Looking into the future: Using AI in hemato-oncology to facilitate personalized and informed interventions

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MLL Munich Leukemia Laboratory

AI, artificial intelligence.

March 2025 | 0225--MRC-179

Disclosures

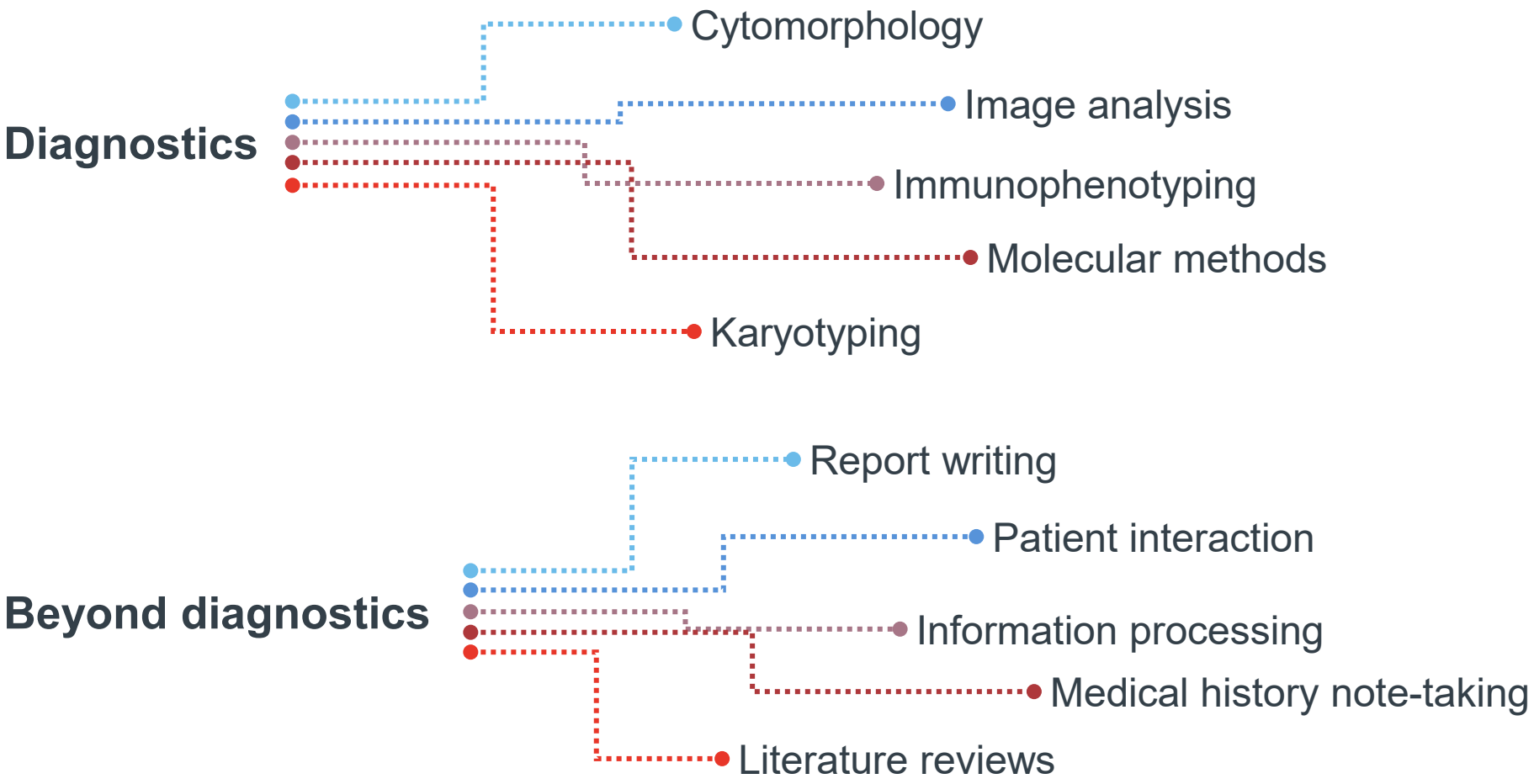
- Dr. Haferlach is part-owner of MLL Munich Leukemia Laboratory

slido

What is your experience with artificial intelligence?

ⓘ Start presenting to display the poll results on this slide.

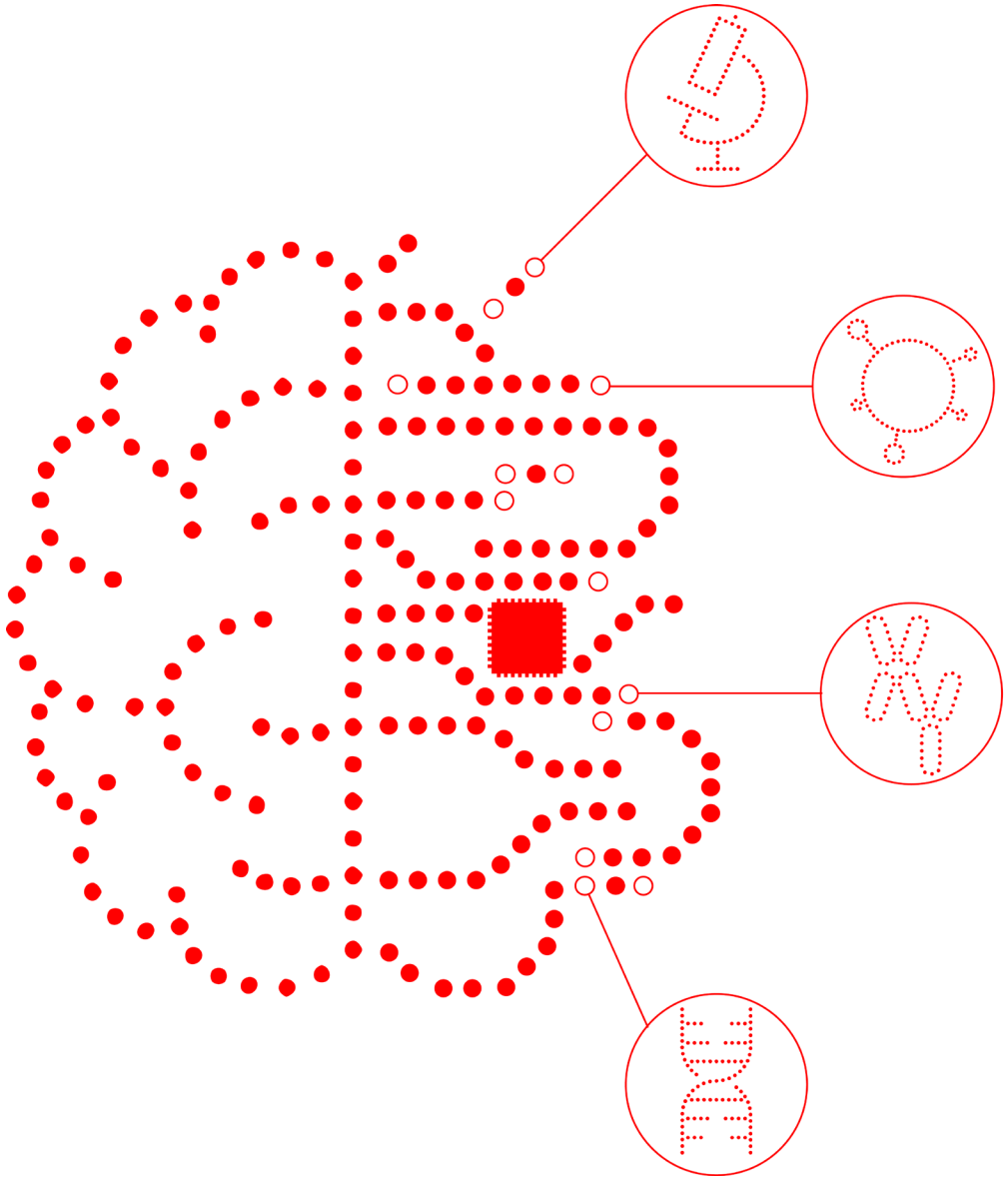
Applications of AI in hemato-oncology



AI, artificial intelligence.
Slide content provided courtesy of Munich Leukemia Laboratory.

Current diagnostic tools for leukemias

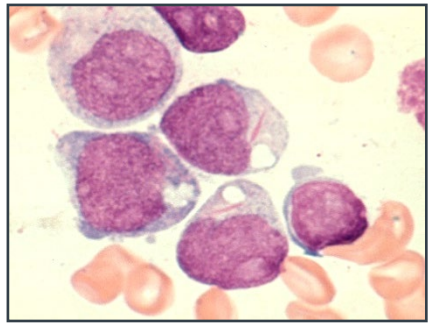
Key diagnostic tools include cytomorphology, cytogenetics, immunophenotyping, histology, FISH, and molecular genetics



FISH, fluorescence *in situ* hybridization.

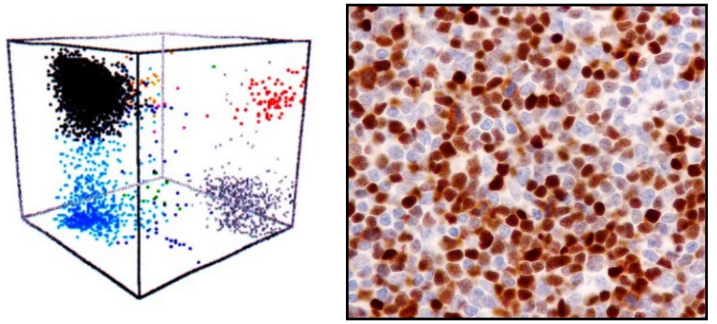
Diagnostic tools in leukemias 2025+

Cytomorphology

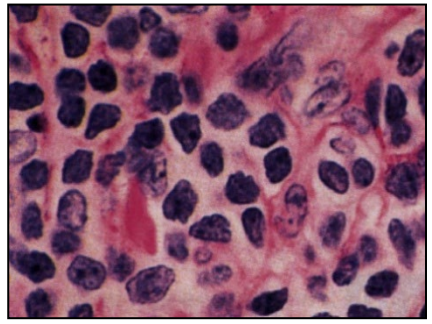


Cytogenetics

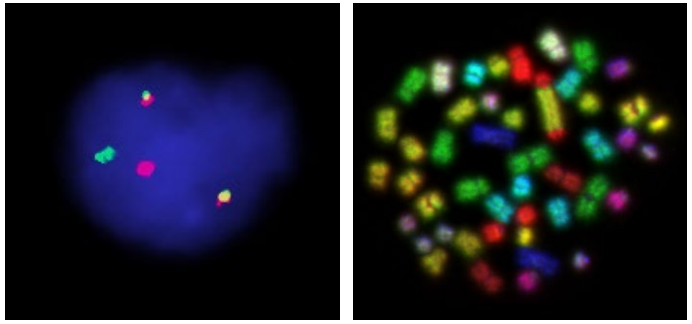
Immunophenotyping



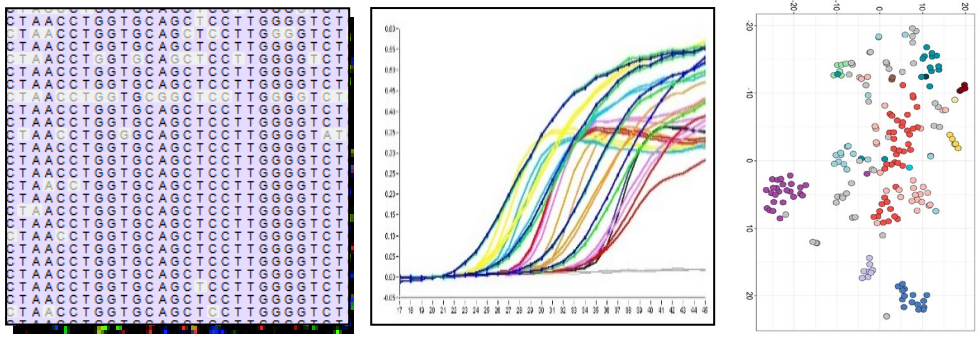
Histology



FISH



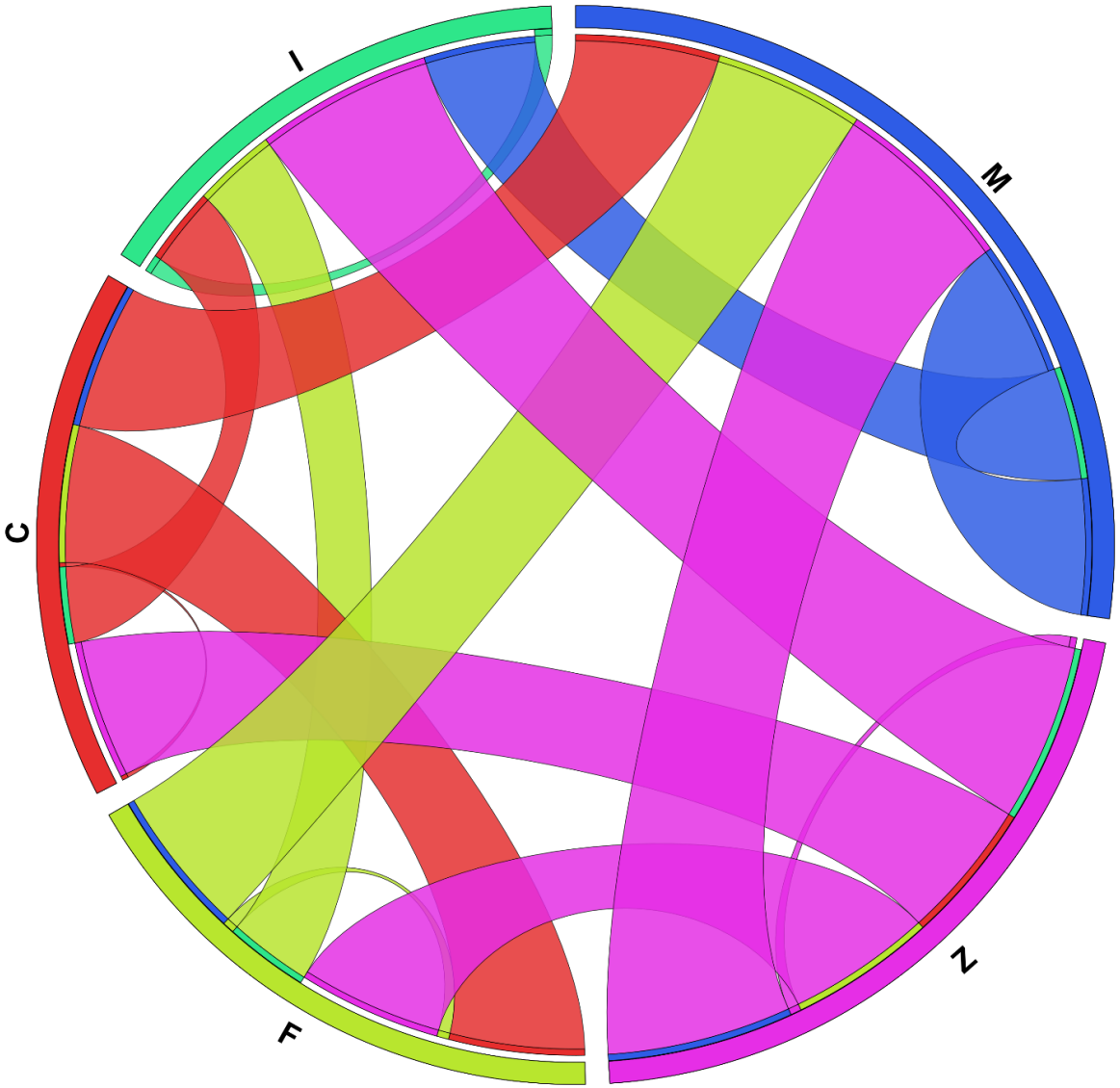
Molecular genetics



Slide content provided courtesy of Munich Leukemia Laboratory.
FISH, fluorescence *in situ* hybridization.

