLEMENTATION

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BACKGROUND

- Optical genome mapping (OGM) is a novel method for detecting chromosomal structural and copy number variants by imaging and mapping ultra-long fluorescently-labelled DNA
- OGM detects cancer-associated variants with hundreds- to thousands-fold higher resolution than standard cytogenetic methods (karyotyping(CG)/FISH)
- Our clinical laboratory in British Columbia, Canada's largest tertiary care hospital implemented OGM as front-line standard-of-care testing for all newly diagnosed acute leukemias in parallel with CG/FISH

AIM

- To prospectively describe performance and impact on diagnosis of OGM in acute leukemia diagnostic genomic profiling

METHODS

- OGM was performed per manufacturer protocols on bone marrow aspirate or, when unavailable, blood using a Bionano Saphyr instrument and Rare Variant Analysis informatics (paired with De Novo or Guided Assembly for ALL)
- Detected variants were filtered and reported using population thresholds and a custom 277-gene/region file and validated laboratory protocols for variant identification and classification in indication-specific contexts
- All patients received concurrent CG/FISH (limited) analysis as routinely indicated

RESULTS

- 90 adults (mean age 55 years, 47% female) with acute leukemia had OGM performed at diagnosis, including 62 with acute myeloid leukemia (AML), 27 with lymphoblastic leukemia, including 22 B lineage (B-ALL) and 5 T lineage (T-ALL), and one mixed phenotype acute leukemia (T/myeloid)
- OGM provided adequate data for reporting for 88 individuals (98%) with a mean time to result availability of 11.8 calendar days following sample procurement
- Both instances of OGM failure resulted from inadequate bone marrow aspirate volume and insufficient circulating disease for processing

Table 1. Variants identified by OGM and impact on pathologic diagnosis and risk stratification, among cases for which any detectable OGM or cytogenetic abnormalities were identified

	AML	B-ALL	T-ALL
OGM variants, mean	1.4	4.7	3
Additional variants versus CG/FISH, mean	0.6	3.4	3
Change in pathologic diagnosis, frequency	9 (15%)	1 (5%)	0
Change in risk, frequency	12 (19%)	11 (50%)	0

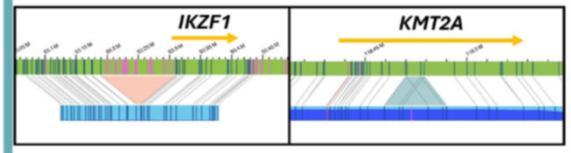

Figure 1. Select cryptic risk-modifying abnormalities identified solely by OGM. Additional variants predicting increased risk were identified in 12 individuals with AML and 11 individuals with B-ALL; these abnormalities included *IKZF1* deletion (left), *KMT2A* partial tandem duplication (right), complex karyotype (not shown), and cryptic deletion of *RUNX1* (not shown)

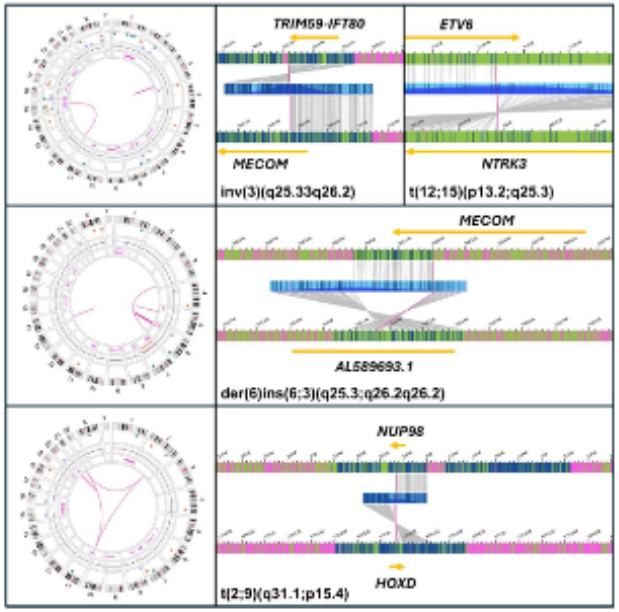

Figure 2. Select cryptic novel driver rearrangements identified by OGM. OGM changed 11% of pathologic diagnoses: 9 AML (3 *MECOM* and 2 *NUP98* rearrangements, 2 *RUNX1* deletions, an unbalanced 7q rearrangement, and a germline *CHEK2* deletion) and 1 B-ALL (*ZNF384* rearrangement). 4 novel rearrangements were defined, including *MECOM::IL12A-AS1/TRIM59-IFT80* resulting from inv(3) in AML (top), *MECOM::AL589693.1* resulting from unbalanced ins(6;3)(q25.3;q26.2q26.2) in oligoblastic AML (middle), and *NUP98::HOXD8* resulting from t(2;9) in AML (bottom)

CONCLUSION

OGM expands the spectrum of detectable cytogenomic abnormalities in acute leukemias, resulting in meaningful disease reclassification and enhanced risk stratification in these diseases, and can permit patients access to previously inaccessible targeted therapies. Data regarding the prognostic impact and actionability of recurrent variants newly detectable or characterizable by OGM are urgently needed to maximally leverage this transformative technology.

Contact: eric.mcginnis@vch.ca

SAT-1538

und am Ende….

Vielen Dank für Ihre Aufmerksamkeit

Universitätsklinikum Tübingen