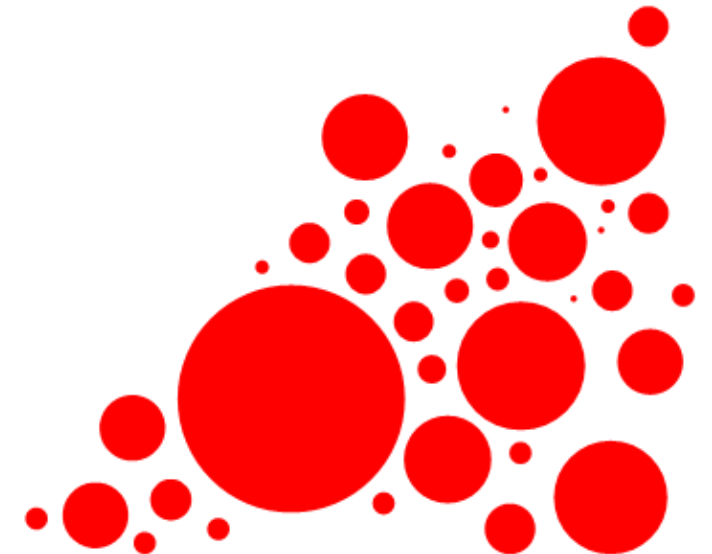




Artificial intelligence in hematological diagnostics: Game changer or gadget ?

Torsten Haferlach
MLL Munich Leukemia Laboratory



Disclosures

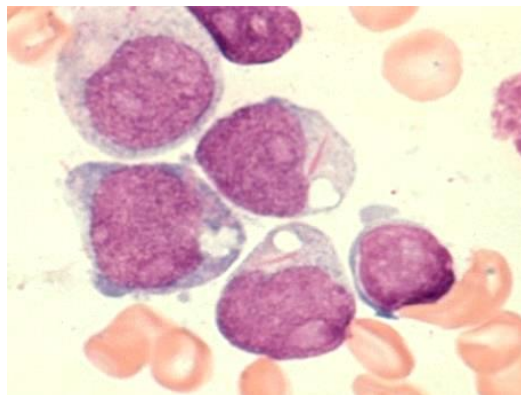


- T. Haferlach is part owner of MLL Munich Leukemia Laboratory

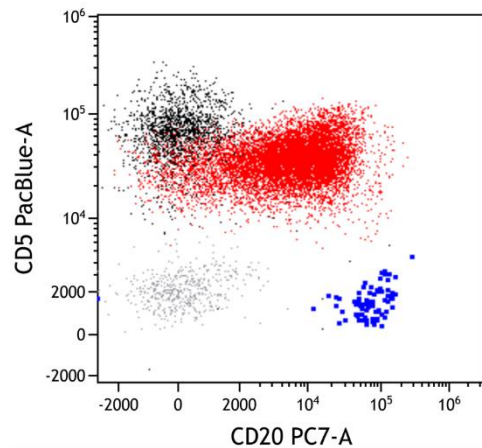
Diagnostics at MLL



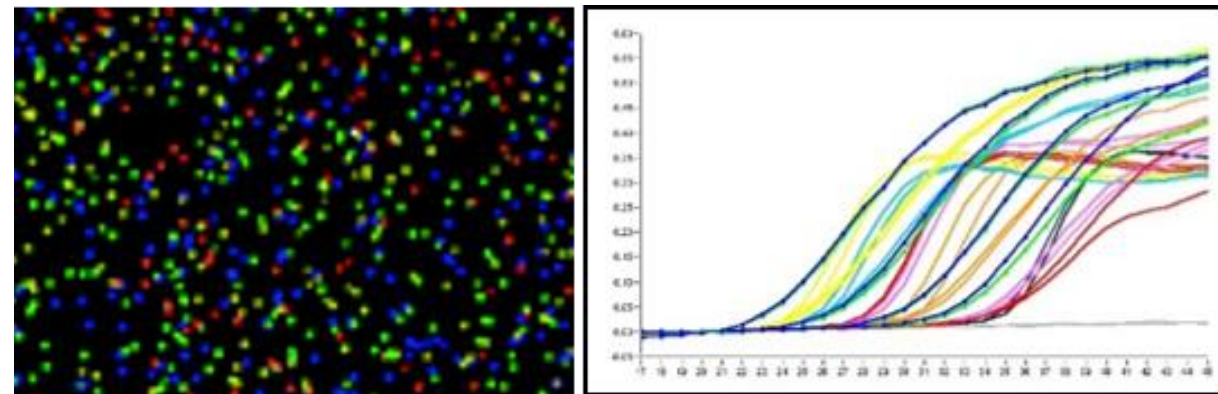
Cytomorphology



Immunophenotyping



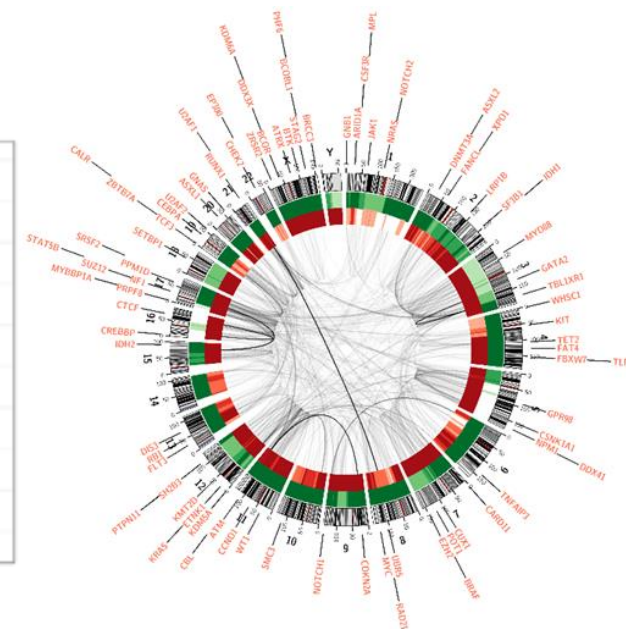
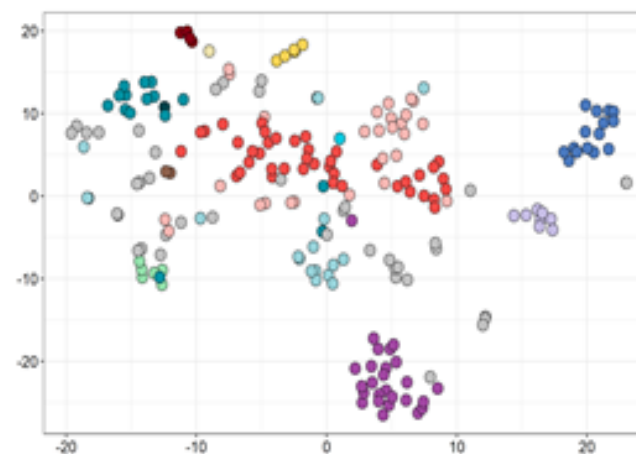
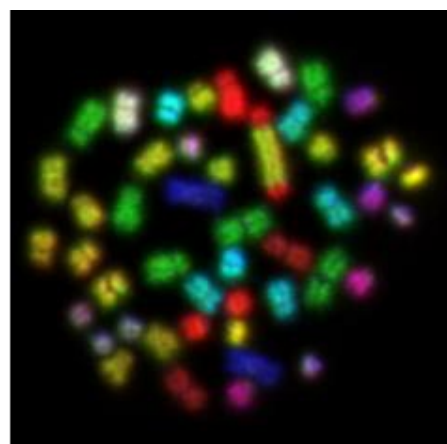
Molecular Genetics