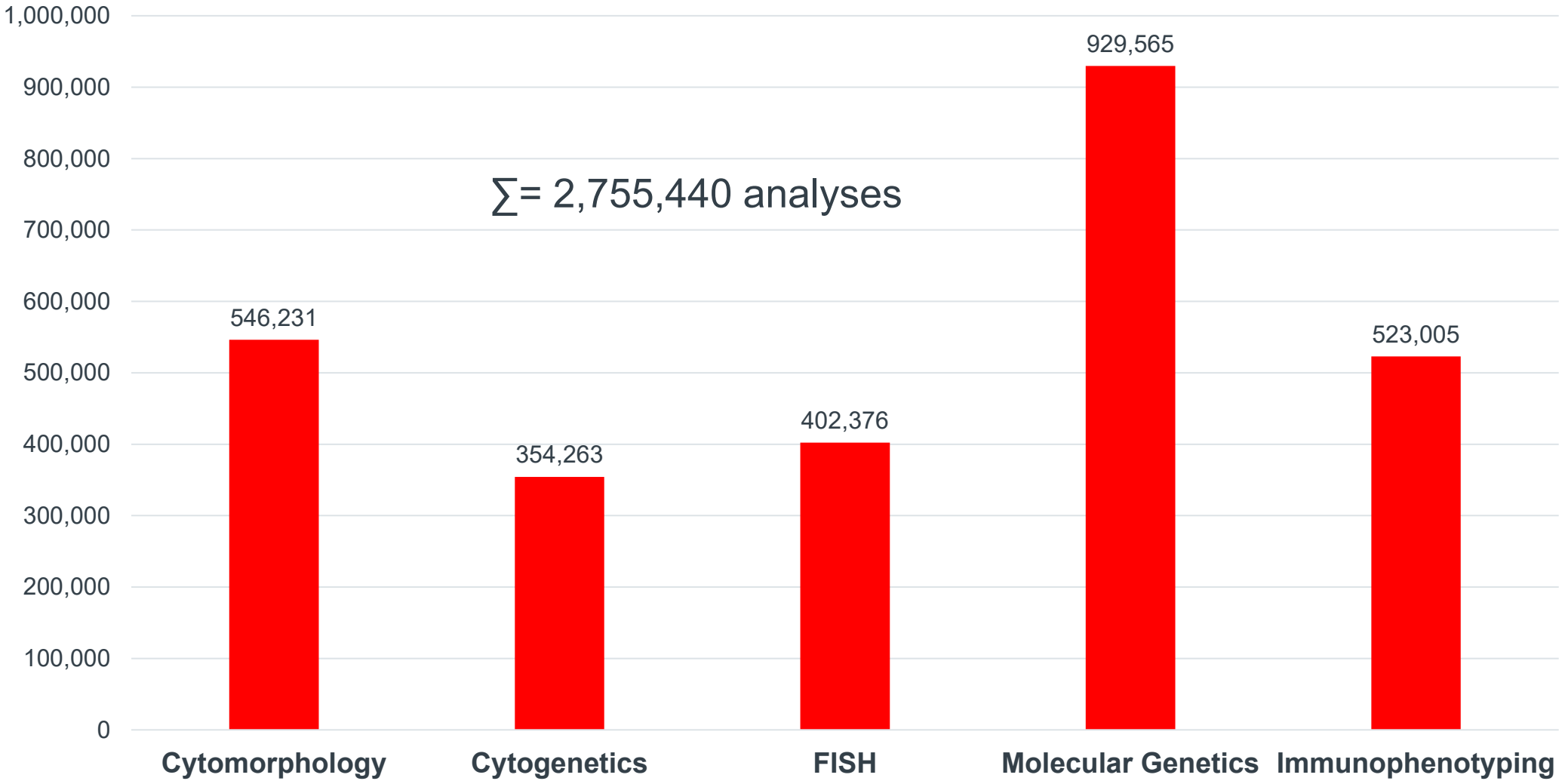
Composition of gold standards in MLL

Z = Cytomorphology
C = Cytogenetics
F = FISH
M = Molecular genetics
I = Immunophenotyping



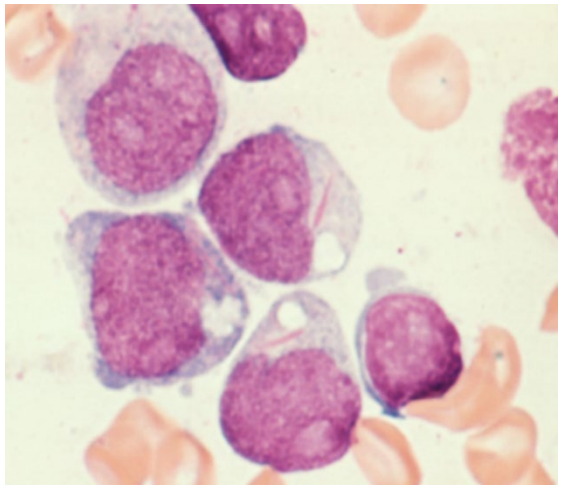
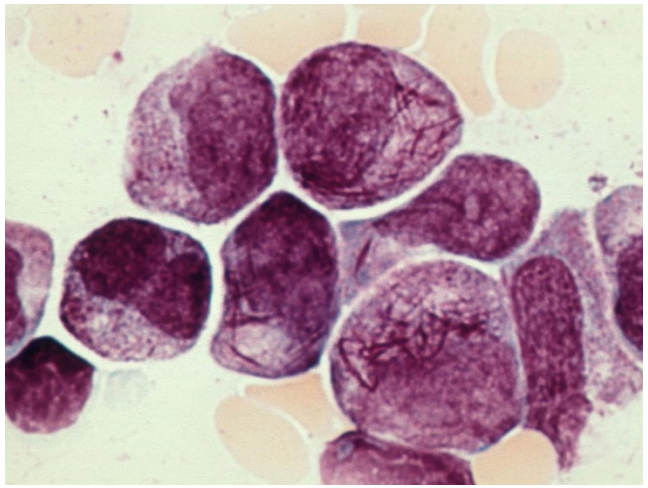
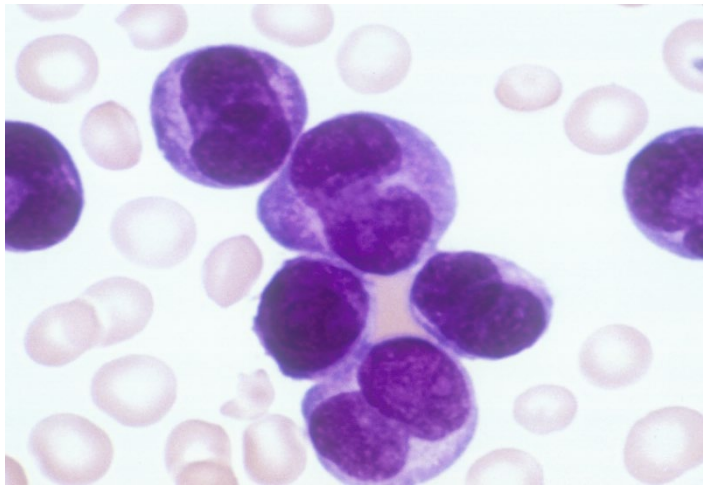
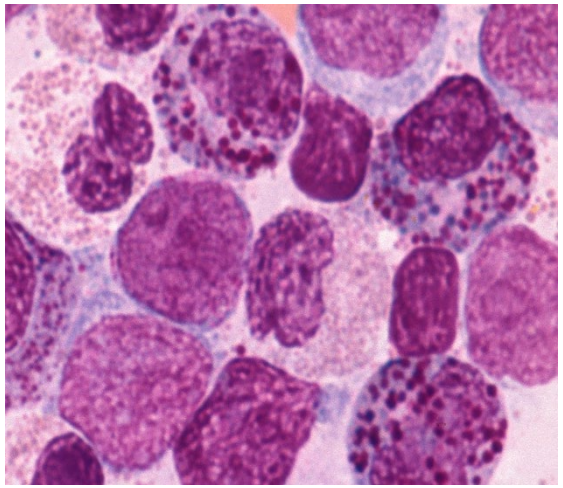
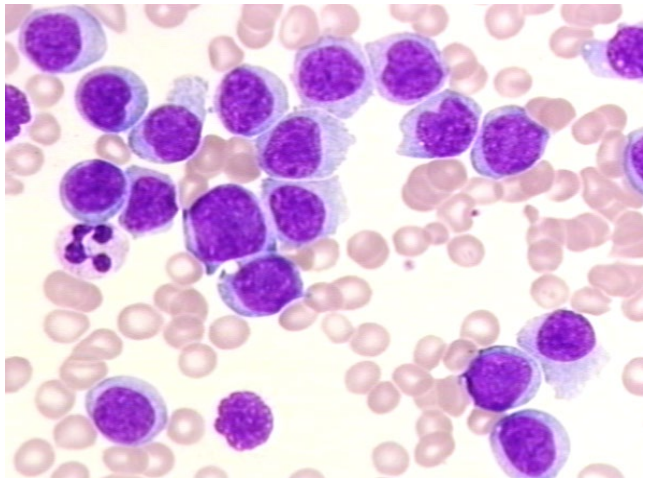
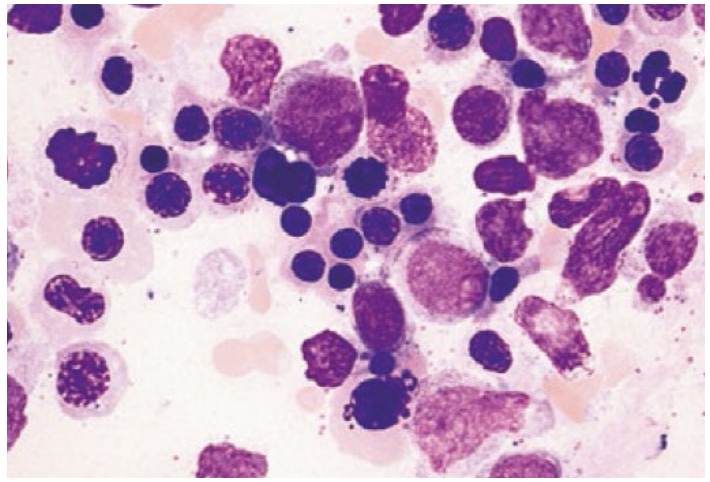
Slide content provided courtesy of MLL.
FISH, fluorescence *in situ* hybridization; MLL, Munich Leukemia Laboratory.

Diagnostic analyses at MLL since 2005



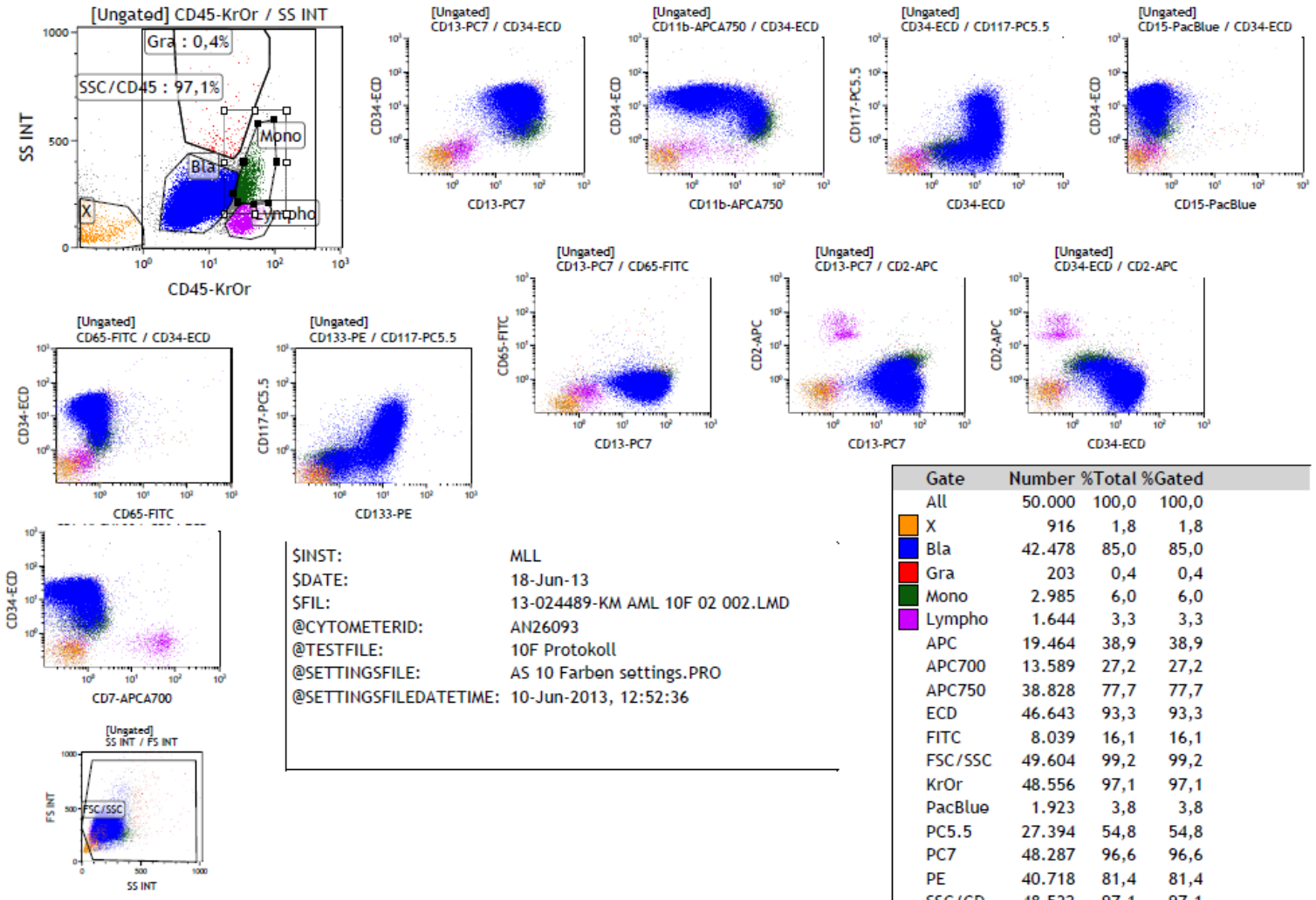
Status as of January 23, 2025. Slide content provided courtesy of MLL.
FISH, fluorescence *in situ* hybridization; MLL, Munich Leukemia Laboratory.

Cytomorphology: Phenotype

Slide content provided courtesy of Munich Leukemia Laboratory.

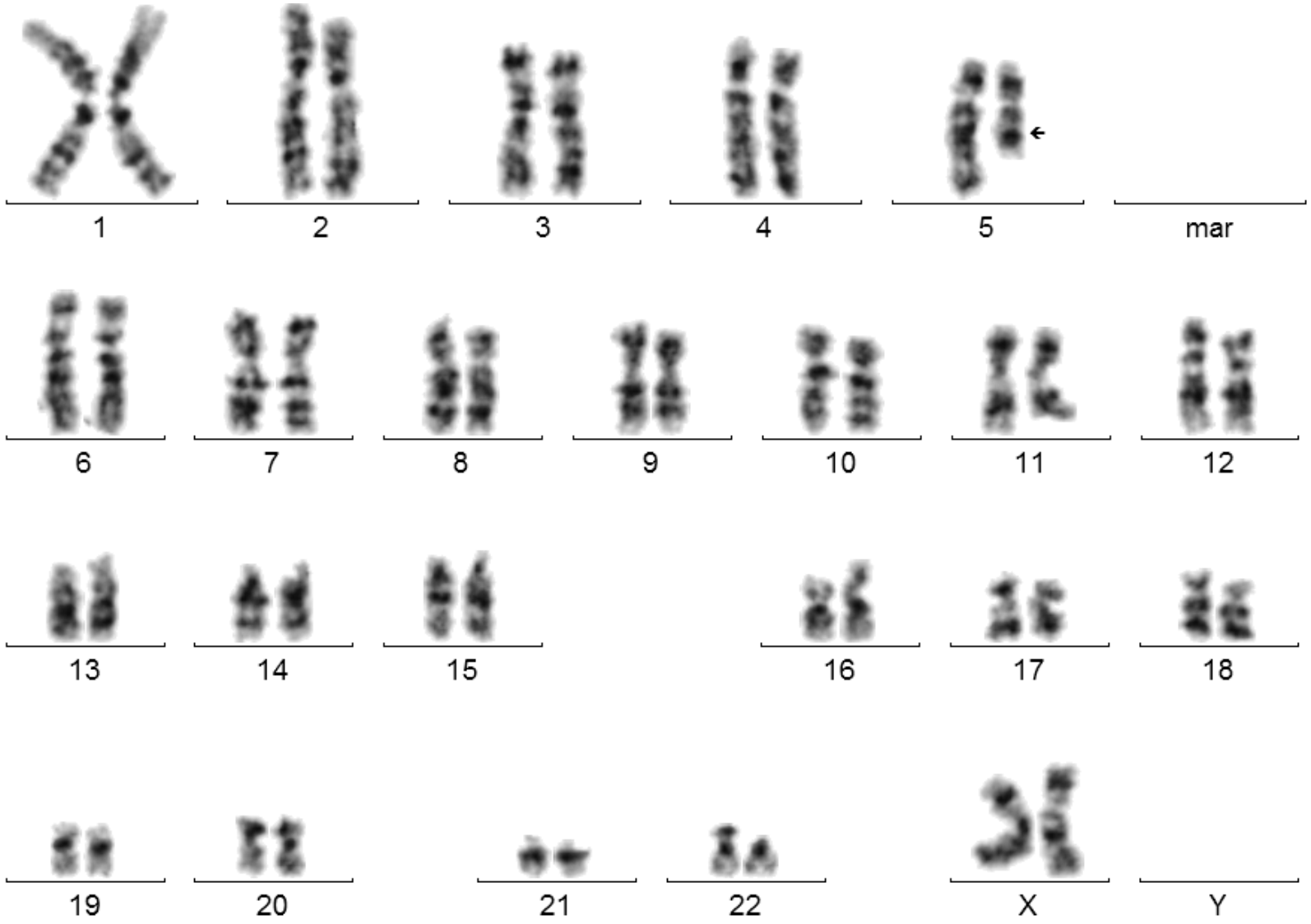
Immunophenotyping: AML (10-color–staining)



Gate	Number	%Total	%Gated
All	50.000	100,0	100,0
X	916	1,8	1,8
Bla	42.478	85,0	85,0
Gra	203	0,4	0,4
Mono	2.985	6,0	6,0
Lympho	1.644	3,3	3,3
APC	19.464	38,9	38,9
APC700	13.589	27,2	27,2
APC750	38.828	77,7	77,7
ECD	46.643	93,3	93,3
FITC	8.039	16,1	16,1
FSC/SSC	49.604	99,2	99,2
KrOr	48.556	97,1	97,1
PacBlue	1.923	3,8	3,8
PC5.5	27.394	54,8	54,8
PC7	48.287	96,6	96,6
PE	40.718	81,4	81,4
SSC/CD...	48.532	97,1	97,1

Slide content provided courtesy of Munich Leukemia Laboratory.
AML, acute myeloid leukemia; APC, allophycocyanin; APCA, APC-Alexa Fluor; Bla, blast cells; CD, cluster of differentiation; ECD, Phycoerythrin-Texas Red®-X; FITC, fluorescein isothiocyanate; FSC, forward scatter; Gra, granulocytes; KrOr, krome orange; Lympho, lymphocytes; Mono, monocytes; PC, phycoerythrin-cyanine; PE, phycoerythrin; SSC, side scatter; SS INT, side scatter intensity.