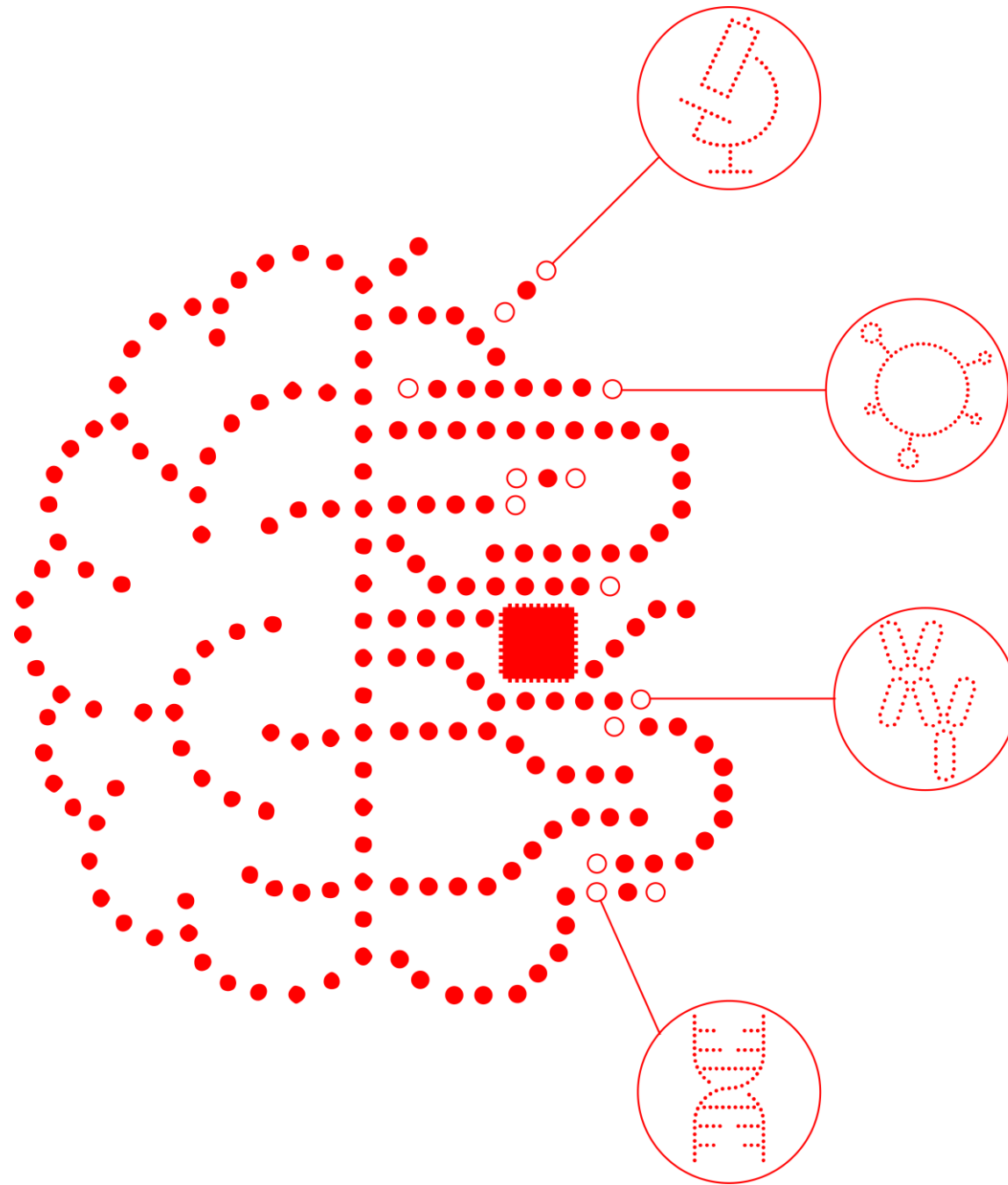


Cytogenetics



FISH





How to confuse a phenotype driven machine learning model



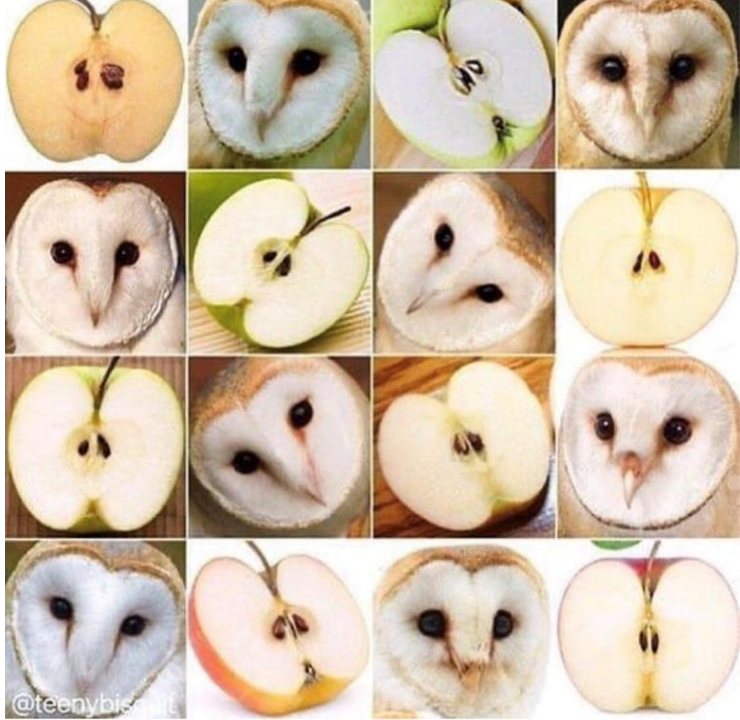
Chihuahua or muffin?



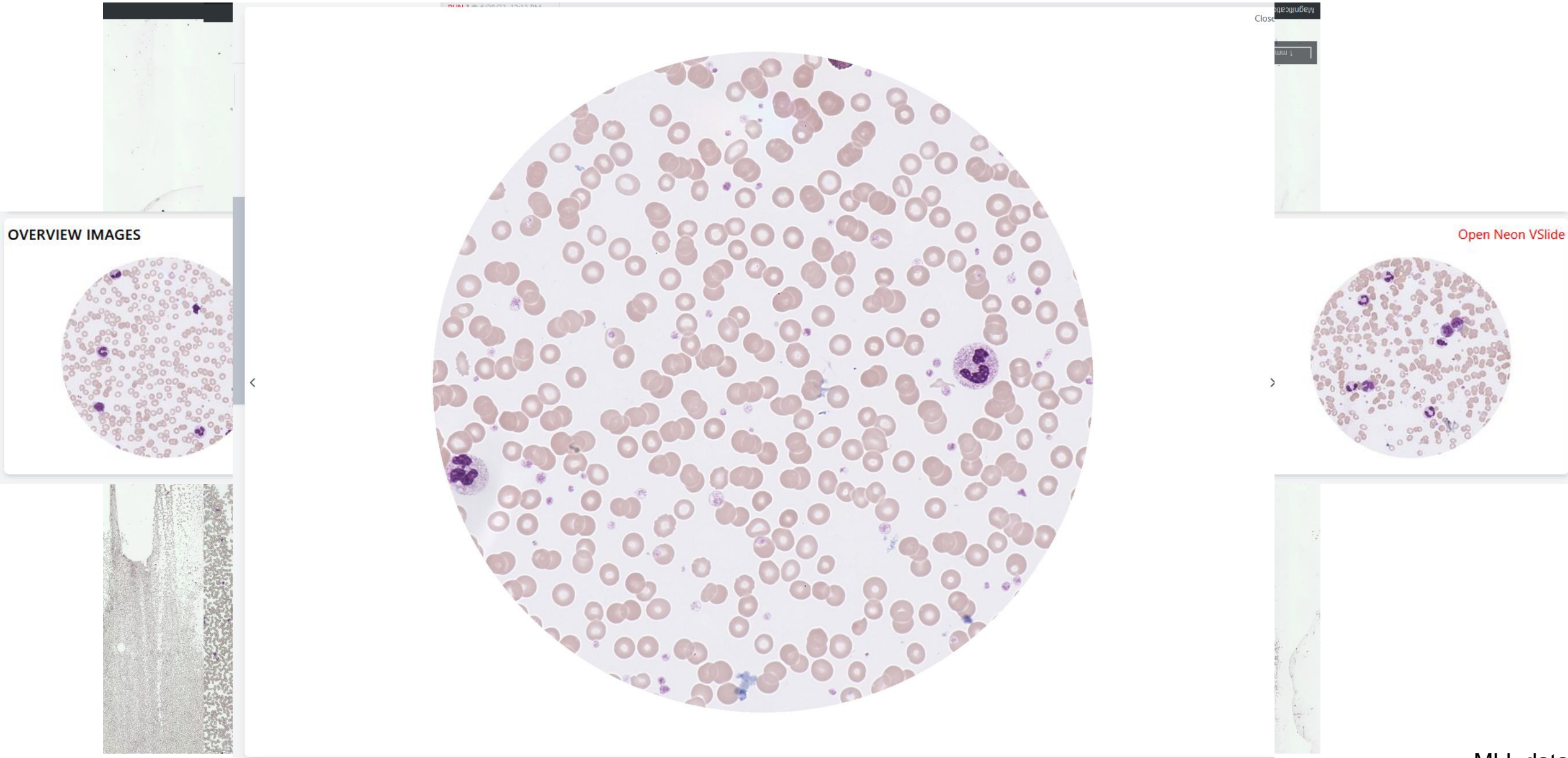
Dog or bagel?



Owl or apple?



The digital way to cell images



Digitalization of blood cells (100x)



Metafer 4
3.16.147 | MetaCyte

Mode File Slide Cells Scoring Training MetaCyte Configure Stage Filters Tools Help

33 1:1

Scanning ... Adm

20-068009 TEST RD.1 0

Params : Blood-v8.No_1
Magnif : 10.0
Field : 0 of 160
Fields / s : 0.0
T Elapsed : 0:00
Remaining :

Setup
Search Fields
Gallery
Relocate

(time lapse)

Digitalization of blood cells

„Close-Up“ of single cells (400x oil): 500 cells/smear (~ 4:30 min)



Metafer 4 | MetaCyte 3.16.147

Mode File Slide Cells Scoring Training MetaCyte Configure Stage Filters Tools Help

33 1:1

Scan 2:
40x Leukocytes Classification/DNN

Scanning ... Adm

Params : Blood-v8.DNN-Detection
Magnif. : 39.8
Field : 0 of 79
Fields / s : 0.0
T Elapsed : 0:04
Remaining :

Setup
Search Fields
Gallery
Relocate

20-068009 TEST RD.1~A 0

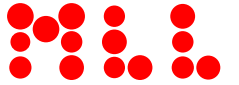
???

5 - 4 - 3 - 2 - 1 3

(time lapse)

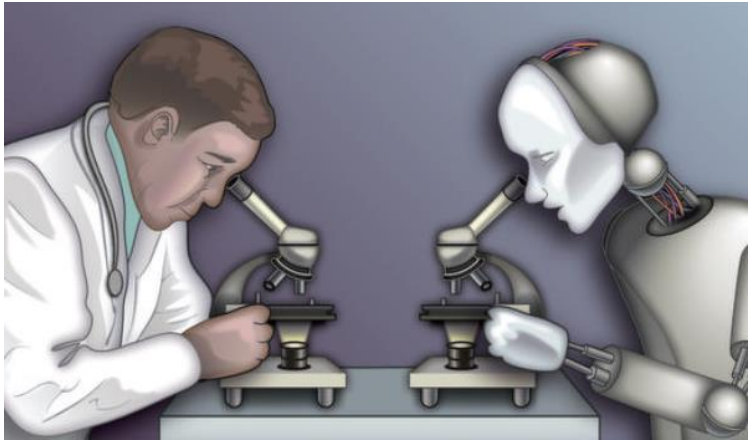
BELUGA Study („Better LeUkemia diaGnostics through AI“)

(Clinicaltrials.gov, NCT04466059)

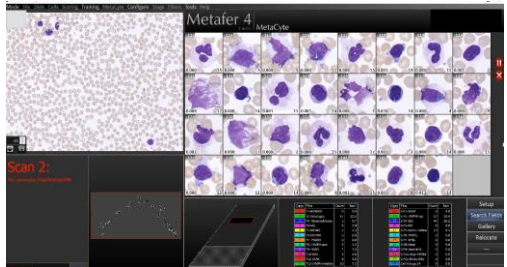
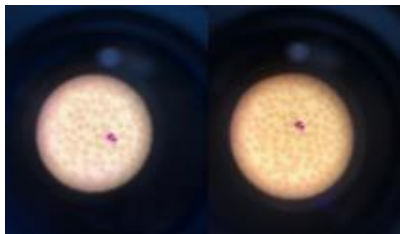
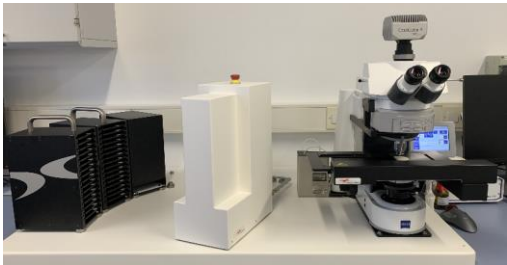


29,119 patient samples (Jan 2021 – Jul 2022)

$\Sigma = 2,911,915$ cells differentiated



$\Sigma = 14,322,972$ cells differentiated



54%	Segmented Neutrophils	48%
1%	Bands	1,47%
2.3%	Concordance 94.5% for malignant/critical cells	2,69%
0.76%		2%
6.96%		7.05%
30.91%		Lymphocytes
1.11%	Pathogenic blasts	3.25%



Cloud Platform: Flow Cytometry



Overview Gating

no evidence of MDS with a probability of 99.36%

Diagnoses Breakdown

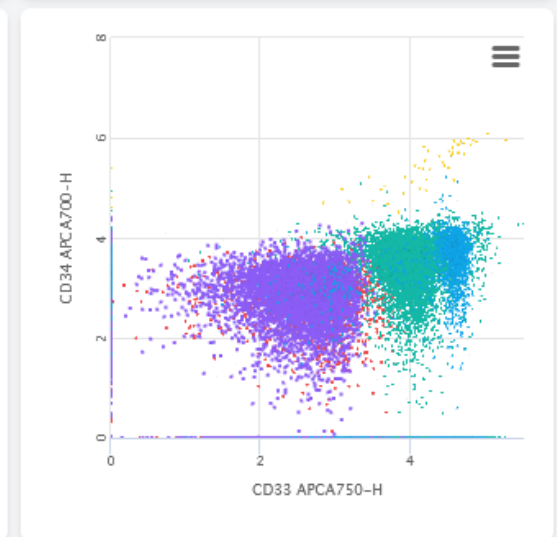
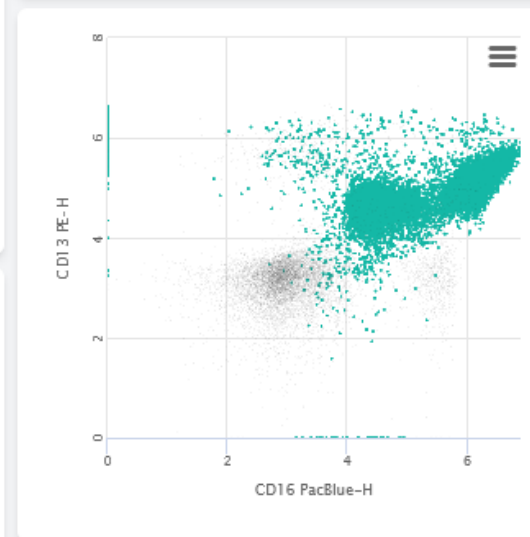
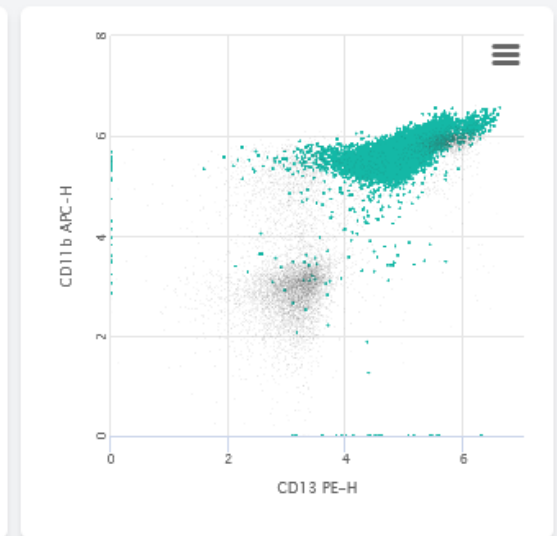
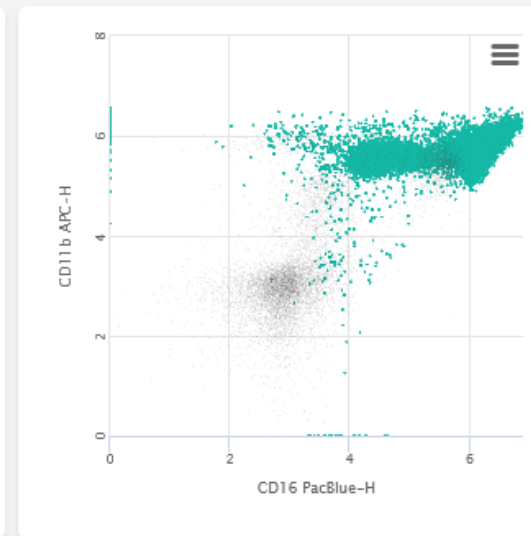
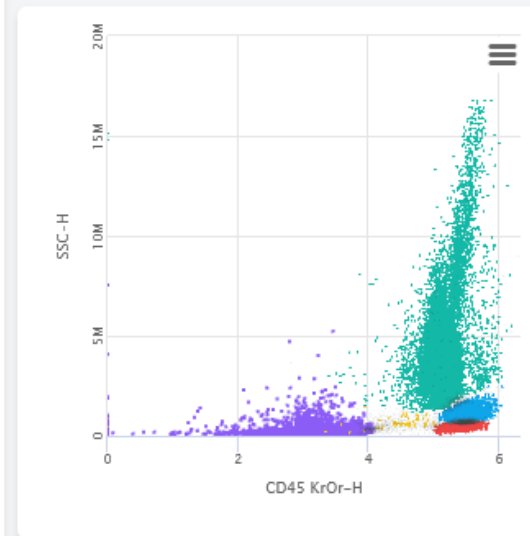


● Probability

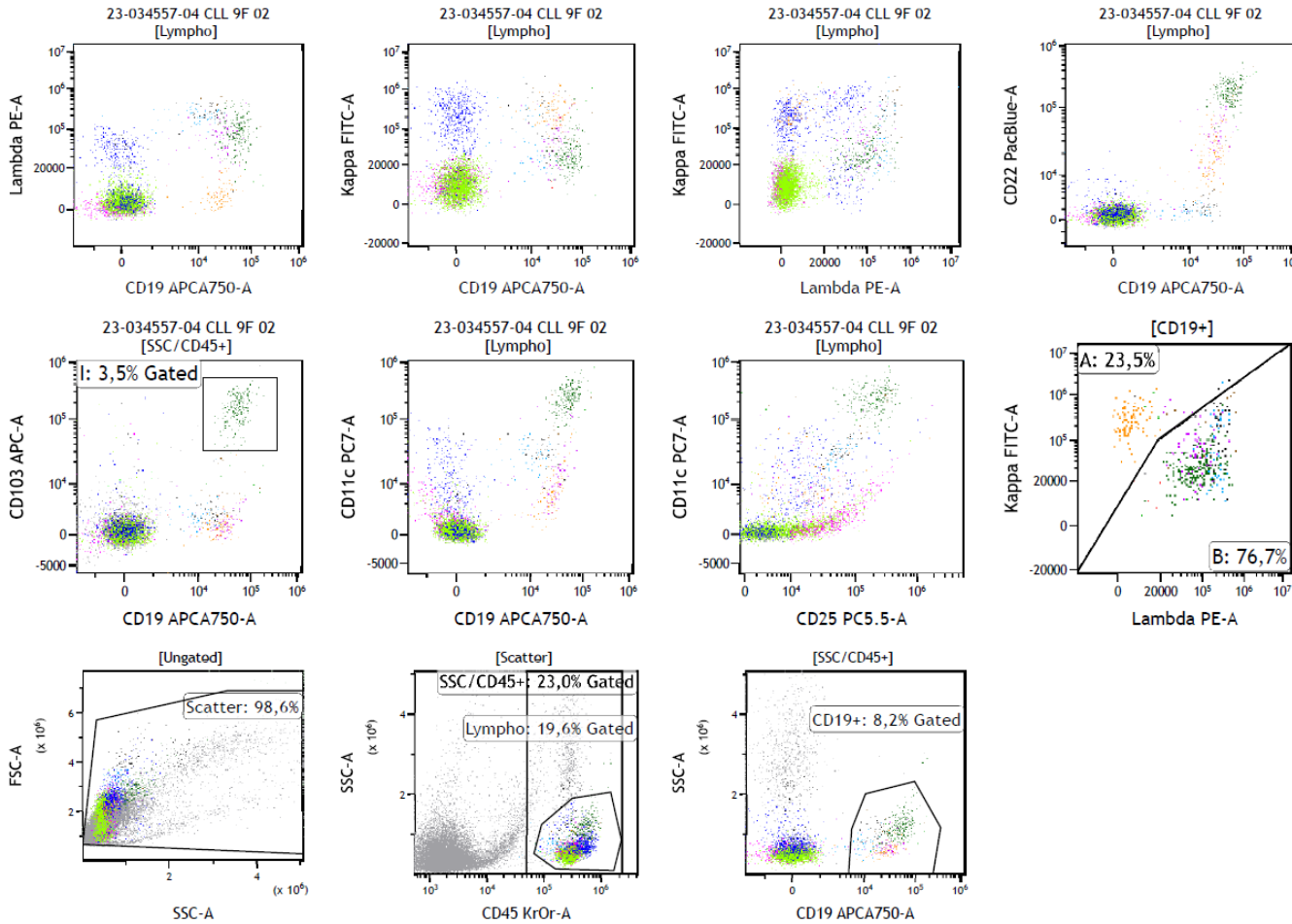
no evidence of MDS	99.36%
Consistent with MDS	0.64%

SUBGROUP	COUNT	PCTG.
All	126,475	100%
blasts	320	0%
debris	40,887	
granulocytes	46,257	37%
lymphocytes	16,736	13%
monocytes	8,362	7%