Karyotype: 46,XX,del(5)(q15q32)



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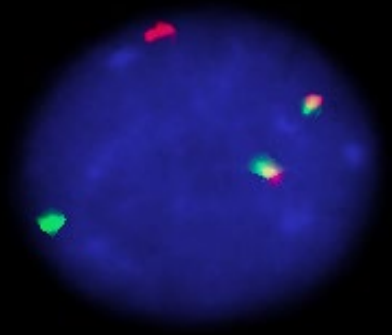
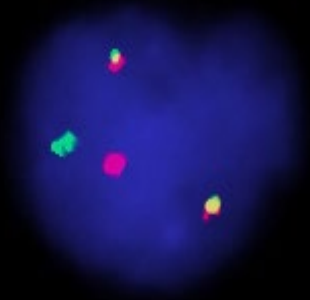
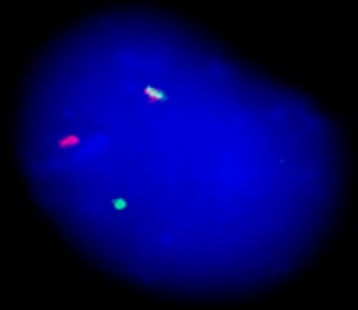
RUNX1::RUNX1T1



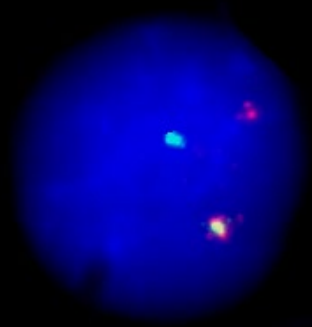
PML::RARA



CBFB rearrangement



KMT2A rearrangement



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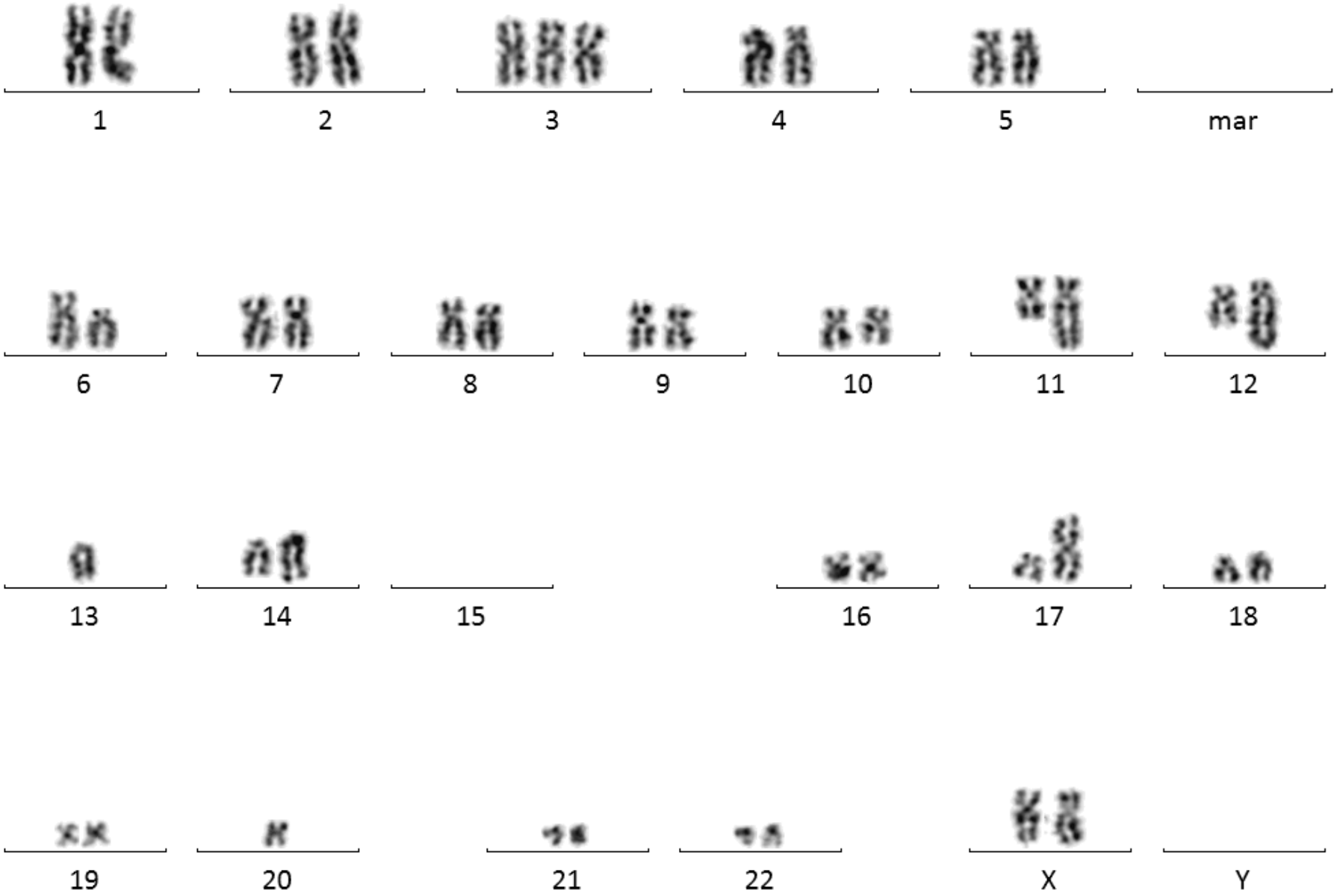

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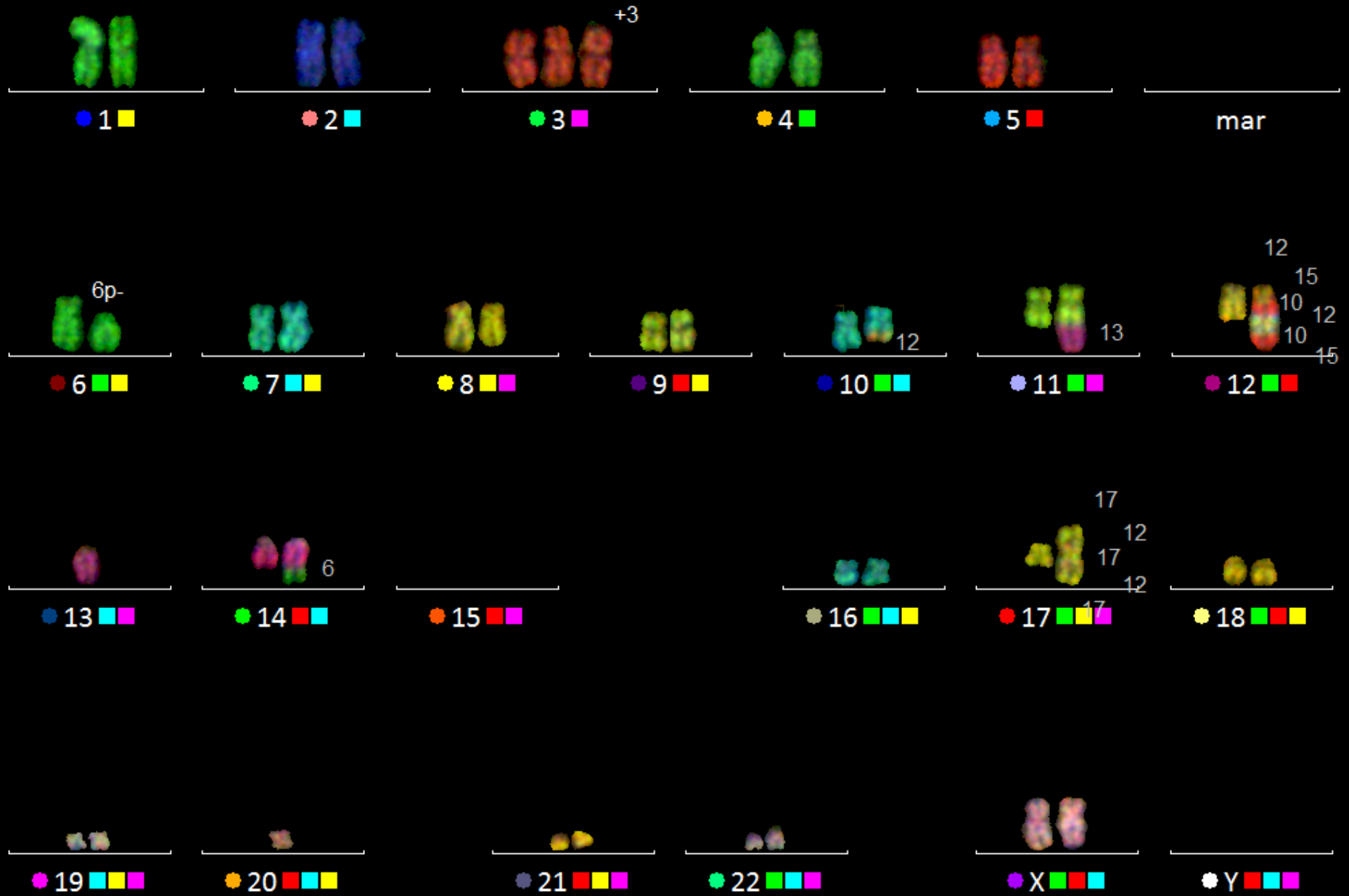

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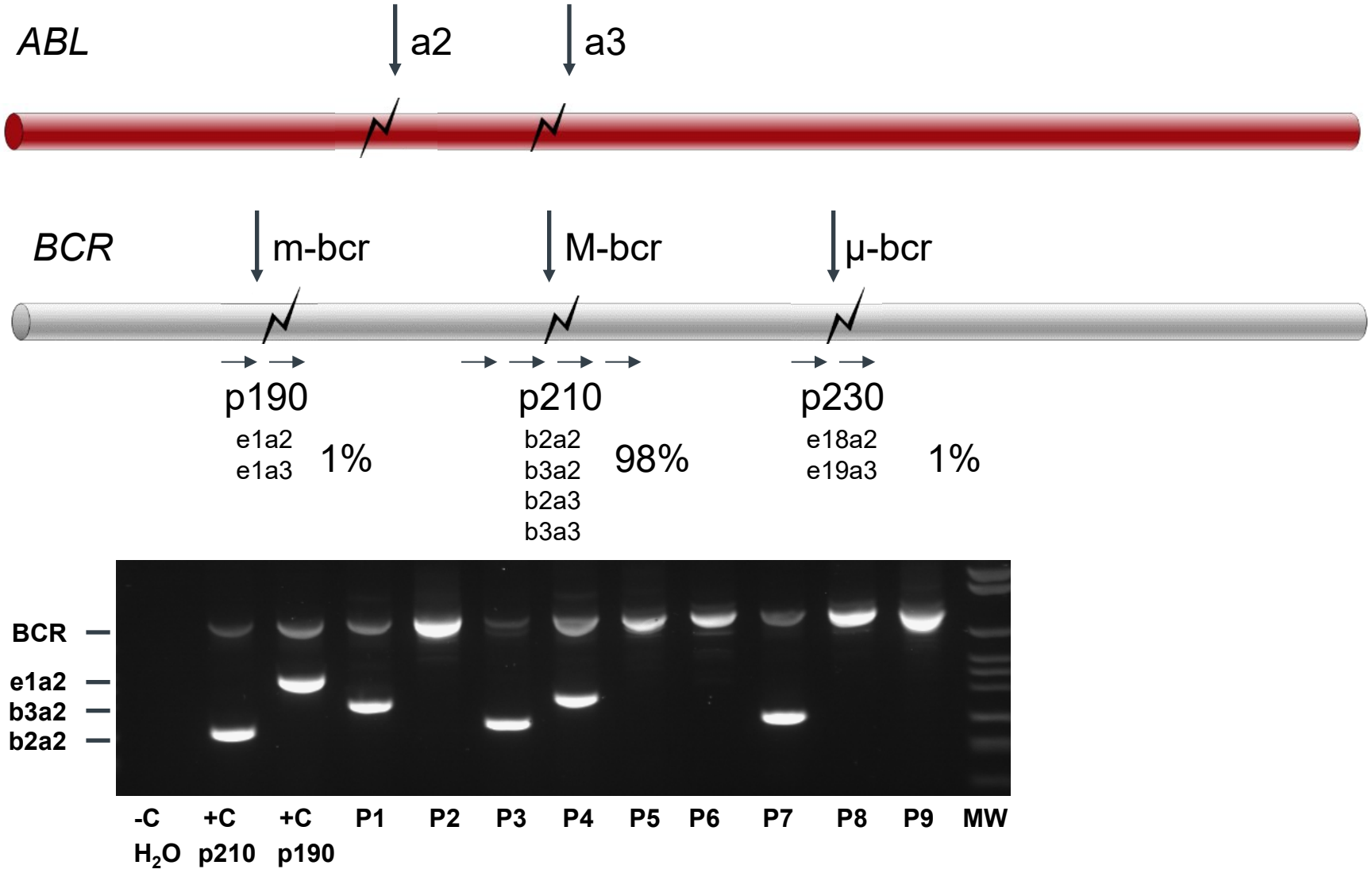
BCR::ABL1 multiplex PCR



Slide content provided courtesy of Munich Leukemia Laboratory.
PCR, polymerase chain reaction.