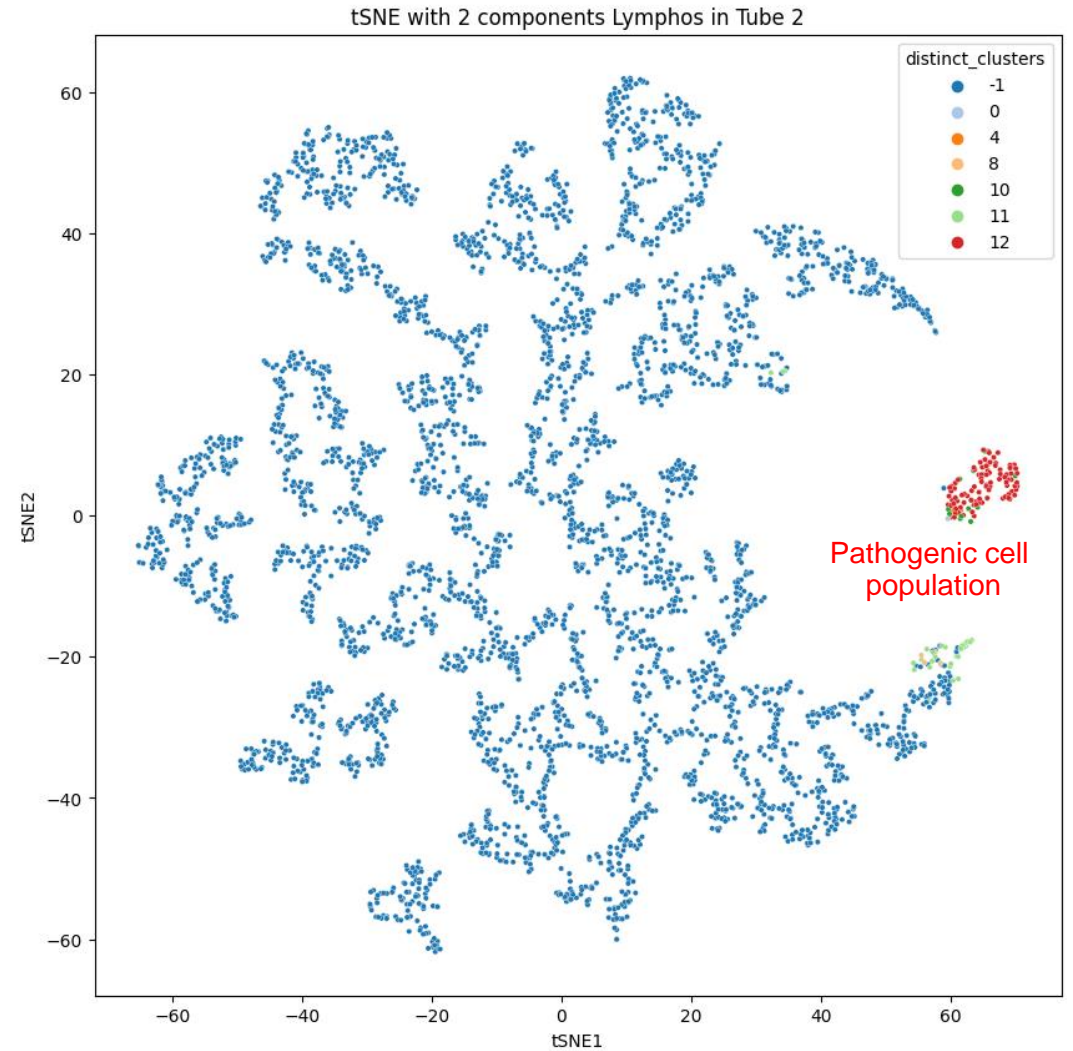
MDS01



Dimensionality reduction



Traditional expert human review
High complexity

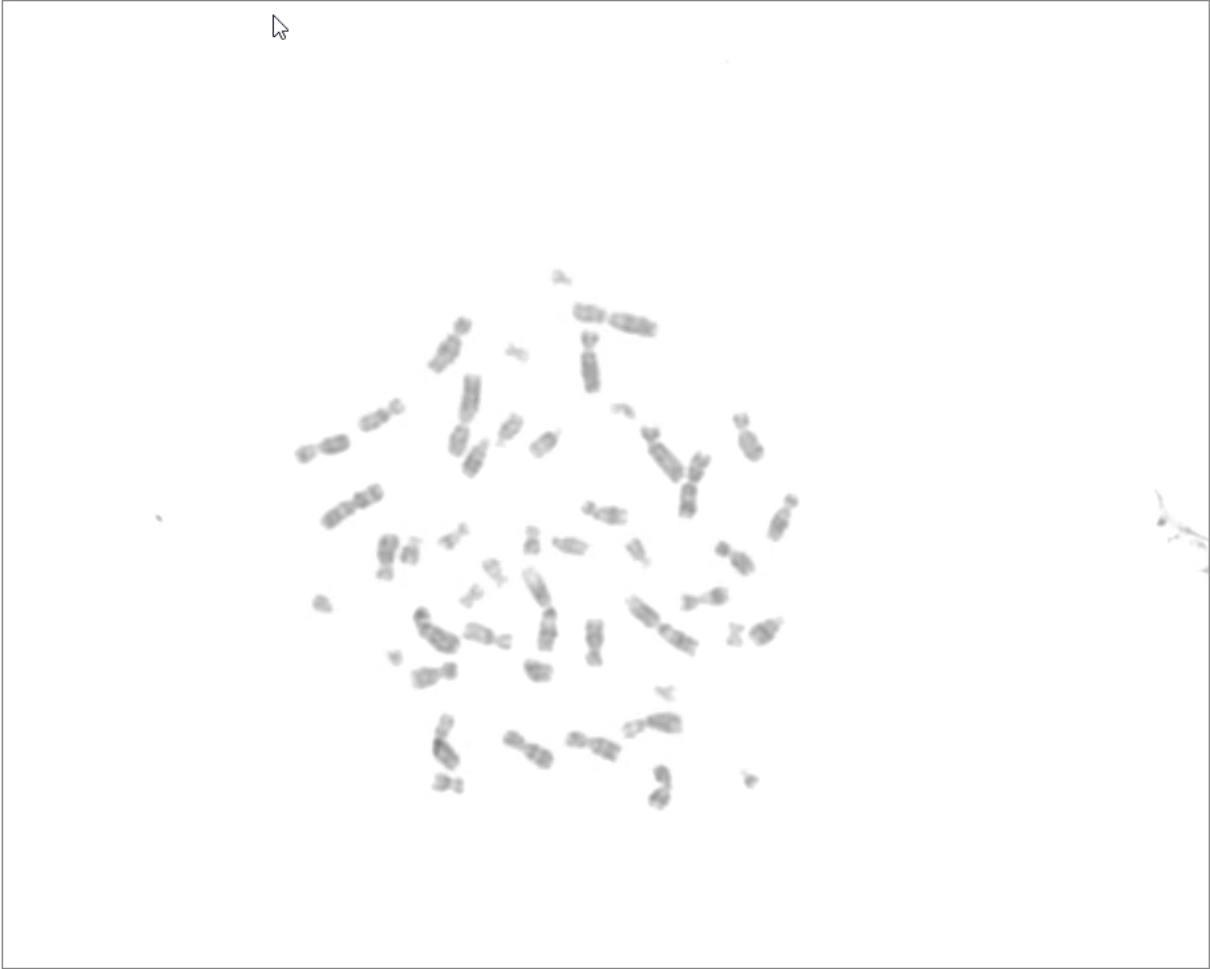


AI based – reduction of complexity
Easy to understand even for non-experts

Manual classification










MetaSystems Ikaros [100%]
Datei Bearbeiten Ansicht Metaphase Filter Objekte Hilfe



1 2 3 4 5 met
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X Y


Objektschwelle
Metaphase Maskieren
Objekte löschen
Objekte trennen
Überlappungen
Objekte prüfen
Beschriften



21-018349KE1-A	◀ 084a ▶	◀ A ▶	0	44	2021-srv16	210309
	-870/-12512		CID:84		WP	GBand

AI-based classification

MetaSystems Ikaros [100%]
Datei Bearbeiten Ansicht Metaphase Filter Objekte Hilfe



1 2 3 4 5 mar
6 7 8 9 10 11 12
13 14 15 16 17 18
19 20 21 22 X Y

Objektschwelle
Metaphase Maskieren
Objekte löschen
Objekte trennen
Überlappungen
Objekte prüfen
Beschriften

21-018349KE1-A ◀ 084a ▶ ◀ A ▶ 1 2021-srv16 210309
-870/-12512 CID:84 WP GBand

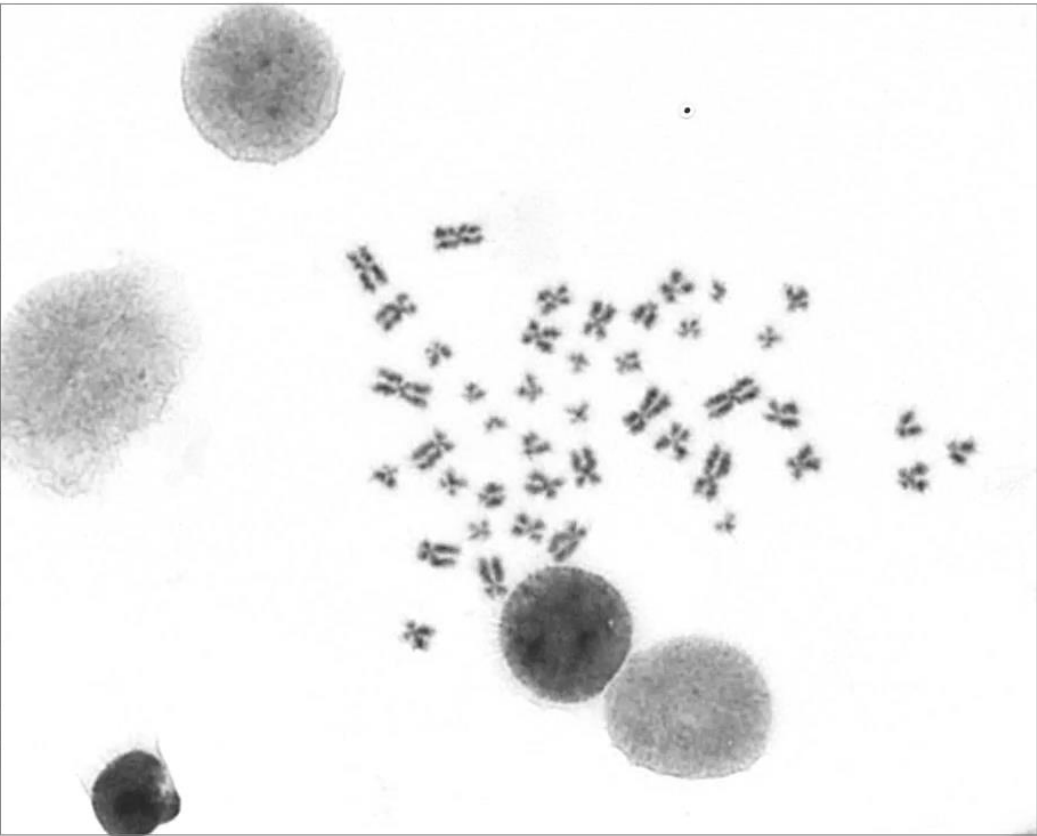


AI-based Batch-Karyotyping (20 metaphases)

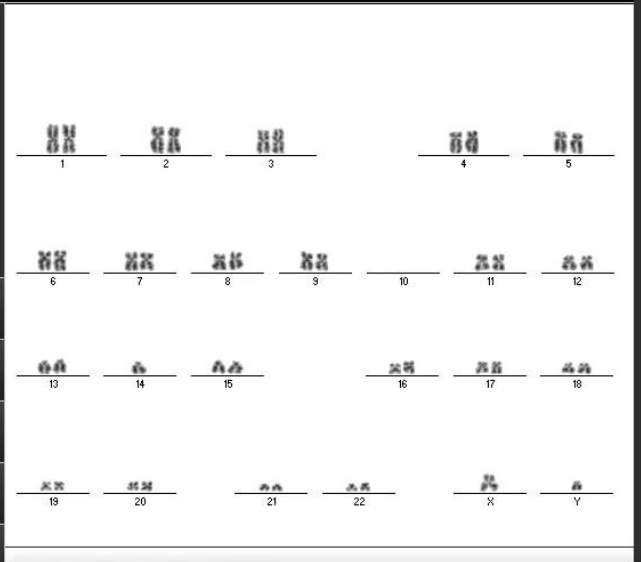


MetaSystems **ikaros** V 5.10.116

Metaphase Filter Objekte Hilfe



Objektschwelle
Metaphase Maskieren
Objekte löschen
Objekte trennen
Überlappungen
Objekte prüfen
Beschriften



210413

Datei Start Freigegeben Ansicht

An Schnellzugriff anheften Kopieren Einfügen Zwischenablage Organisieren Neu Eigenschaften Öffnen Auswählen

MP-... > 210413 "210413" durchsuchen

Name	Änderung
Dokumente	
Bilder	
210413	
Cfg	
Lokaler Datenträger	
Sptlks	
OneDrive	
Dieser PC	
3D-Objekte	

0 Elemente

17-020544KP1-E ◀ 201 ▶ ◀ A ▶ p 43 mllpc466-local 210413
-7626/-4135 CID:694 WP GRand

Molecular methods: Panel sequencing



Gene	ROI	Gene	ROI
ASXL1	E12, E13	PDGFRA	CCS
ASXL2	E12, E13	PDGFRB	CCS
ATRX	CCS	PHF6	CCS
BCOR	CCS	PIGA	CCS
BCORL1	CCS	PPM1D	CCS
BRAF	CCS	PRPF8	CCS
CALR	E09	PTEN	CCS
CBL	CCS	PTPN11	CCS
CEBPA	CCS	RAD21	CCS
CSF3R	E14-E17	RUNX1	CCS
CSNK1A1	E03, E04	SETBP1	E04
CUX1	CCS	SF1	CCS
DDX41	CCS	SF3A1	CCS
DNMT3A	CCS	SF3B1	E13-E16
ETNK1	E03	SH2B3	CCS
ETV6	CCS	SMC1A	CCS
EZH2	CCS	SMC3	CCS
FBXW7	CCS	SRSF2	E01
FLT3	E14-E20	STAG2	CCS
GATA1	CCS	SUZ12	CCS
GATA2	CCS	TET2	CCS
IDH1	E04, E07	TP53	CCS
IDH2	E04, E07	U2AF1	E02, E06
IL6R	rs2228145	U2AF2	E02, E06
JAK2	CCS	UBA1	CCS
KIT	CCS	WT1	E07, E09
KRAS	CCS	ZEB2	CCS
MPL	CCS	ZRSR2	CCS
MYD88	CCS		
NF1	CCS		
NOTCH1	E26-E28, E34		
NPM1	E11		
NRAS	CCS		

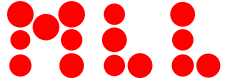
myeloid panel

Gene	ROI	Gene	ROI
ARID1A	CCS	KLHL6	CCS
ATM	CCS	KMT2D	CCS
ATR	CCS	KRAS	CCS
BCL10	CCS	MAP2K1	CCS
BCL2	CCS	MEF2B	CCS
BIRC3	CCS	MYC	CCS
BRAF	CCS	MYD88	CCS
BTK	E15	NOTCH1	E26-E28, E34
CARD11	CCS	NOTCH2	E26, E27, E34
CCL22	CCS	NRAS	CCS
CCND1	UTR+CCS	PAX5	E03
CD28	CCS	PHF6	CCS
CD79B	CCS	PLCG1	CCS
CREBBP	CCS	PLCG2	CCS
CXCR4	CCS	POT1	CCS
DIS3	CCS	PTEN	CCS
DNMT3A	CCS	RHOA	CCS
EGR1	CCS	RPS15	CCS
EP300	CCS	RUNX1	CCS
ETV6	CCS	SF3B1	E13-E16
EZH2	CCS	SGK1	CCS
FBXW7	CCS	SOCS1	CCS
FLT3	E14-E20	STAT3	E20, E21
FOXO1	CCS	STAT5B	CCS
FYN	CCS	STAT6	CCS
ID3	CCS	TET2	CCS
IDH2	E04, E07	TNFAIP3	CCS
IKZF1	CCS	TP53	CCS
IL7R	CCS	UBR5	E58
IRF4	CCS	VAV1	E04, E07
JAK1	CCS	XPO1	CCS
JAK2	CCS	ZEB2	CCS
JAK3	CCS		
KLF2	CCS		

lymphoid panel

Data Interpretation: NGS

Variant annotation & interpretation



COSMIC

COSMIC ID	DNA	Protein	SNP	Somatic status	FATHMM-MKL	Count	Samples
COSM53042	c.2644C>T	p.R882C	No	Reported in another cancer sample as somatic Confirmed somatic variant	PATHOGENIC	442	more...
COSM87001	c.2644C>A	p.R882S	No	Reported in another cancer sample as somatic Confirmed somatic variant	PATHOGENIC	44	more...