Molecular methods: Panel sequencing

Gene	ROI
ASXL1	E12, E13
ASXL2	E12, E13
ATRX	CCS
BCOR	CCS
BCORL1	CCS
BRAF	CCS
CALR	E09
CBL	CCS
CEBPA	CCS
CSF3R	E14-E17
CSNK1A1	E03, E04
CUX1	CCS
DDX41	CCS
DNMT3A	CCS
ETNK1	E03
ETV6	CCS
EZH2	CCS
FBXW7	CCS
FLT3	E14-E20
GATA1	CCS
GATA2	CCS
IDH1	E04, E07
IDH2	E04, E07
IL6R	rs2228145
JAK2	CCS
KIT	CCS
KRAS	CCS
MPL	CCS
MYD88	CCS
NF1	CCS
NOTCH1	E26-E28, E34
NPM1	E11
NRAS	CCS

Gene	ROI
PDGFRA	CCS
PDGFRB	CCS
PHF6	CCS
PIGA	CCS
PPM1D	CCS
PRPF8	CCS
PTEN	CCS
PTPN11	CCS
RAD21	CCS
RUNX1	CCS
SETBP1	E04
SF1	CCS
SF3A1	CCS
SF3B1	E13-E16
SH2B3	CCS
SMC1A	CCS
SMC3	CCS
SRSF2	E01
STAG2	CCS
SUZ12	CCS
TET2	CCS
TP53	CCS
U2AF1	E02, E06
U2AF2	E02, E06
UBA1	CCS
WT1	E07, E09
ZEB2	CCS
ZRSR2	CCS

myeloid panel

Gene	ROI
ARID1A	CCS
ATM	CCS
ATR	CCS
BCL10	CCS
BCL2	CCS
BIRC3	CCS
BRAF	CCS
BTK	E15
CARD11	CCS
CCL22	CCS
CCND1	UTR+CCS
CD28	CCS
CD79B	CCS
CREBBP	CCS
CXCR4	CCS
DIS3	CCS
DNMT3A	CCS
EGR1	CCS
EP300	CCS
ETV6	CCS
EZH2	CCS
FBXW7	CCS
FLT3	E14-E20
FOXO1	CCS
FYN	CCS
ID3	CCS
IDH2	E04, E07
IKZF1	CCS
IL7R	CCS
IRF4	CCS
JAK1	CCS
JAK2	CCS
JAK3	CCS
KLF2	CCS

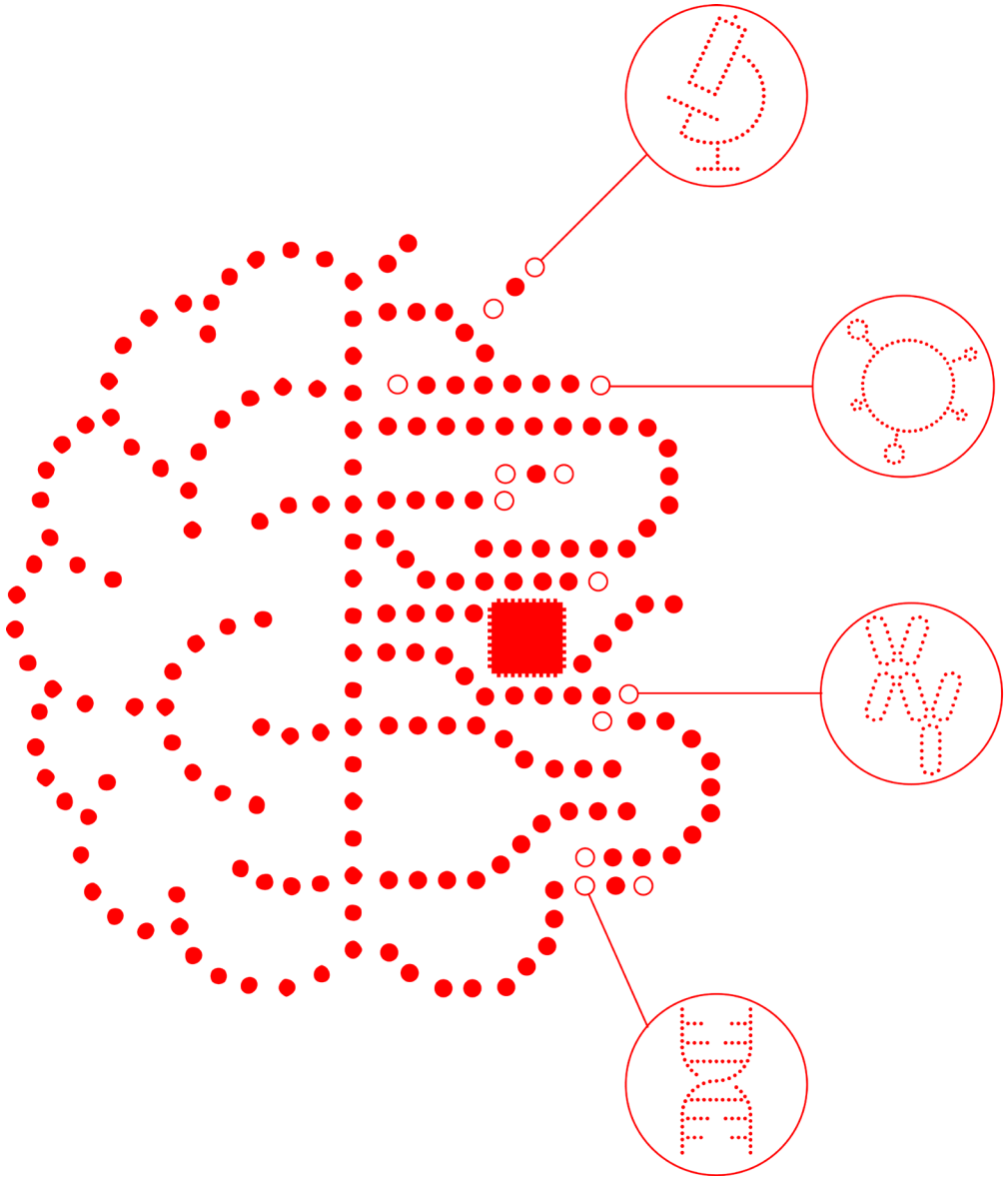
Gene	ROI
KLHL6	CCS
KMT2D	CCS
KRAS	CCS
MAP2K1	CCS
MEF2B	CCS
MYC	CCS
MYD88	CCS
NOTCH1	E26-E28, E34
NOTCH2	E26, E27, E34
NRAS	CCS
PAX5	E03
PHF6	CCS
PLCG1	CCS
PLCG2	CCS
POT1	CCS
PTEN	CCS
RHOA	CCS
RPS15	CCS
RUNX1	CCS
SF3B1	E13-E16
SGK1	CCS
SOCS1	CCS
STAT3	E20, E21
STAT5B	CCS
STAT6	CCS
TET2	CCS
TNFAIP3	CCS
TP53	CCS
UBR5	E58
VAV1	E04, E07
XPO1	CCS
ZEB2	CCS

lymphoid panel

Slide content provided courtesy of Munich Leukemia Laboratory.
ROI, region of interest.

Next steps to advance diagnostics?
AI – large language models

AI and LLMs hold significant potential to improve healthcare, but they must be used in compliance with relevant regulations



AI, artificial intelligence; LLM, large language model.

Current and proposed regulations for the use of AI

FDA 2021 action plan outlines five goals:[1]

- Tailored regulatory framework
- Good machine learning practices
- Patient-centered approach with increased transparency
- Reducing algorithm bias
- Real-world performance

7 pages

EU 2024 AI Act includes:[3]

- Enhanced oversight
- Explainability
- Data integrity
- Human in the loop
- International standards

458 pages

WHO regulatory considerations 2023 on AI suggest:[2]

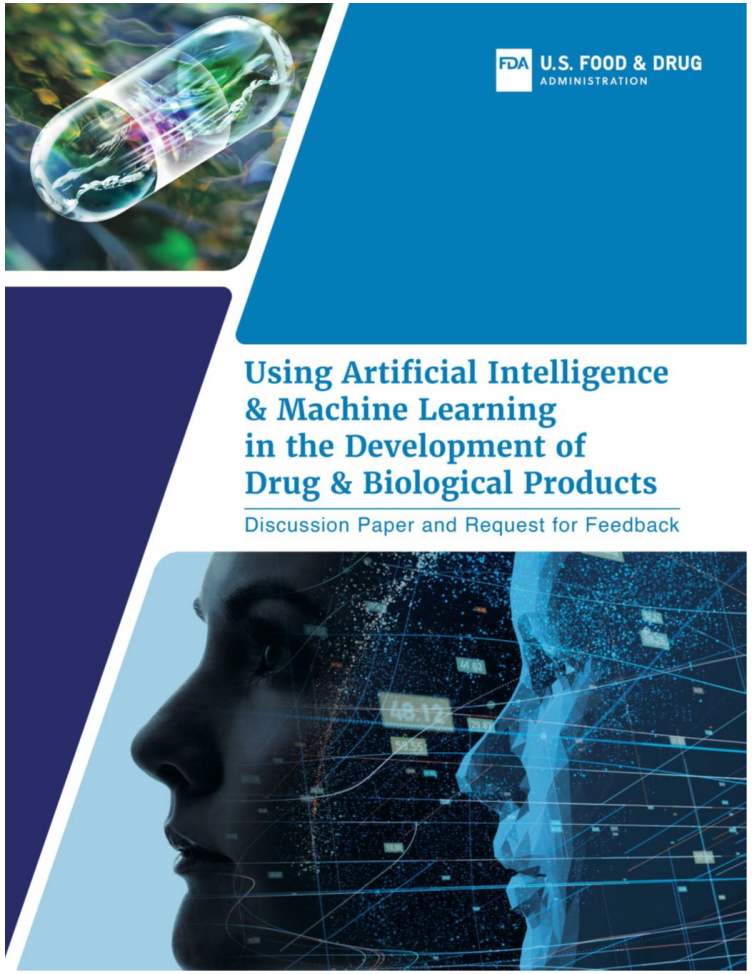
- Documentation and transparency
- Risk management and AI systems development lifecycle approaches
- Intended use and analytical and clinical validation
- Data quality
- Privacy and data protection

80 pages

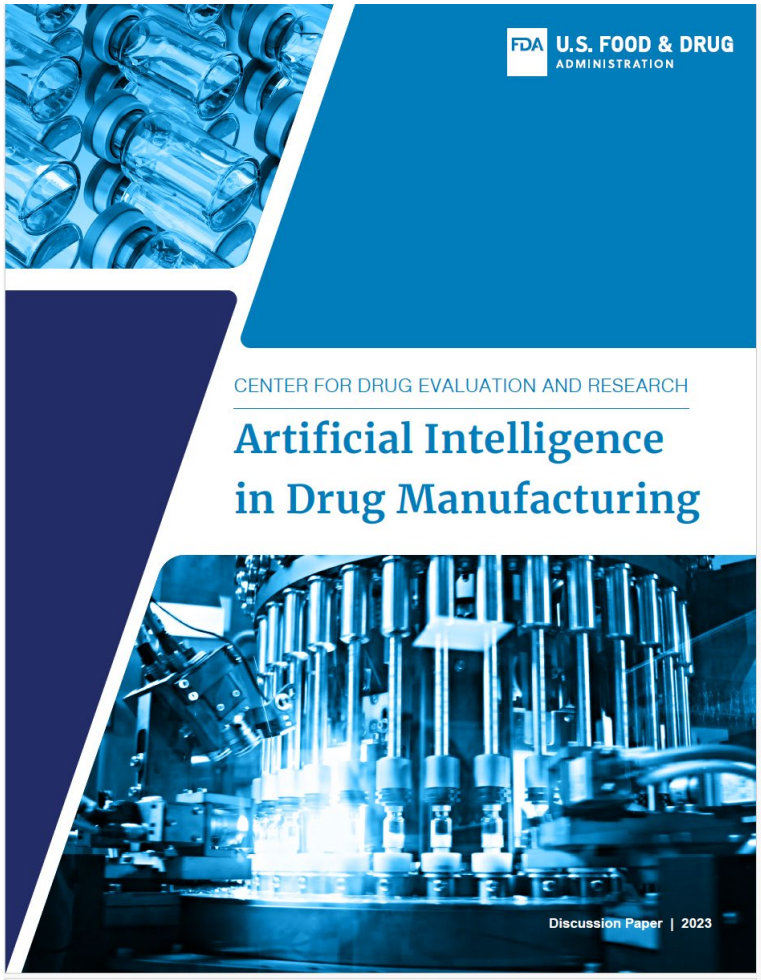
AI, artificial intelligence; FDA, US Food and Drug Administration; WHO, World Health Organization.

1. FDA. Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan, January 2021. Available at: https://www.fda.gov/media/145022/download. Accessed February 2025.
2. WHO. WHO outlines considerations for regulation of artificial intelligence for health; October 19, 2023. Available at: https://www.who.int/news/item/19-10-2023-who-outlines-considerations-for-regulation-of-artificial-intelligence-for-health. Accessed February 2025. 3. European Parliament. Corrigendum; April 19, 2024. Available at: https://www.europarl.europa.eu/doceo/document/TA-9-2024-0138-FNL-COR01_EN.pdf. Accessed February 2025.

Current and proposed regulations for the use of AI



5/2023, 31 pages[1]



2023, 16 pages[2]

AI, artificial intelligence.

1. US Food and Drug Administration. Using Artificial Intelligence & Machine Learning in the Development of Drug & Biologic Products; May 2023 (revised February 2025). Available at: https://www.fda.gov/media/167973/download. Accessed February 2025. 2. US Food and Drug Administration. Artificial Intelligence in Drug Manufacturing; 2023. Available at: https://www.fda.gov/media/165743/download. Accessed February 2025.

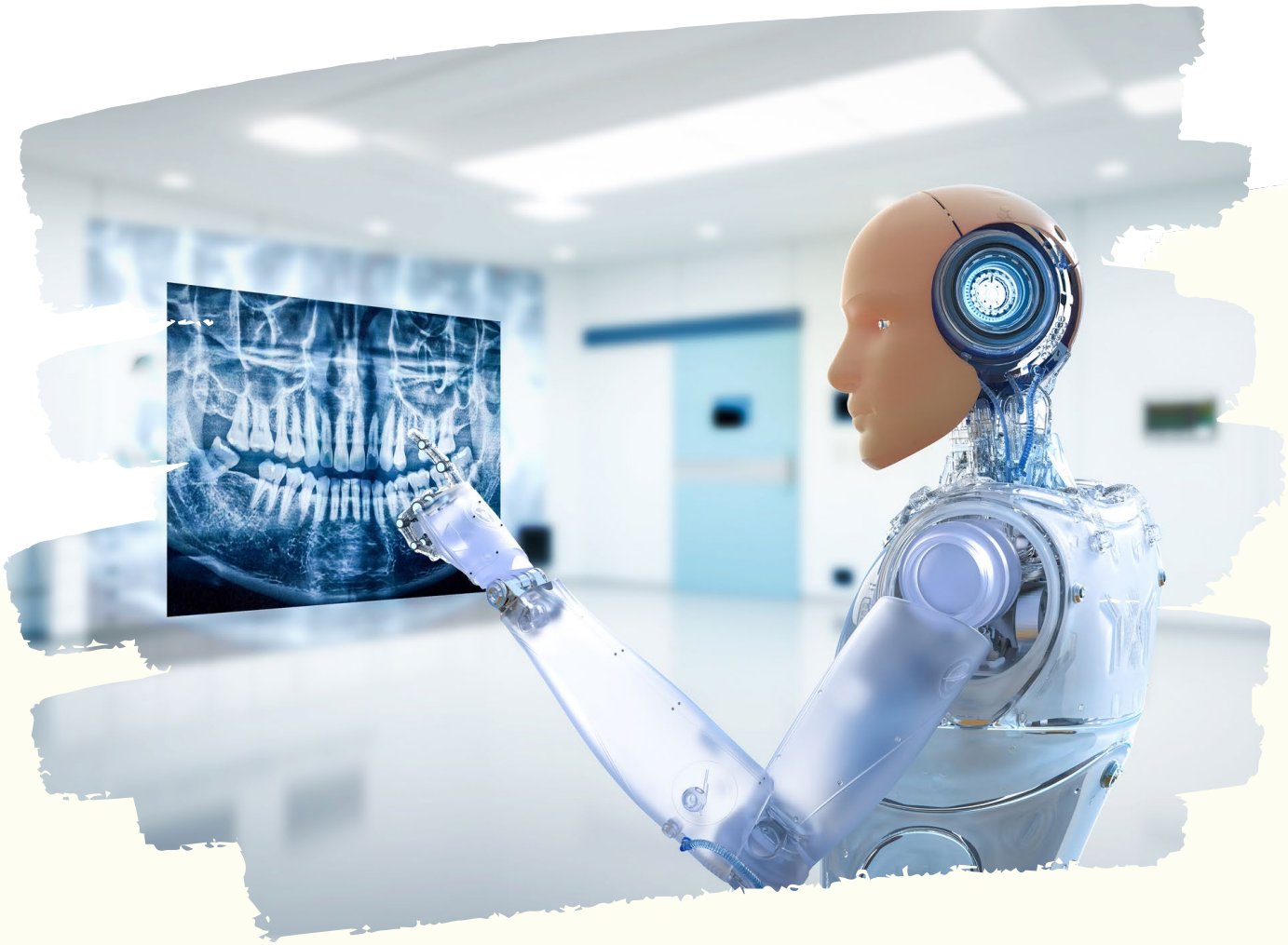


Image-based AI

Cell classification and karyotype analyses for diagnostics can be performed rapidly and with high accuracy by AI

AI, artificial intelligence.

AI training: Identifying cats

AI, artificial intelligence; CNN, convolutional neural network.

How to confuse a phenotype-driven machine learning model

Chihuahua or muffin?

Credit: https://twitter.com/teenybiscuit.

How to confuse a phenotype-driven machine learning model

Chihuahua or muffin?

Dog or bagel?

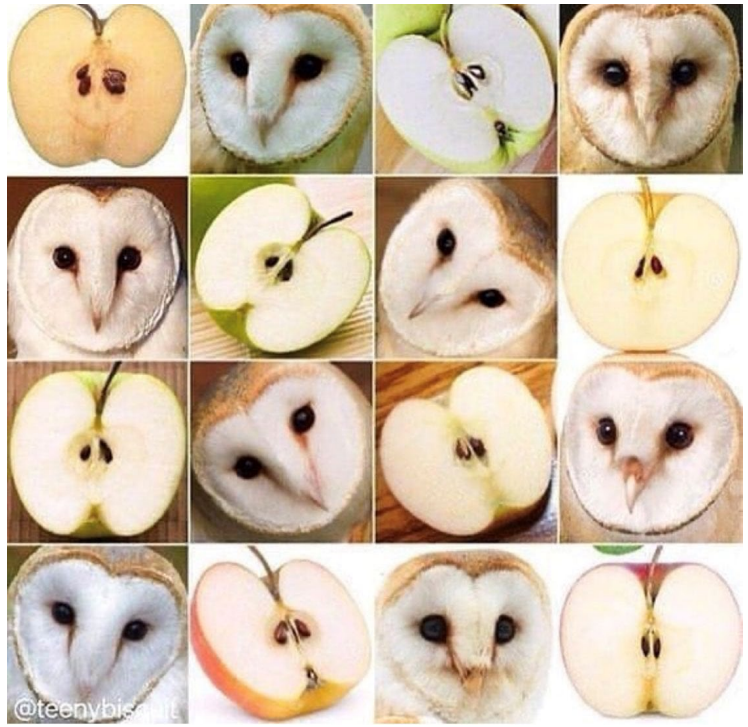
Credit: https://twitter.com/teenybiscuit.