DNA pos. may differ, as different transcripts are used. Query based on chromosomal coordinates.

DNMT3A
c.2644C>T

ClinVar

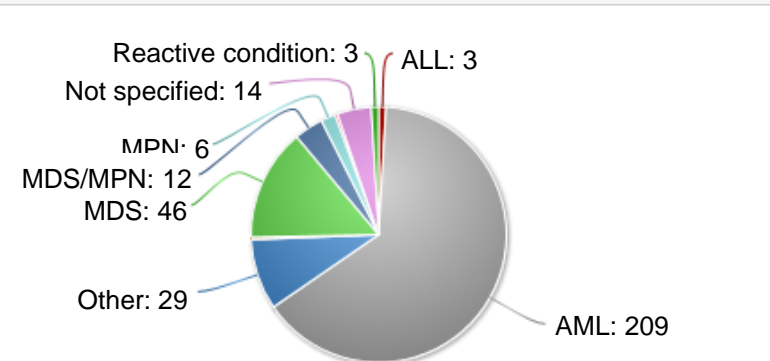
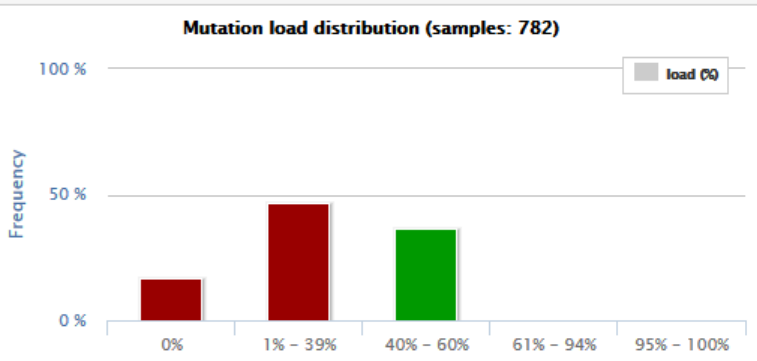
ID	HGVS	Type	Clinical Significance	Origin	ReviewStatus	Number Submitters	Last Evaluated	dbSNP	Cytogenetics	Guidelines	PhenotypeIDs
362761	c.2644C>T (p.Arg882Cys)	single nucleotide variant	Pathogenic/Likely pathogenic	somatic	no assertion criteria provided	1	May 31, 2016	rs377577594	2p23.3		MedGen MedGen MedGen OMIM OMIM Orpha Orpha SNOMED CT
362762	c.2644C>G (p.Arg882Gly)	single nucleotide variant	Pathogenic	somatic	no assertion criteria provided	1	Oct 02, 2014	rs377577594	2p23.3		MedGen OMIM Orpha SNOMED CT
362763	c.2644C>A (p.Arg882Ser)	single nucleotide variant	Pathogenic	somatic	no assertion criteria provided	1	Oct 02, 2014	rs377577594	2p23.3		MedGen OMIM Orpha SNOMED CT

DNA pos. may differ, as different transcripts are used. Query based on chromosomal coordinates.

dbNSFP

Location (hg19)	ref	alt	AAref	AAalt	MLL Predictor	Ensemble Predictions	Individual Predictions	Alt. Allele Freqs
chr2:25457243	G	A	R	C	Pathogenic (1.000)	REVEL CADD DANN Eigen Eigen-PC more...	Mutation Taster PROVEAN VEST3 M-CAP SIFT more...	GnomAD: 0.0126% ESP_EA: 0.0465%

Mouse-over dotted-underlined key words for additional information.



Variant interpretation

Variant annotation



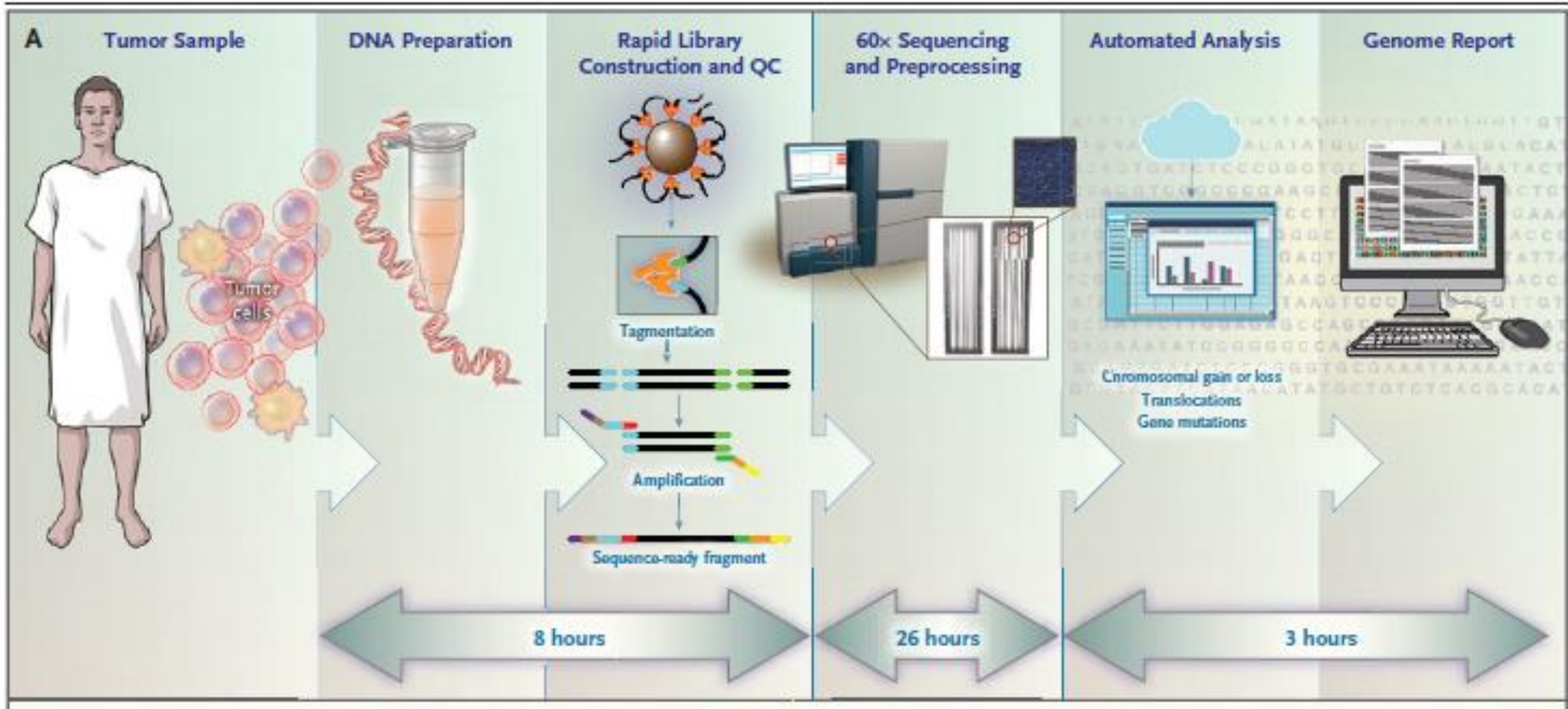
Variant interpretation

- DB (COSMIC, ClinVar, etc.)
- In-house database
- **MLL predictor (AI based)**



Report-ready variants

WGS and WTS as diagnostic tools





NCCN Guidelines Version 2.2023 Acute Myeloid Leukemia (Age ≥18 years)



EVALUATION FOR AML

- History and physical (H&P)
- Complete blood count (CBC), platelets, differential, comprehensive metabolic panel (CMP), uric acid, lactate dehydrogenase (LDH)
- B12 and folic acid evaluation
- Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen
- Bone marrow (BM) core biopsy and aspirate analyses, including immunophenotyping by immunohistochemistry (IHC) stains + flow cytometry, and the analysis of chromosomal structural variations by cytogenetics, fluorescence in situ hybridization (FISH), or **whole genome sequencing** ([See AML-A](#))
- Molecular analyses (*ASXL1*, *c-KIT*, *FLT3* [ITD (internal tandem duplication) and TKD (tyrosine kinase domain)], *NPM1*, *CEBPA* [biallelic], *IDH1*, *IDH2*, *RUNX1*, *TP53*, and other mutations^a) ([See AML-A](#))
- Comprehensive pathology report, including diagnosis of AML (acute myeloid leukemia) with recurrent cytogenetics vs. AML not otherwise specified (NOS), blast count, cellularity, morphologic dysplasia, and mutation status if available

DIAGNOSTIC STUDIES

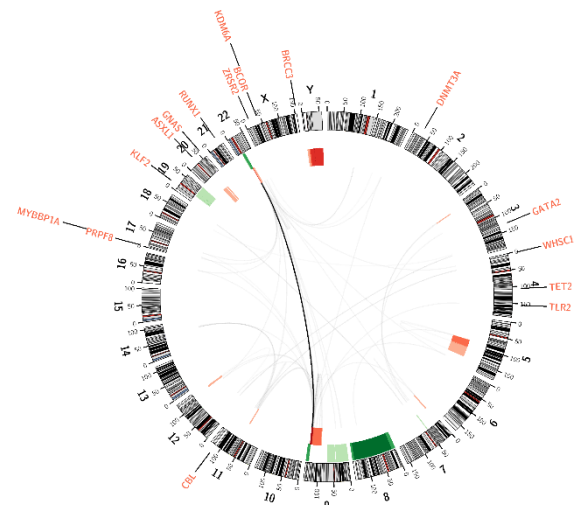
Multidisciplinary diagnostic studies^{d,e,j}

DIAGNOSIS^{d,e,f,j}

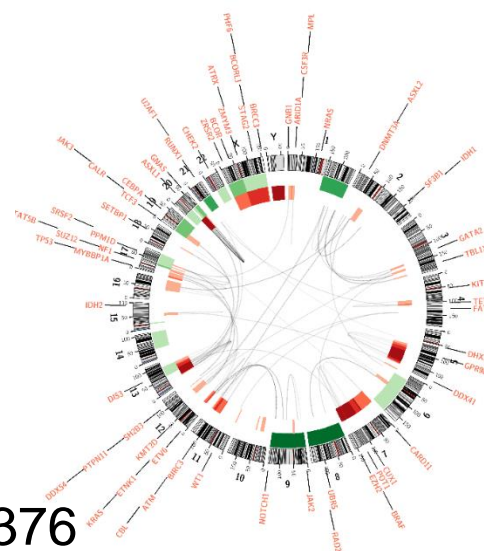
Acute promyelocytic
In patients with clinical features of APL, start (ATRA) upon first suspicion. Initiation of ATRA may be complicated by bleeding and molecular testing. If bleeding complication occurs, discontinue ATRA and manage as for AML.

AML:
To appropriately stratify therapy options, expect of molecular and cytogenetic for immediately actionable chromosomal abnormalities. binding factor [CBF], *NPM1*, *IDH1*, *IDH2*)
• For patients with hyperleukocytosis uncontrolled with hydroxyurea, leukapheresis, one dose cytarabine (1–

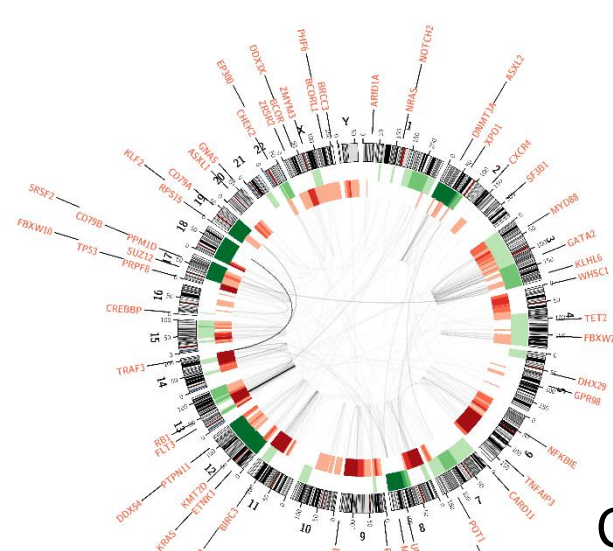
Genomic profiles in 5k cohort



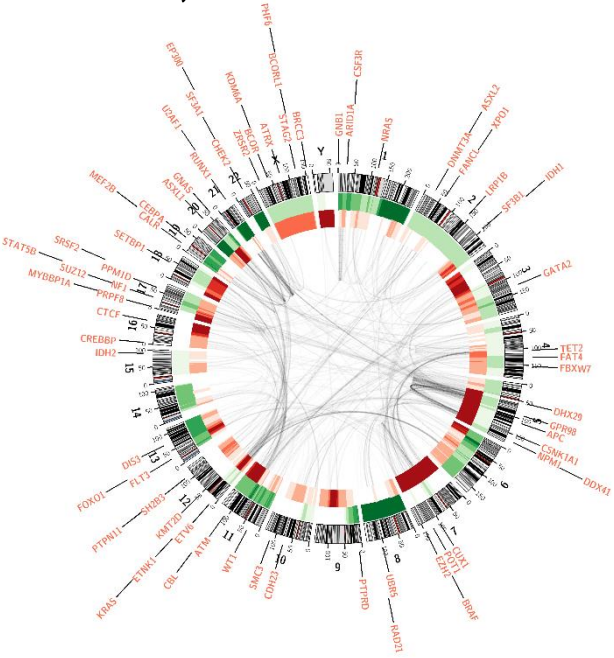
CML, n=107



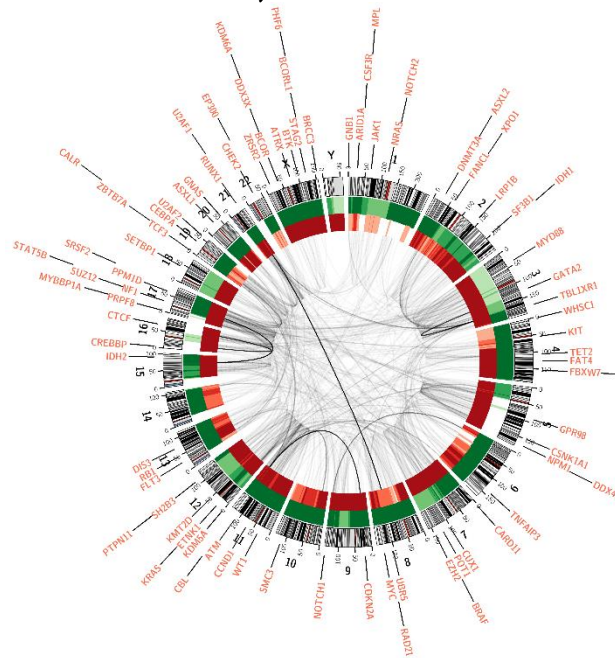
MPN, n=376



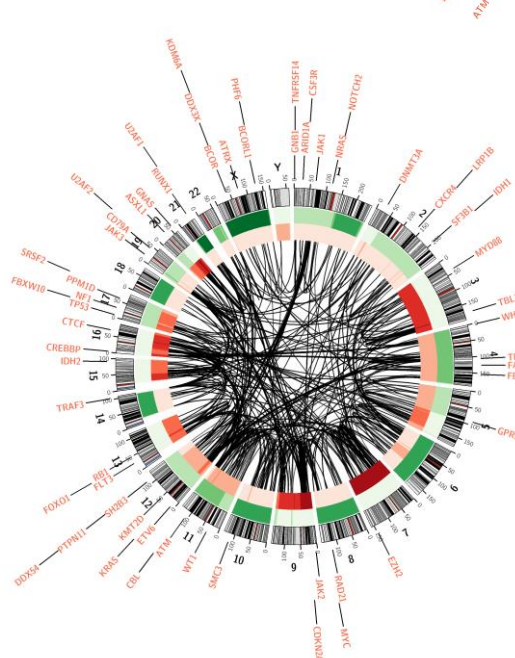
CLL: n=317



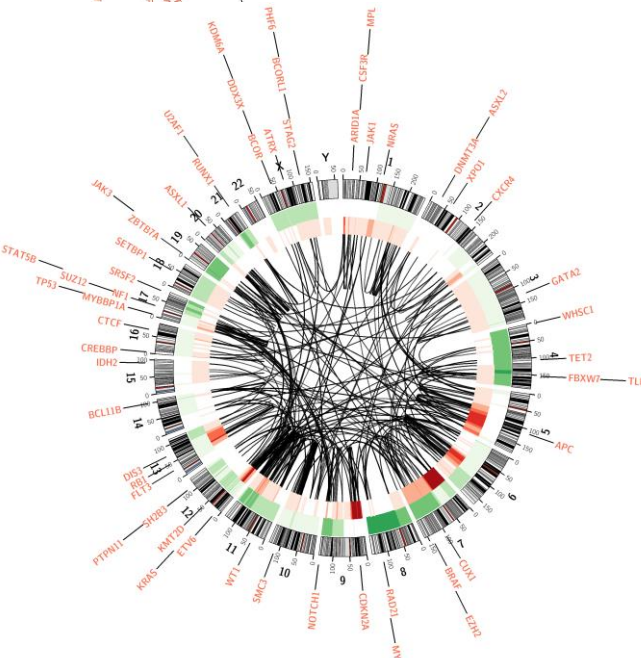
MDS, n=783



AML, n=614

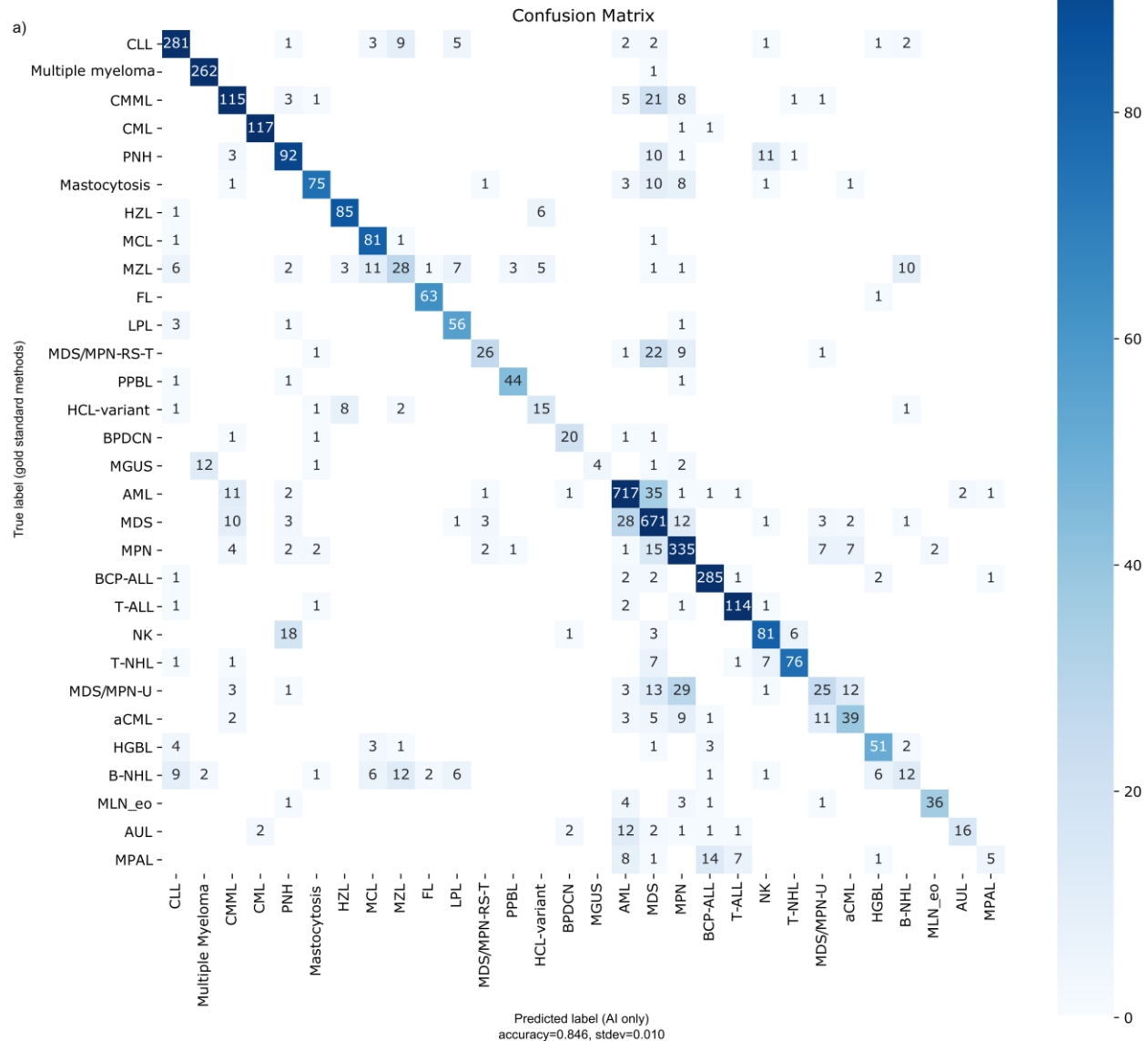


B-ALL (n=324)