How to confuse a phenotype-driven machine learning model

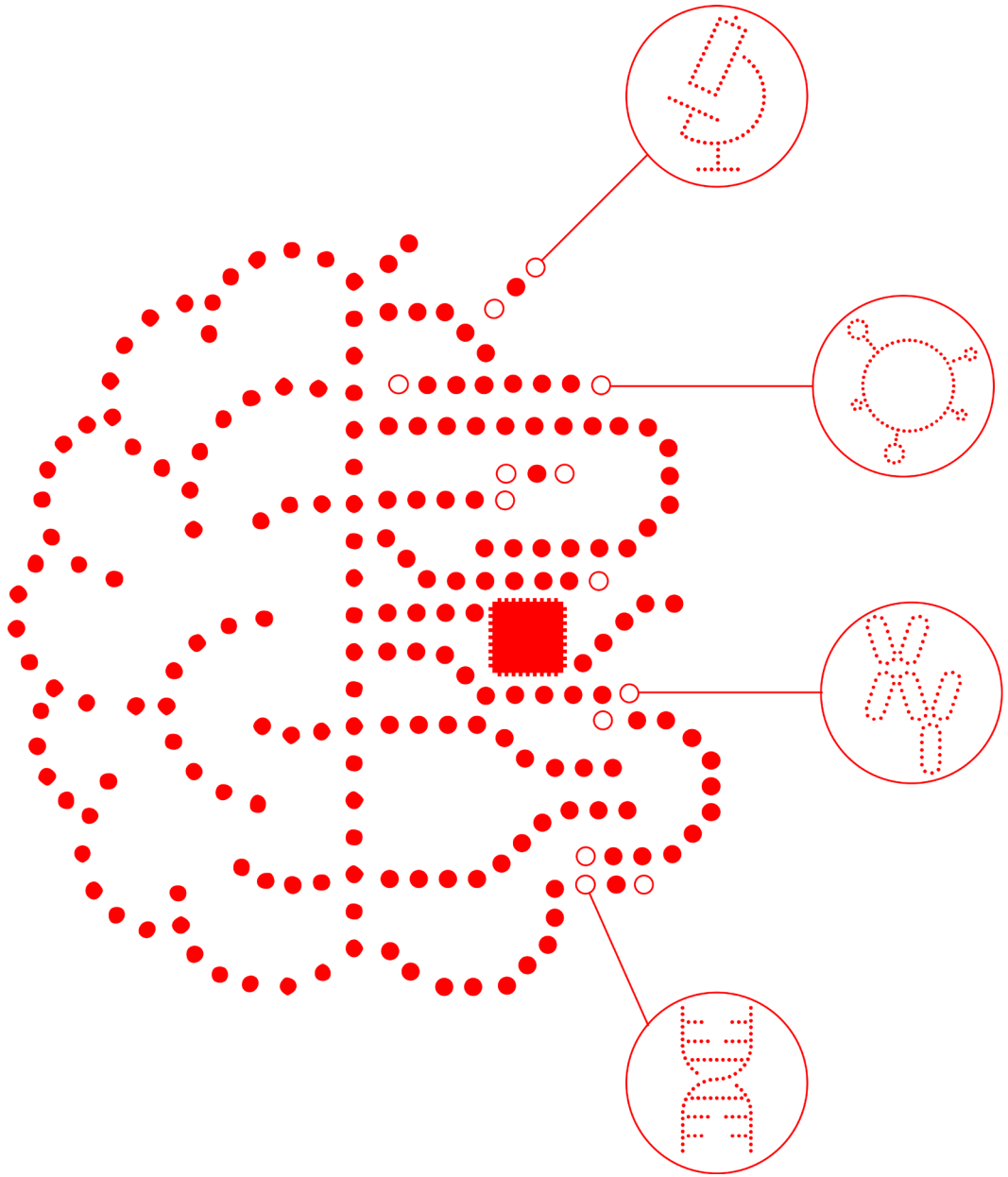
Chihuahua or muffin?

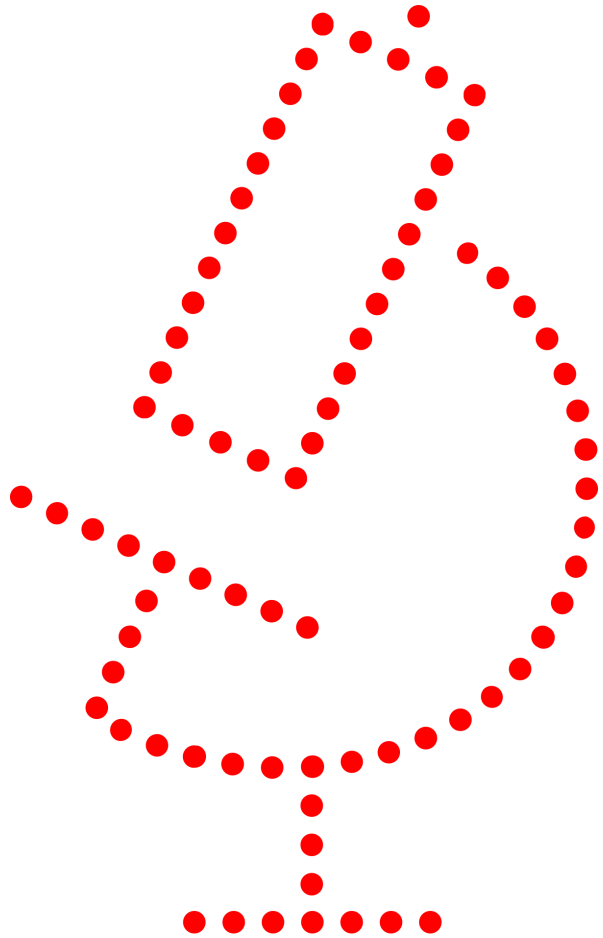
Dog or bagel?

Owl or apple?



Credit: https://twitter.com/teenybiscuit.





Sophisticated cell counting cannot beat statistics

Table III
95%-CONFIDENCE LIMITS for various percentages of blood cells of a given type as determined by differential counts.

a	n = 100	n = 200	n = 500	n = 1000
0	0- 4	0- 2	0- 1	0- 1
1	0- 6	0- 4	0- 3	0- 2
2	0- 8	0- 6	0- 4	1- 4
3	0- 9	1- 7	1- 5	2- 5
4	1- 10	1- 8	2- 7	2- 6
5	1- 12	2- 10	3- 8	3- 7
6	2- 13	3- 11	4- 9	4- 8
7	2- 14	3- 12	4- 10	5- 9
8	3- 16	4- 13	5- 11	6- 10
9	4- 17	5- 14	6- 12	7- 11
10	4- 18	6- 16	7- 13	8- 13
15	8- 24	10- 21	11- 19	12- 18
20	12- 30	14- 27	16- 24	17- 23
25	16- 35	19- 32	21- 30	22- 28
30	21- 40	23- 37	26- 35	27- 33
35	25- 46	28- 43	30- 40	32- 39
40	30- 51	33- 48	35- 45	36- 44
45	35- 56	37- 53	40- 50	41- 49
50	39- 61	42- 58	45- 55	46- 54
55	44- 65	47- 63	50- 60	51- 59
60	49- 70	52- 67	55- 65	56- 64
65	54- 75	57- 72	60- 70	61- 68
70	60- 79	63- 77	65- 74	67- 73
75	65- 84	68- 81	70- 79	72- 78
80	70- 88	73- 86	76- 84	77- 83
85	76- 92	79- 90	81- 89	82- 88
90	82- 96	84- 94	87- 93	87- 92
91	83- 96	86- 95	88- 94	89- 93
92	84- 97	87- 96	89- 95	90- 94
93	86- 98	88- 97	90- 96	91- 95
94	87- 98	89- 97	91- 96	92- 96
95	88- 99	90- 98	92- 97	93- 97
96	90- 99	92- 99	93- 98	94- 98
97	91-100	93- 99	95- 99	95- 98
98	92-100	94-100	96-100	96- 99
99	94-100	96-100	97-100	98-100
100	96-100	98-100	99-100	99-100

n is the total number of cells counted, a the observed percentage of cells of the given type. 0 and 100 confidence limits are to be interpreted as nearly 0 and nearly 100.

Rümke CL. The statistically expected variability in differential counting. in: Differential Leukocyte Counting. CAP Conference/Aspen, 1977.

Sophisticated cell counting cannot beat statistics

Table III
95%-CONFIDENCE LIMITS for various percentages of blood cells of a given type as determined by differential counts.

a	n = 100	n = 200	n = 500	n = 1000
0	0- 4	0- 2	0- 1	0- 1
1	0- 6	0- 4	0- 3	0- 2
2	0- 8	0- 6	0- 4	1- 4
3	0- 9	1- 7	1- 5	2- 5
4	1- 10	1- 8	2- 7	2- 6
5	1- 12	2- 10	3- 8	3- 7
6	2- 13	3- 11	4- 9	4- 8
7	2- 14	3- 12	4- 10	5- 9
8	3- 16	4- 13	5- 11	6- 10
9	4- 17	5- 14	6- 12	7- 11
10	4- 18	6- 16	7- 13	8- 13
15	8- 24	10- 21	11- 19	12- 18
20	12- 30	14- 27	16- 24	17- 23
25	16- 35	19- 32	21- 30	22- 28
30	21- 40	23- 37	26- 35	27- 33
35	25- 46	28- 43	30- 40	32- 39
40	30- 51	33- 48	35- 45	36- 44
45	35- 56	37- 53	40- 50	41- 49
50	39- 61	42- 58	45- 55	46- 54
55	44- 65	47- 63	50- 60	51- 59
60	49- 70	52- 67	55- 65	56- 64
65	54- 75	57- 72	60- 70	61- 68
70	60- 79	63- 77	65- 74	67- 73
75	65- 84	68- 81	70- 79	72- 78
80	70- 88	73- 86	76- 84	77- 83
85	76- 92	79- 90	81- 89	82- 88
90	82- 96	84- 94	87- 93	87- 92
91	83- 96	86- 95	88- 94	89- 93
92	84- 97	87- 96	89- 95	90- 94
93	86- 98	88- 97	90- 96	91- 95
94	87- 98	89- 97	91- 96	92- 96
95	88- 99	90- 98	92- 97	93- 97
96	90- 99	92- 99	93- 98	94- 98
97	91-100	93- 99	95- 99	95- 98
98	92-100	94-100	96-100	96- 99
99	94-100	96-100	97-100	98-100
100	96-100	98-100	99-100	99-100

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0	0- 4	0- 2	0- 1	0- 1
1	0- 6	0- 4	0- 3	0- 2
2	0- 8	0- 6	0- 4	1- 4
3	0- 9	1- 7	1- 5	2- 5
4	1- 10	1- 8	2- 7	2- 6
5	1- 12	2- 10	3- 8	3- 7
6	2- 13	3- 11	4- 9	4- 8
7	2- 14	3- 12	4- 10	5- 9
8	3- 16	4- 13	5- 11	6- 10
9	4- 17	5- 14	6- 12	7- 11
10	4- 18	6- 16	7- 13	8- 13
15	8- 24	10- 21	11- 19	12- 18
20	12- 30	14- 27	16- 24	17- 23
25	16- 35	19- 32	21- 30	22- 28
30	21- 40	23- 37	26- 35	27- 33
35	25- 46	28- 43	30- 40	32- 39
40	30- 51	33- 48	35- 45	36- 44
45	35- 56	37- 53	40- 50	41- 49
50	39- 61	42- 58	45- 55	46- 54
55	44- 65	47- 63	50- 60	51- 59
60	49- 70	52- 67	55- 65	56- 64
65	54- 75	57- 72	60- 70	61- 68
70	60- 79	63- 77	65- 74	67- 73
75	65- 84	68- 81	70- 79	72- 78
80	70- 88	73- 86	76- 84	77- 83
85	76- 92	79- 90	81- 89	82- 88
90	82- 96	84- 94	87- 93	87- 92
91	83- 96	86- 95	88- 94	89- 93
92	84- 97	87- 96	89- 95	90- 94
93	86- 98	88- 97	90- 96	91- 95
94	87- 98	89- 97	91- 96	92- 96
95	88- 99	90- 98	92- 97	93- 97
96	90- 99	92- 99	93- 98	94- 98
97	91-100	93- 99	95- 99	95- 98
98	92-100	94-100	96-100	96- 99
99	94-100	96-100	97-100	98-100
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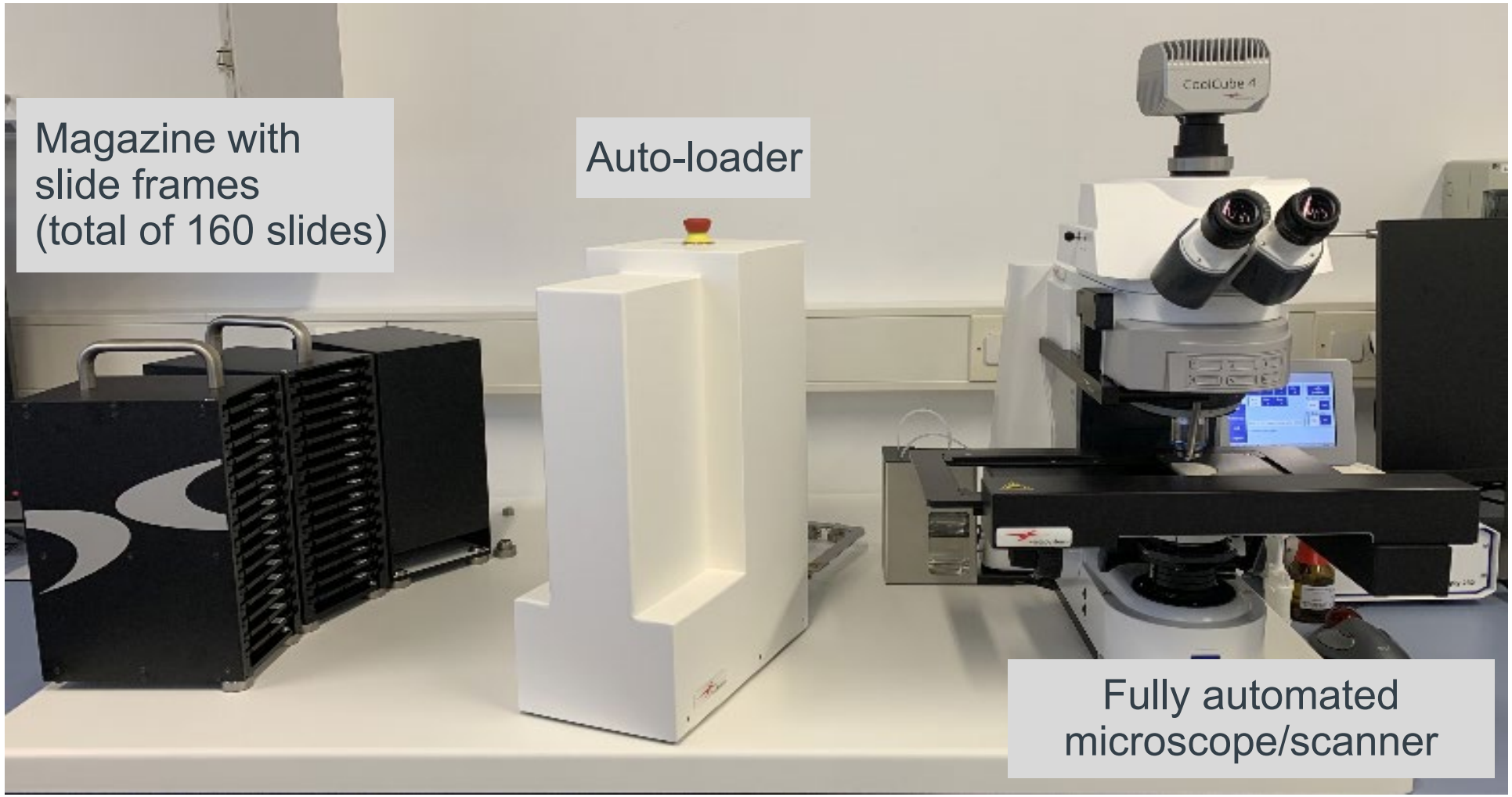
Table III
95%-CONFIDENCE LIMITS for various percentages of blood cells of a given type as determined by differential counts.

a	n = 100	n = 200	n = 500	n = 1000
8	3- 16	4- 13	5- 11	6- 10
9	4- 17	5- 14	6- 12	7- 11
10	4- 18	6- 16	7- 13	8- 13
15	8- 24	10- 21	11- 19	12- 18
20	12- 30	14- 27	16- 24	17- 23
25	16- 35	19- 32	21- 30	22- 28
30	21- 40	23- 37	26- 35	27- 33