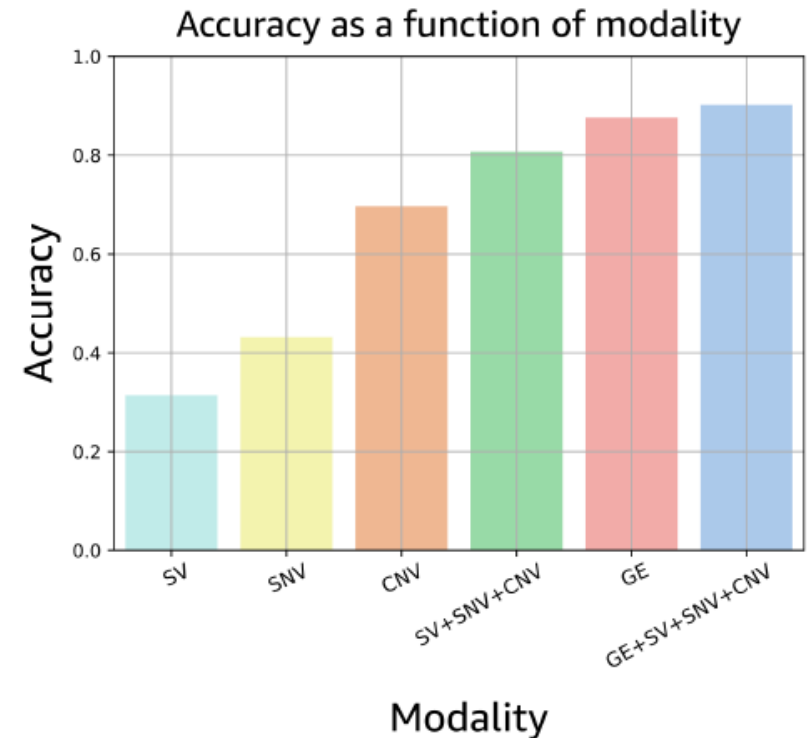


T-ALL (n=133)

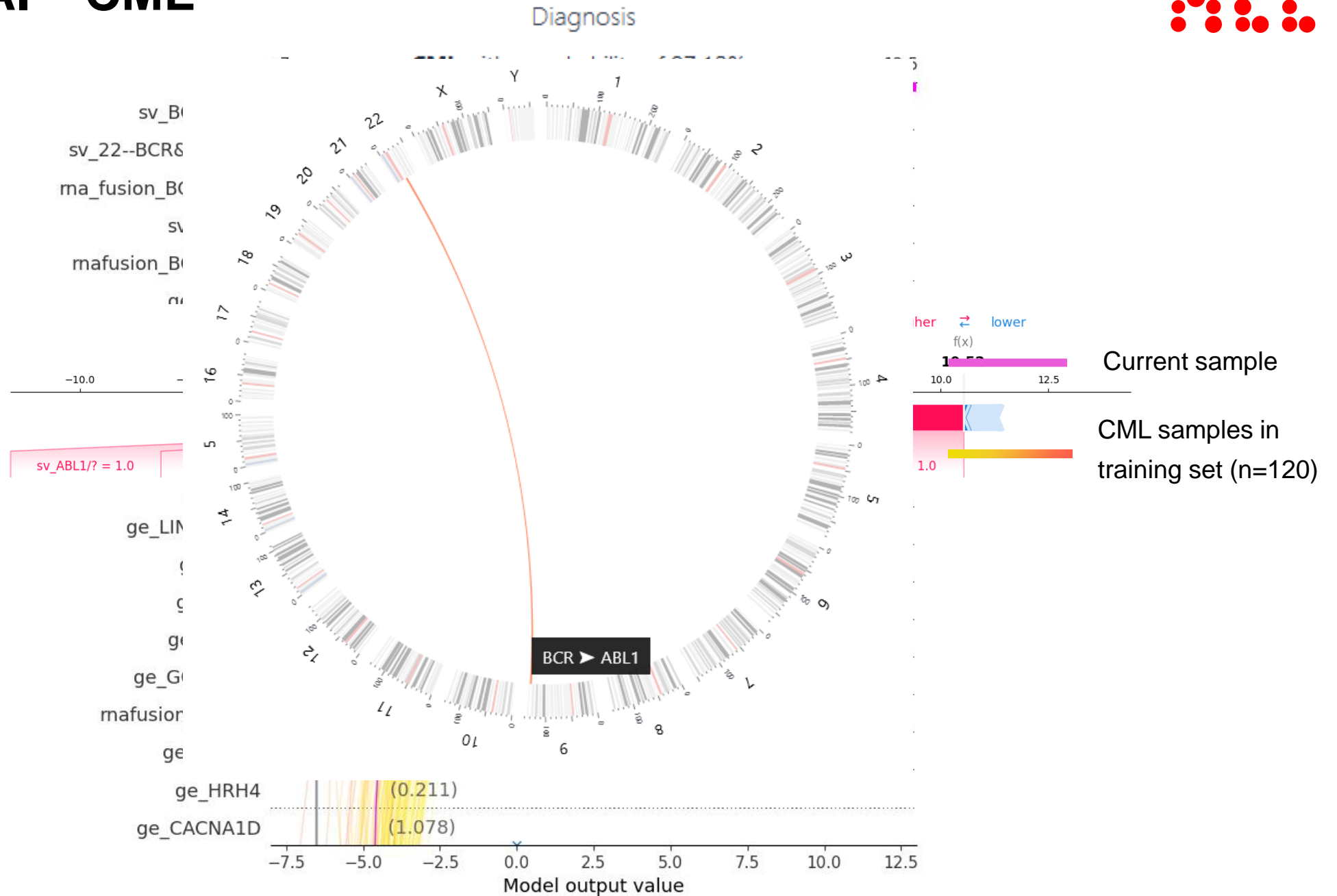
Confusion matrix of model performance



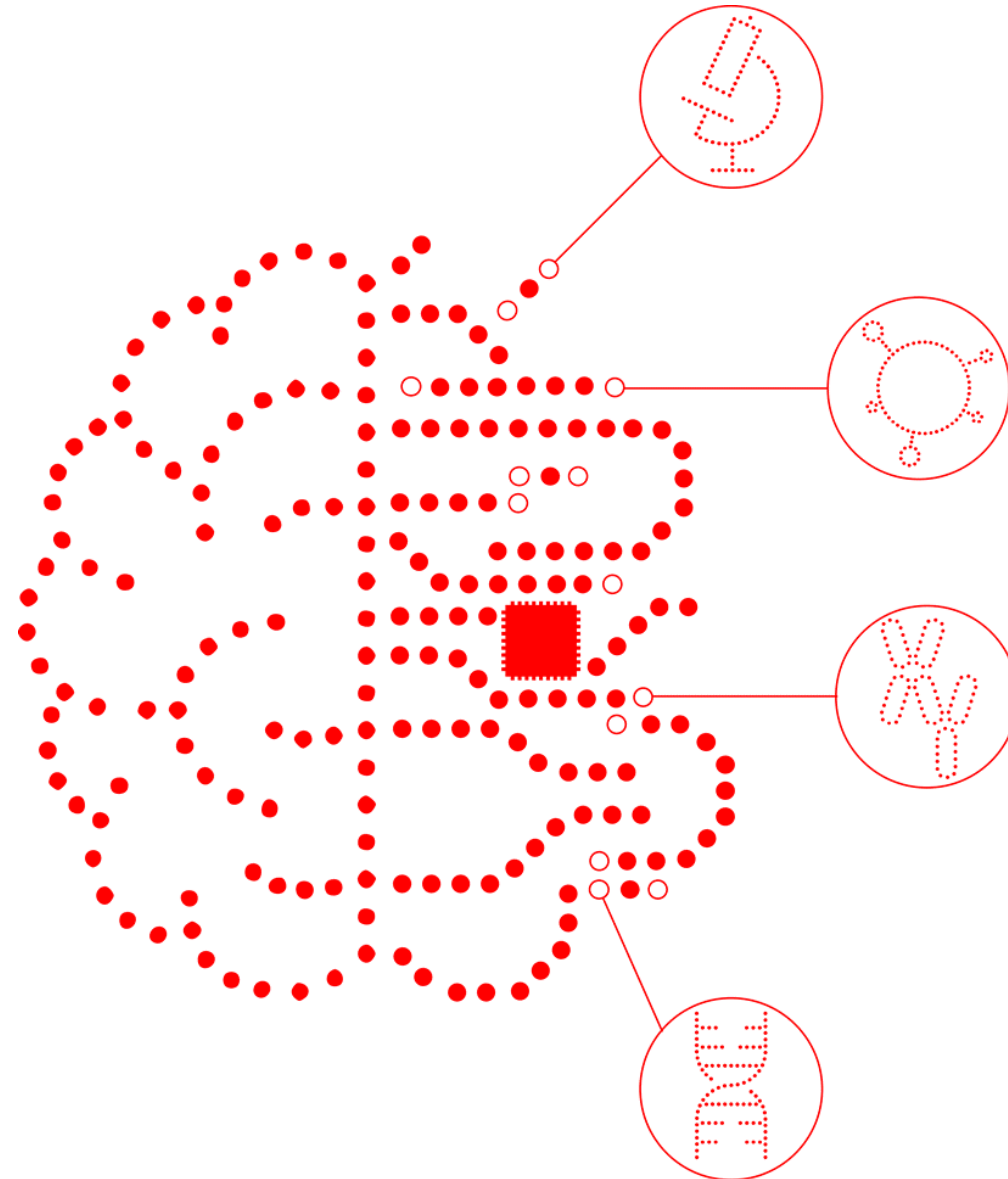
Multi-mode classifier trained on
4689 cases with
32 different hematologic neoplasms
 and normal category
 Dataset was unbalanced (20 – 773 cases)



Transparent AI - CML



Large Language Model (LLM)



Automated diagnosis with Large Language Models (LLM)



Current New Case



1

Similarity Search

Historical Data

LLM



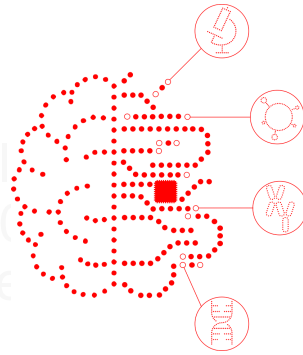
2

Diagnosis Prediction



Human Evaluation

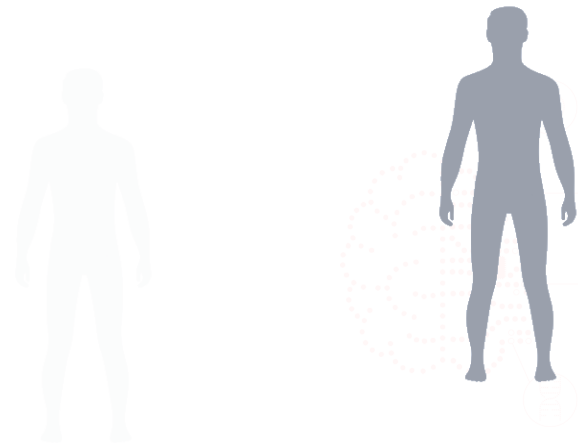
Qualitative detail
evaluation of 10
comes to a corre



86%

Who is the author?