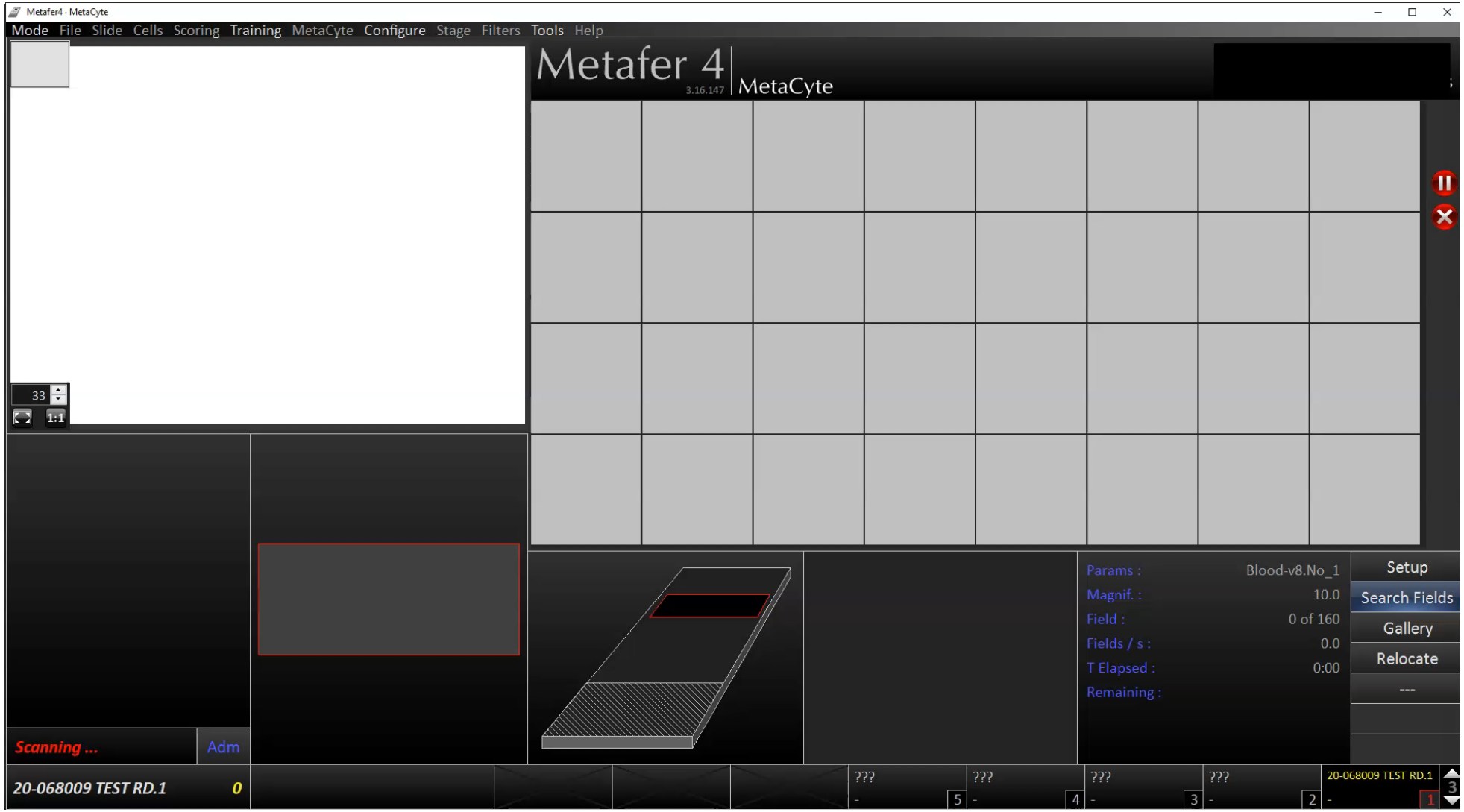
Rümke CL. The statistically expected variability in differential counting. in: Differential Leukocyte Counting. CAP Conference/Aspen, 1977.

Fully automated scanning device



Slide content provided courtesy of Munich Leukemia Laboratory.

Digitalization of blood cells (100×)

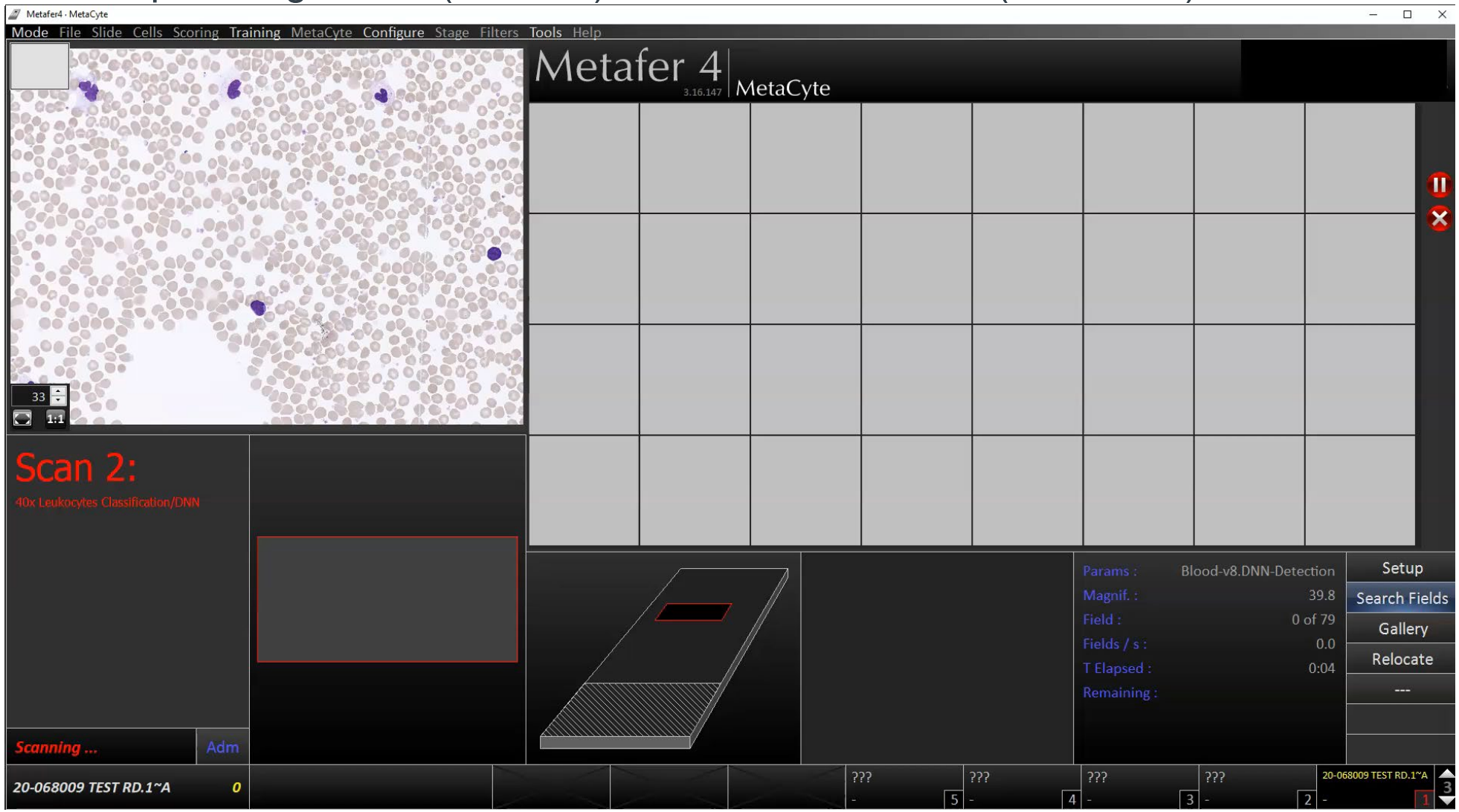


(time lapse)

Slide content provided courtesy of Munich Leukemia Laboratory.

Digitalization of blood cells

‘Close-up’ of single cells (400× oil): 300-500 cells/smear (~4:00 min)



(time lapse)

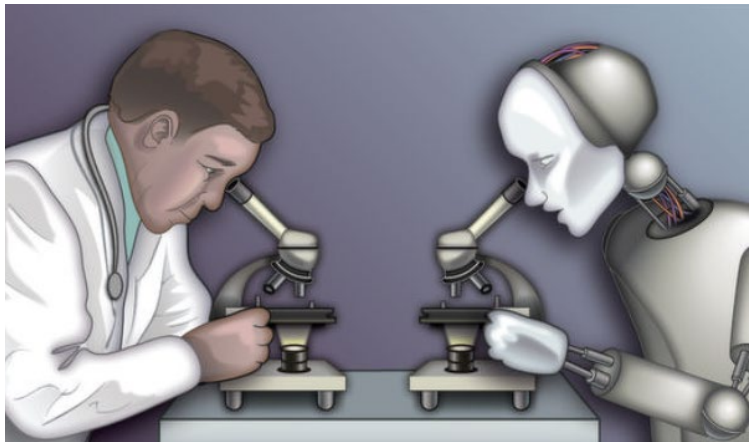
Slide content provided courtesy of Munich Leukemia Laboratory.

BELUGA ('Better LeUkemia diaGnostics through AI') Study

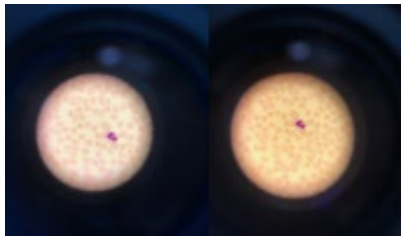
(Clinicaltrials.gov, NCT04466059)

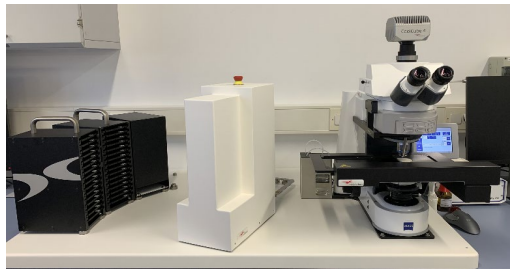
29,119 patient samples (Jan 2021 – Jul 2022)

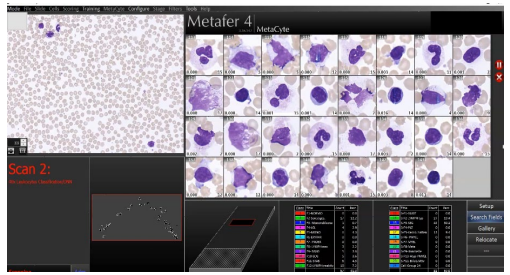
∑ = 2,911,915 cells differentiated



∑ = 14,322,972 cells differentiated







54%	Segmented neutrophils	48%
1%	Bands	1.47%
2.3%	Eosinophils	2.69%
0.76%	Basophils	2%
6.96%	Monocytes	7.05%
30.91%	Lymphocytes	24.53%
1.11%	Pathogenic blasts	3.25%

Haferlach T *et al*. Abstract #787 from ASH 2022; New Orleans, LA, USA, December 10–13, 2022.

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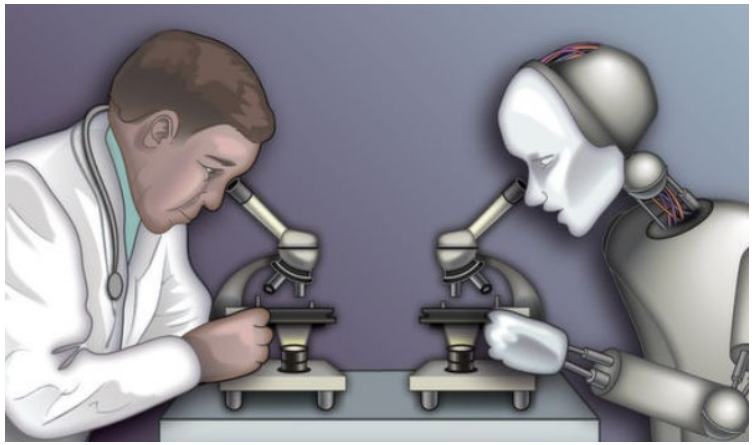

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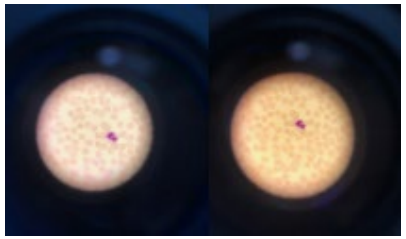
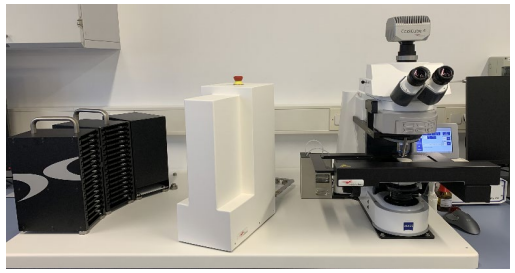
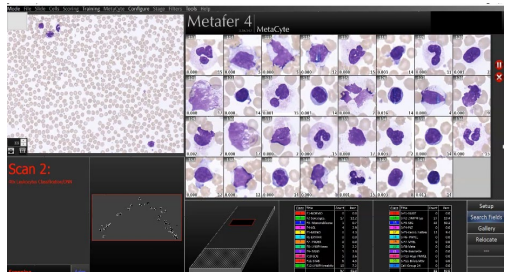


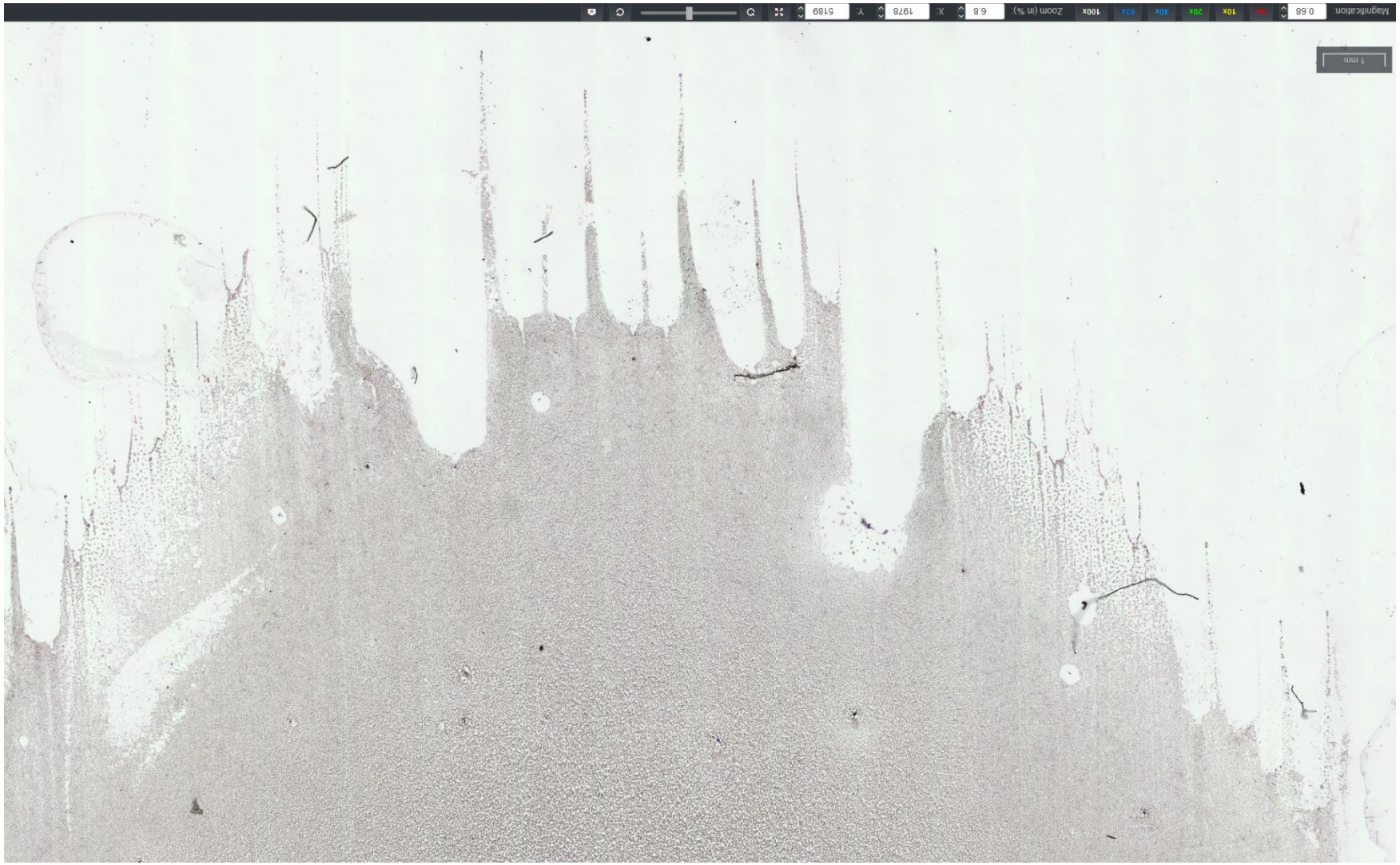




54%	Segmented neutrophils	48%
1%	Bands	1.47%
2.3%	**Concordance: 94.5% for malignant/critical cells**	2.69%
0.76%		2%
6.96%		7.05%
30.91%	Lymphocytes	24.53%
1.11%	Pathogenic blasts	3.25%

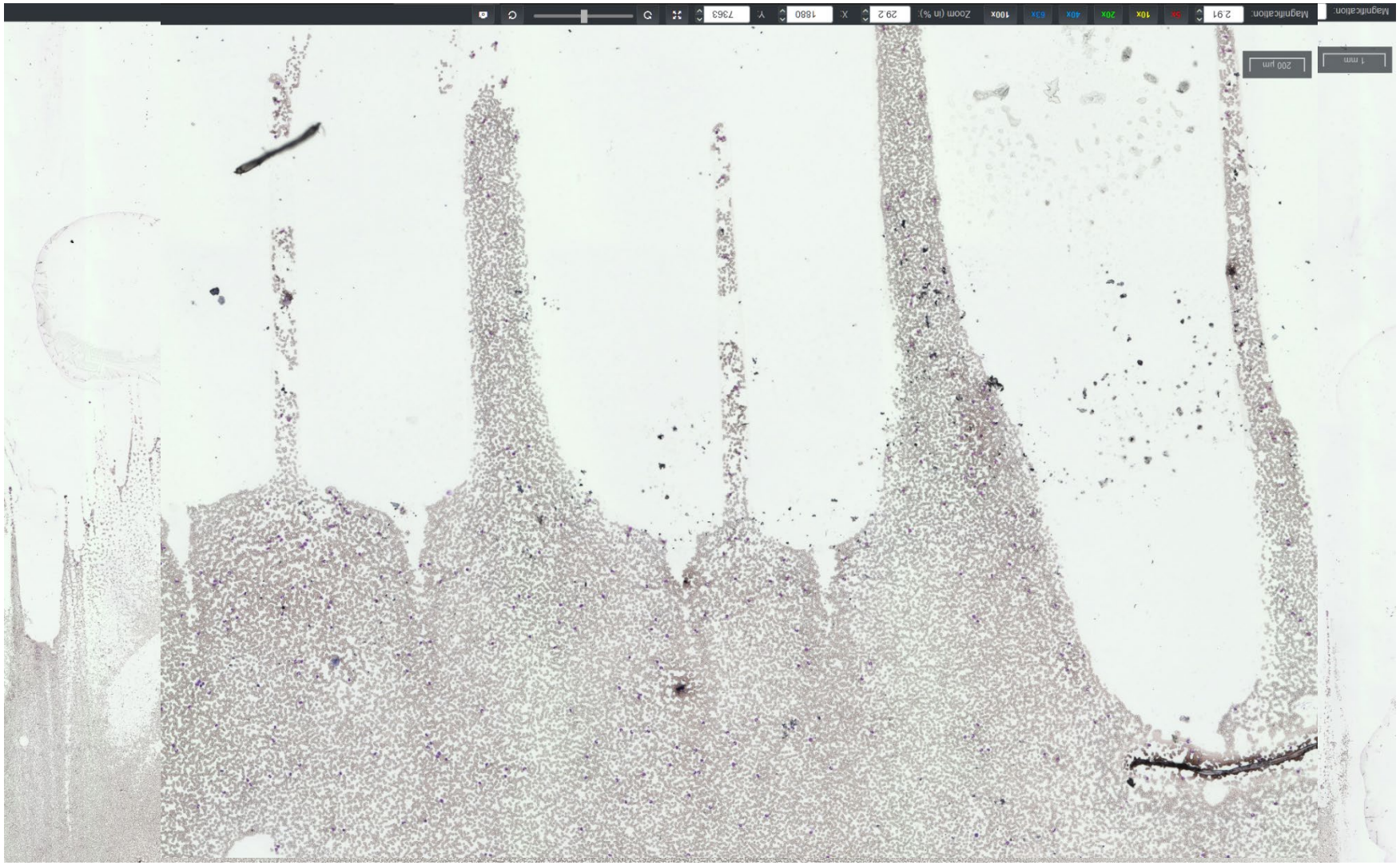
Haferlach T *et al*. Abstract #787 from ASH 2022; New Orleans, LA, USA, December 10–13, 2022.

Digital options for differential counts



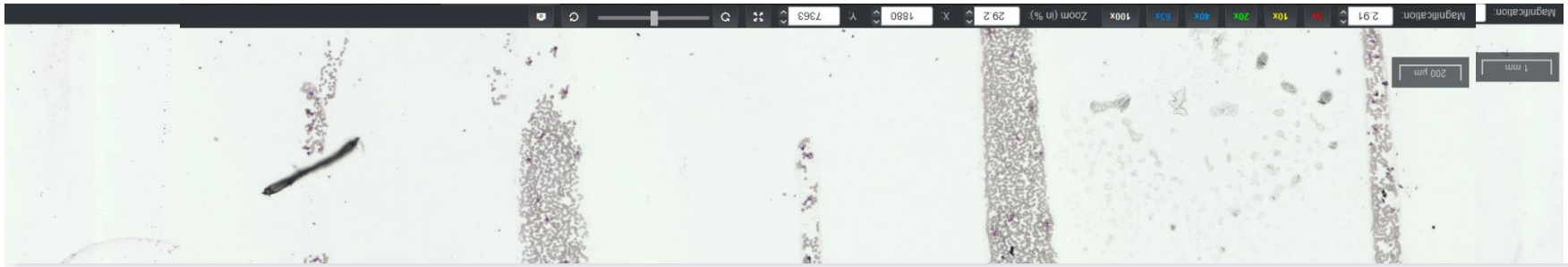
Slide content provided courtesy of Munich Leukemia Laboratory.

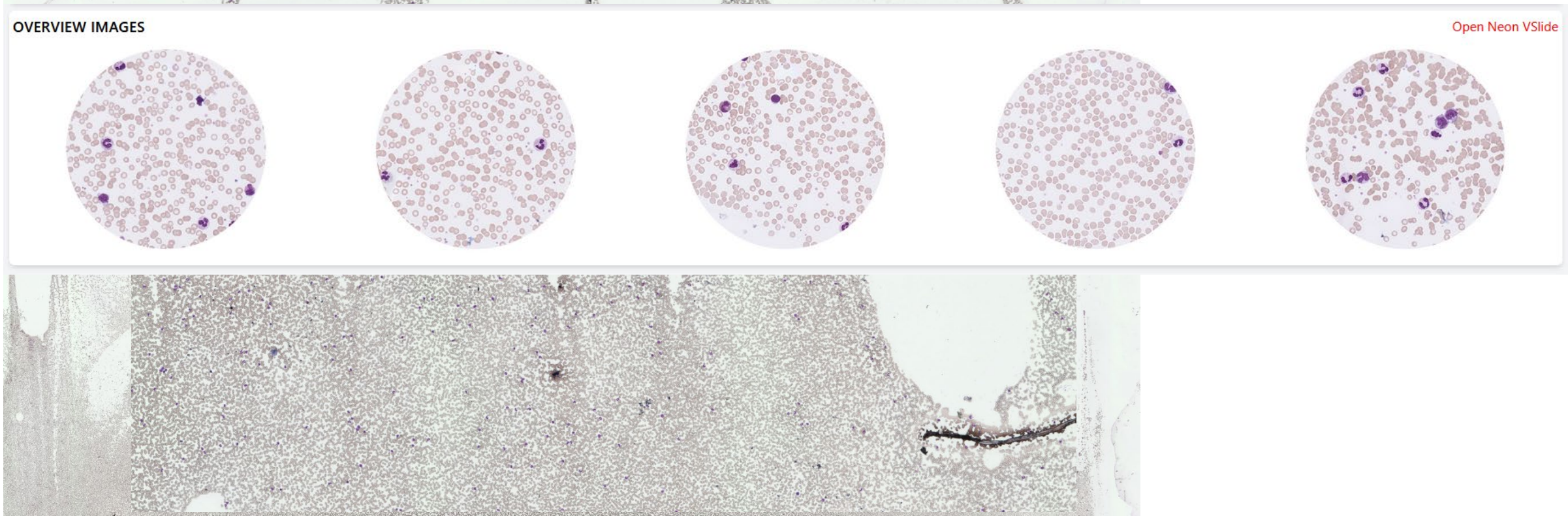
Digital options for differential counts



Slide content provided courtesy of Munich Leukemia Laboratory.

Digital options for differential counts





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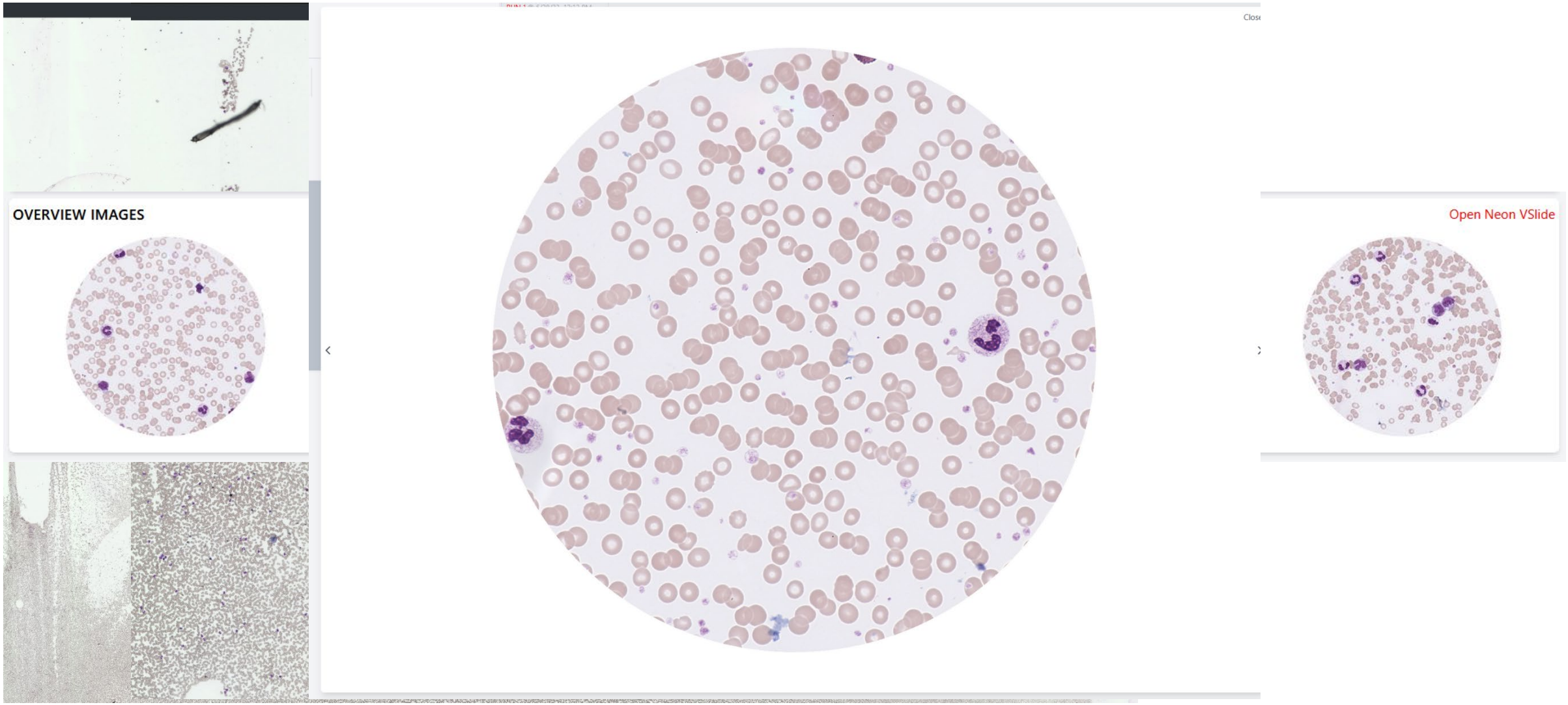
Digital options for differential counts



Slide content provided courtesy of Munich Leukemia Laboratory.

AI-based cell classification

Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.