model: gpt-3.5-turbo-0613 w/ temperature 0.0



MPN not detectable with certainty

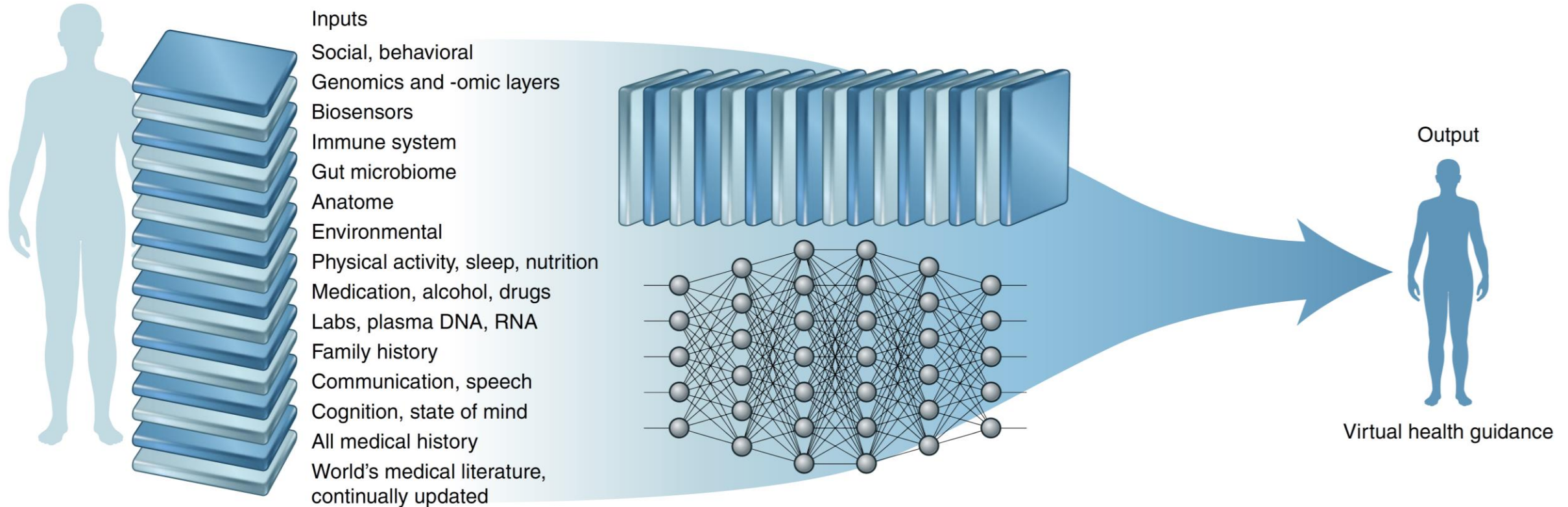
The normocellular peripheral blood shows an almost normal cell distribution. In addition, a slight thrombocytosis without higher-grade anisocytosis is seen microscopically. Purely cytomorphologic evidence of MPN is at least not possible, possibly purely reactive changes are present. In case of negativity of conventional MPN associated mutations (JAK2, CALR, MPL) and persistent suspicion of a disease from the myeloproliferative system, an extended molecular genetic diagnosis (e.g. ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1, TP53, U2AF1) should be considered for clonality detection and in view of the WHO criteria.

MPN not detectable with certainty

The peripheral blood is normocellular and shows a normal distribution of cells, no blasts. In addition, a thrombocytosis with a slight anisocytosis is seen. Purely cytomorphologic evidence of MPN is at least not possible, possibly purely reactive changes are present. In case of negativity of conventional MPN associated mutations (JAK2, CALR, MPL) and persistent suspicion of a disease from the myeloproliferative system, an extended molecular genetic diagnosis (e.g. ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1, TP53, U2AF1) should be considered for clonality detection and in view of the WHO criteria.

The virtual medical coach

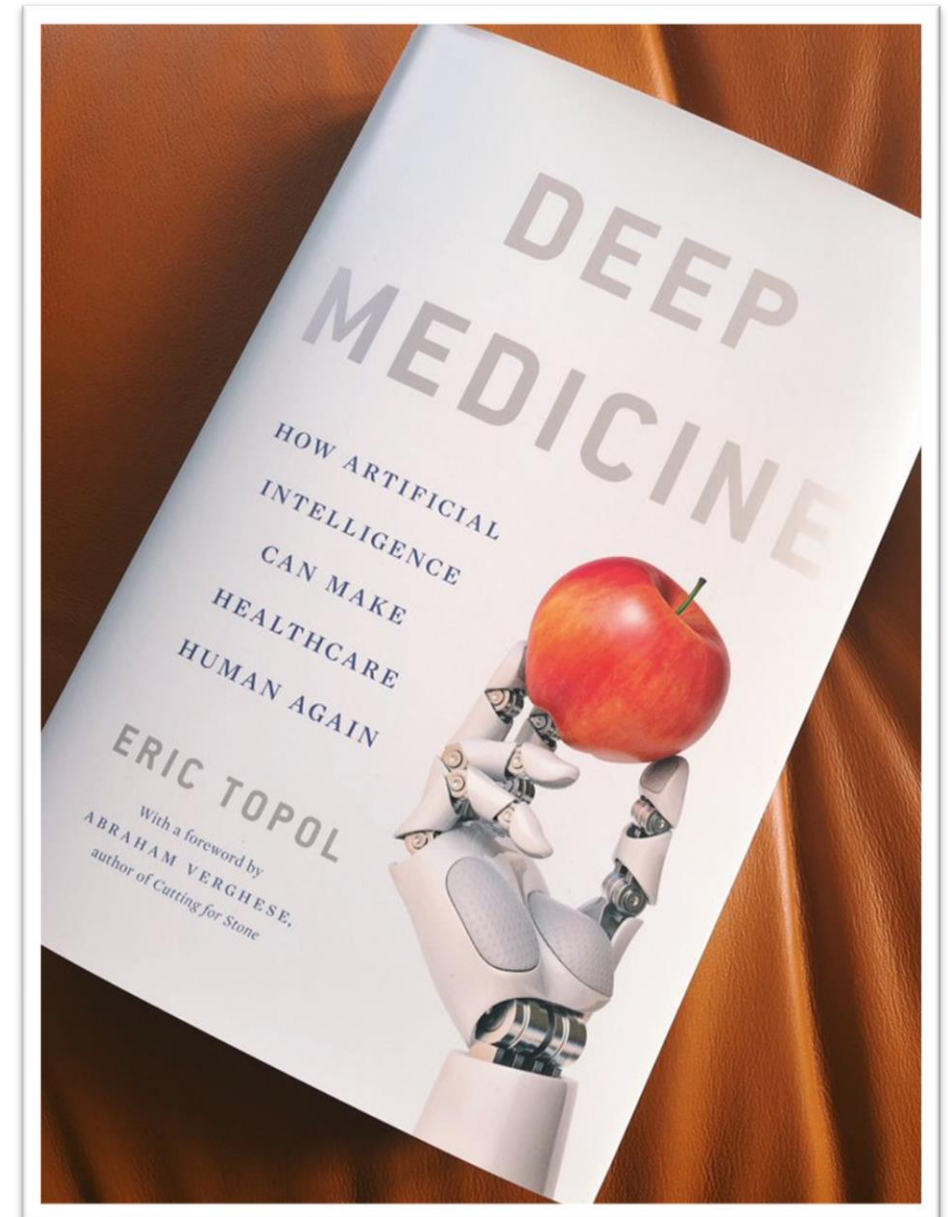
Model for individualized guidance



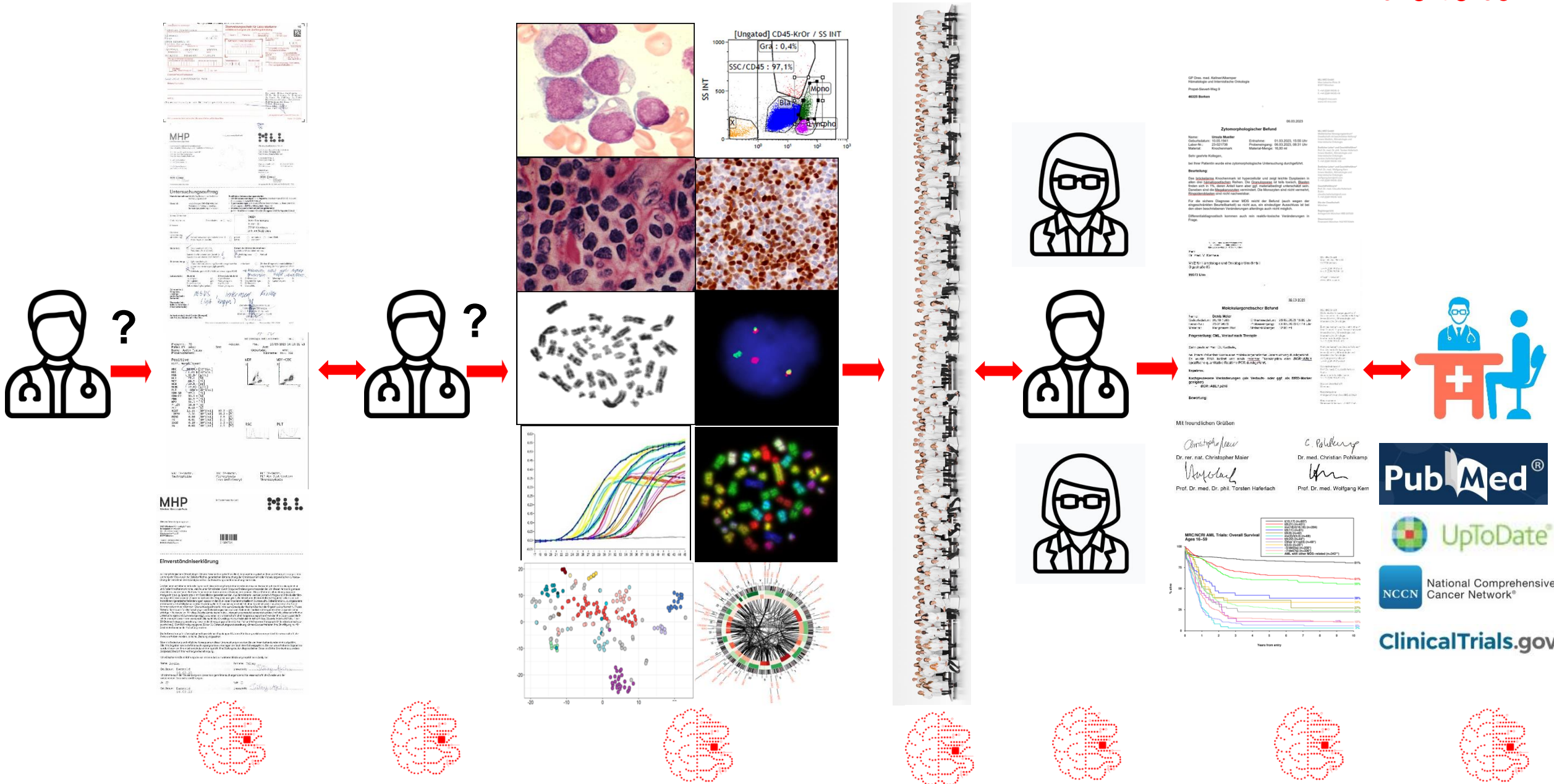
Deep Medicine

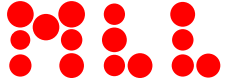


“AI will not replace physicians.
However, physicians who use AI
will replace those who don’t.”



The vision: AI driven lab workflows based on > 1.1 Mio. cases





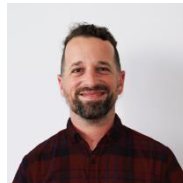
Claudia Haferlach



Wolfgang Kern



Manja Meggendorfer



Sven Maschek



Niroshan Nadarajah



Stephan Hutter

See behind – Go beyond