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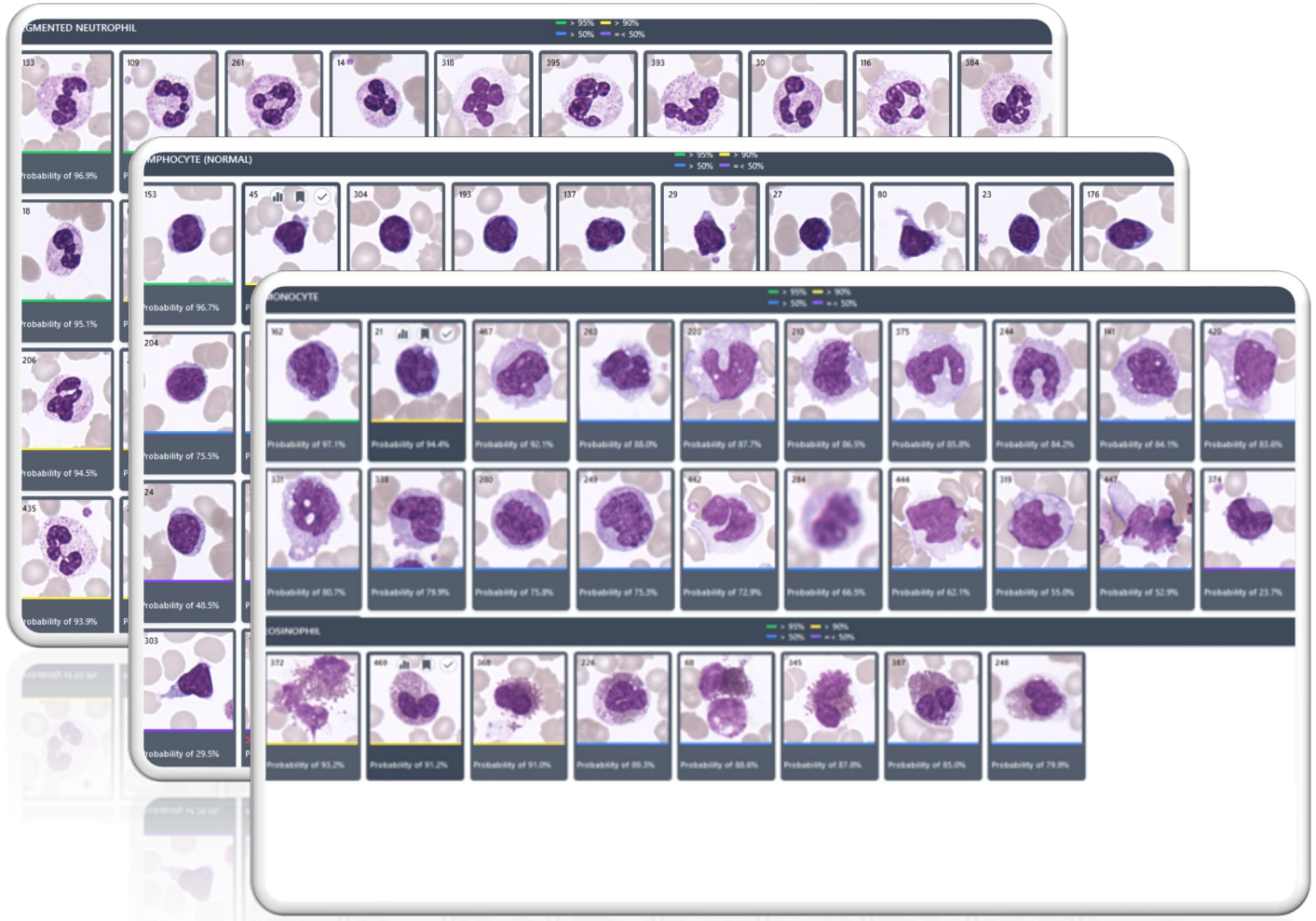
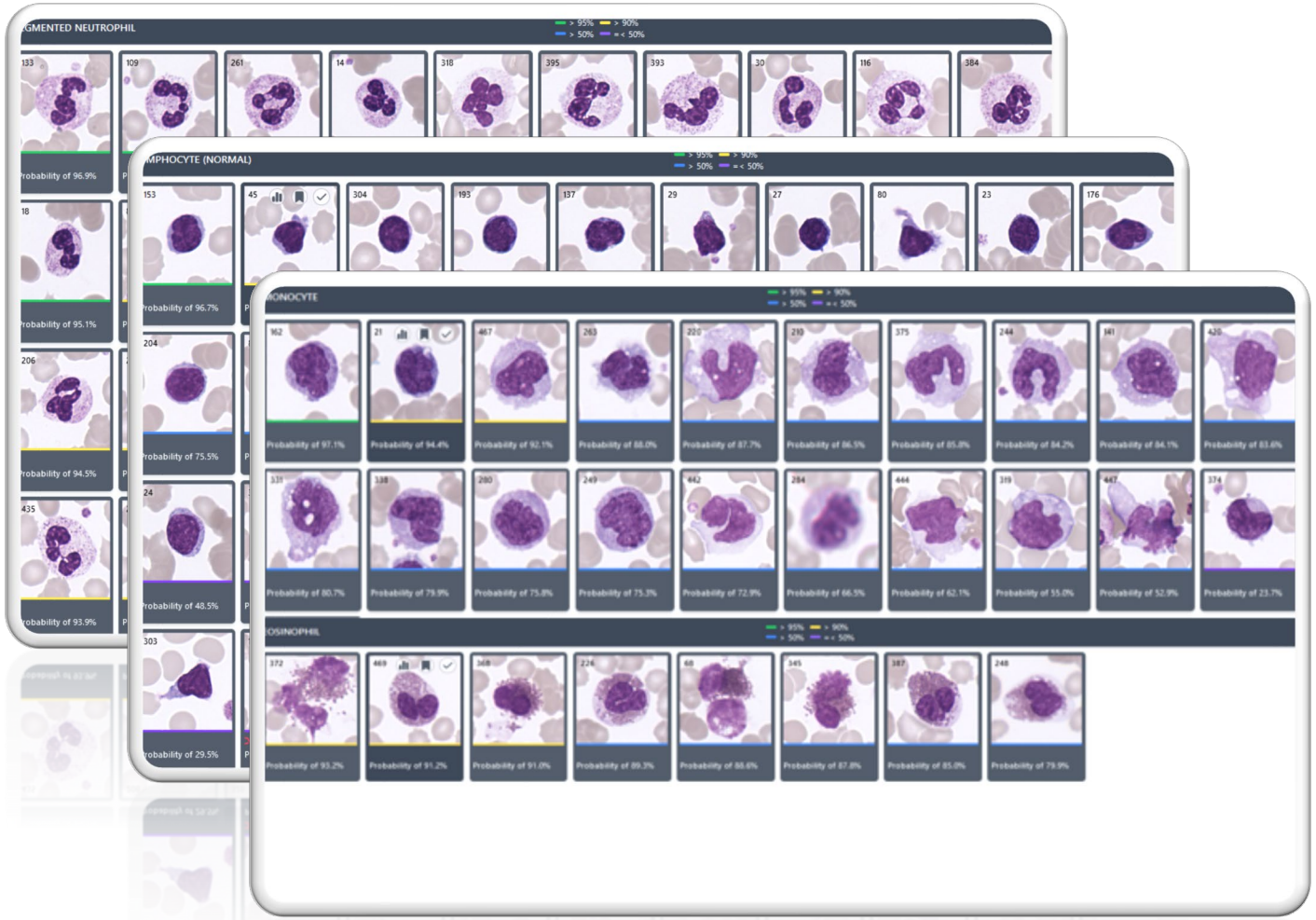
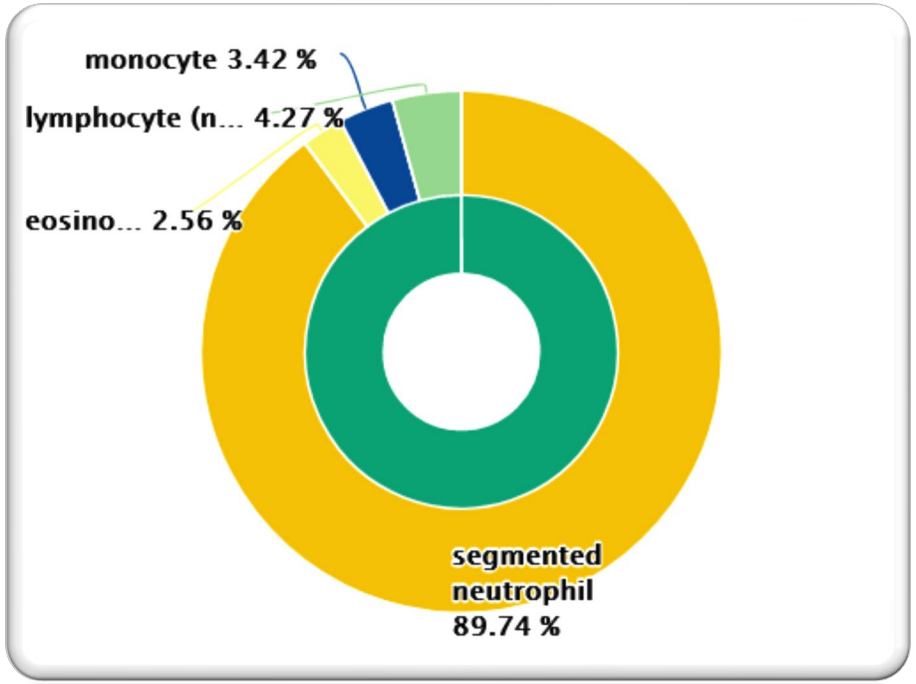


Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.

AI-based cell classification



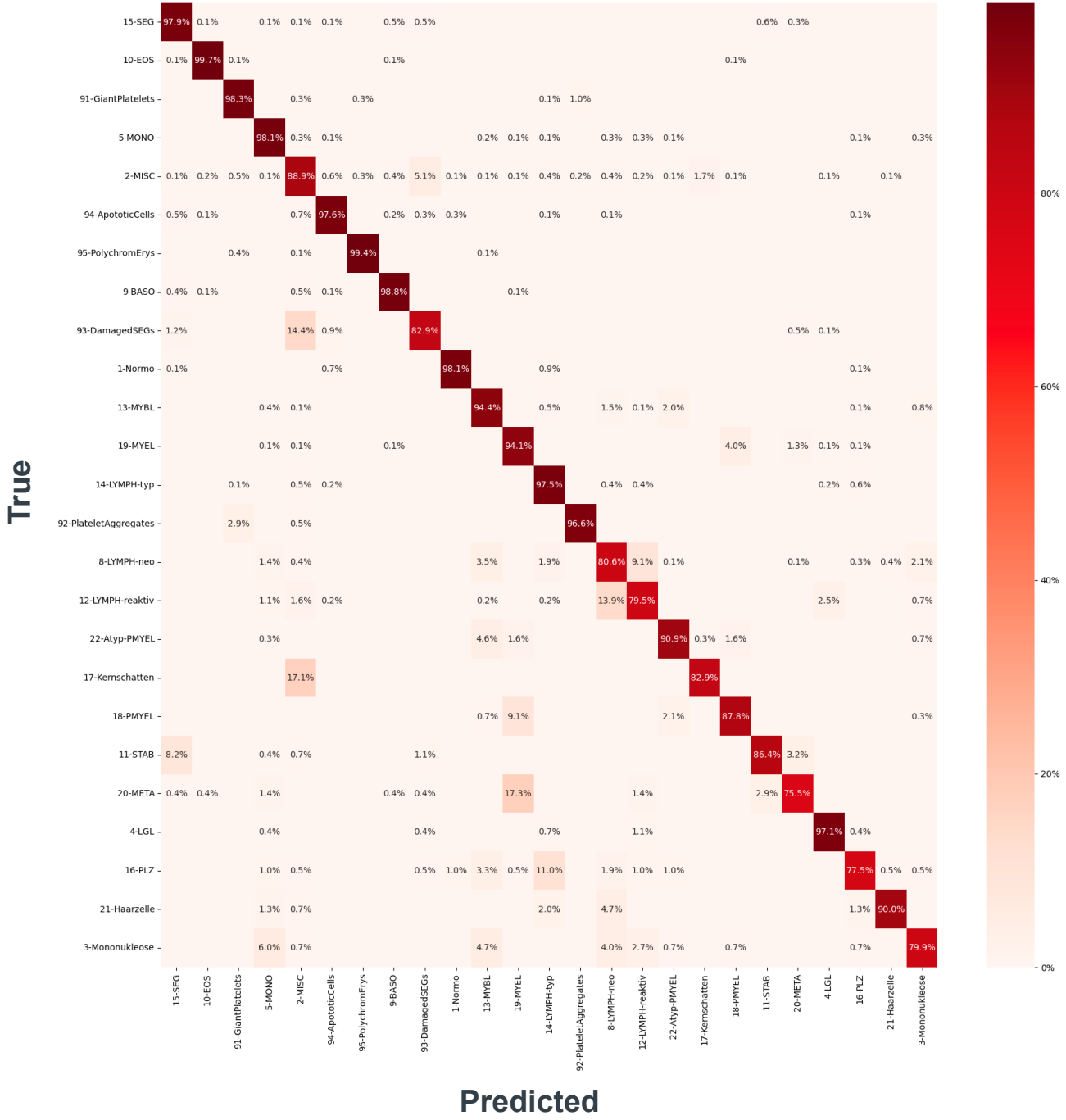


Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.

Classifier performance

Peripheral blood

- 25 cell classes
- Training dataset: n=69,550
- Test dataset: n=19,320
- Accuracy: 93.99%
- (Human baseline: ~85%)



Slide content provided courtesy of Munich Leukemia Laboratory.

Integration into routine diagnostics workflow

Munich Leukemia Laboratory

10× pre-scan and 40× scan of 500 images

3–4 min

Amazon Web Services Cloud

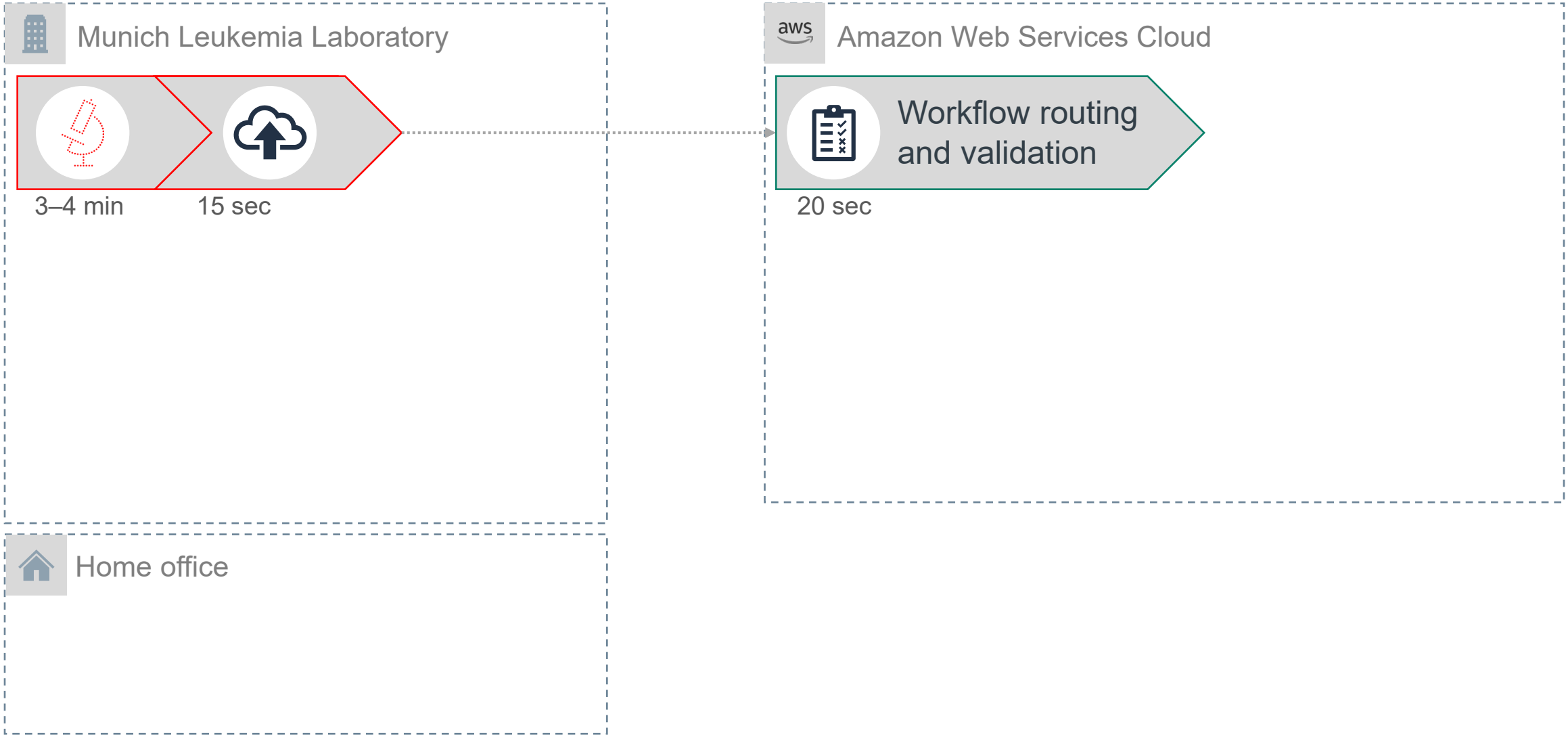
Home office

Slide content provided courtesy of Munich Leukemia Laboratory.

Integration into routine diagnostics workflow

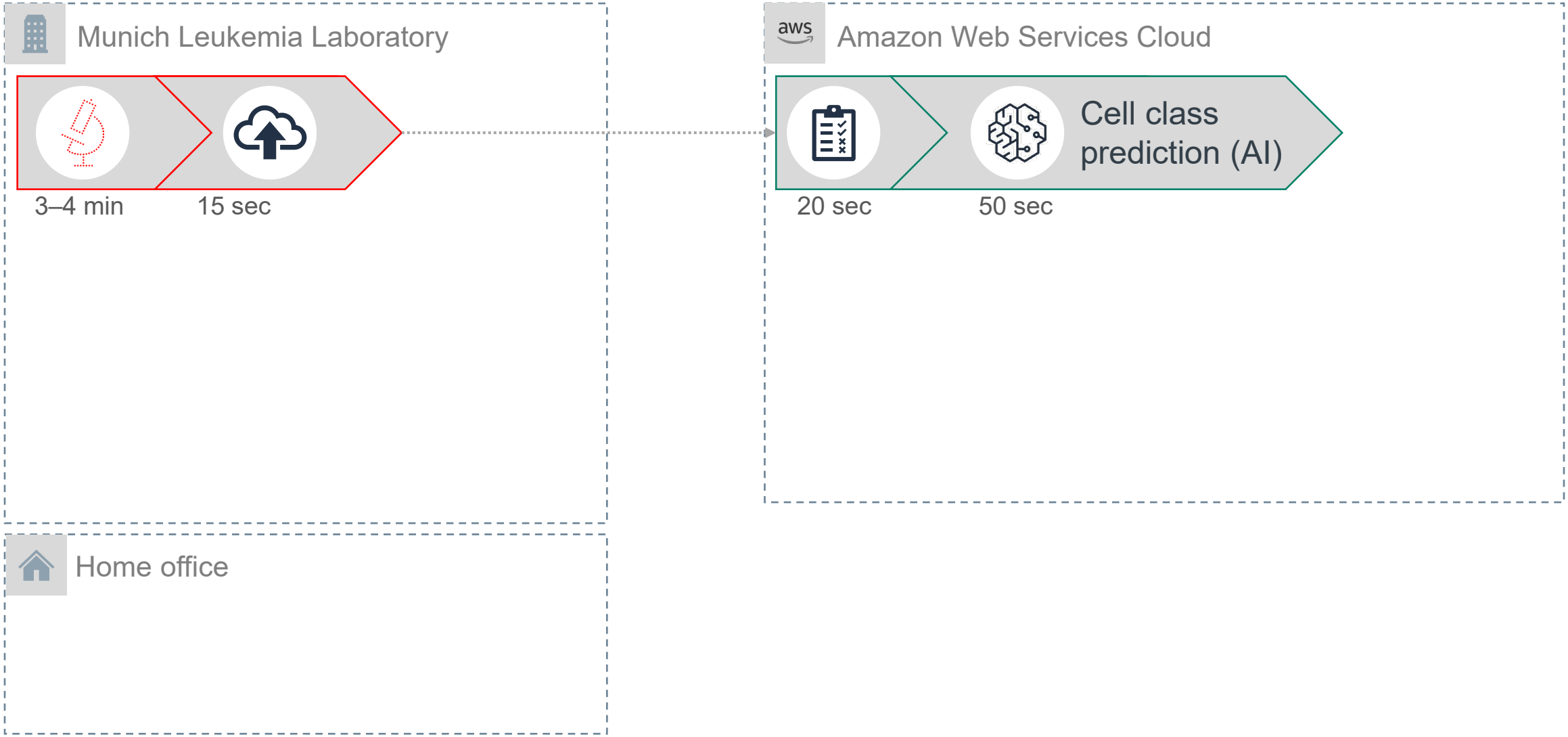
Slide content provided courtesy of Munich Leukemia Laboratory.

Integration into routine diagnostics workflow



Slide content provided courtesy of Munich Leukemia Laboratory.

Integration into routine diagnostics workflow



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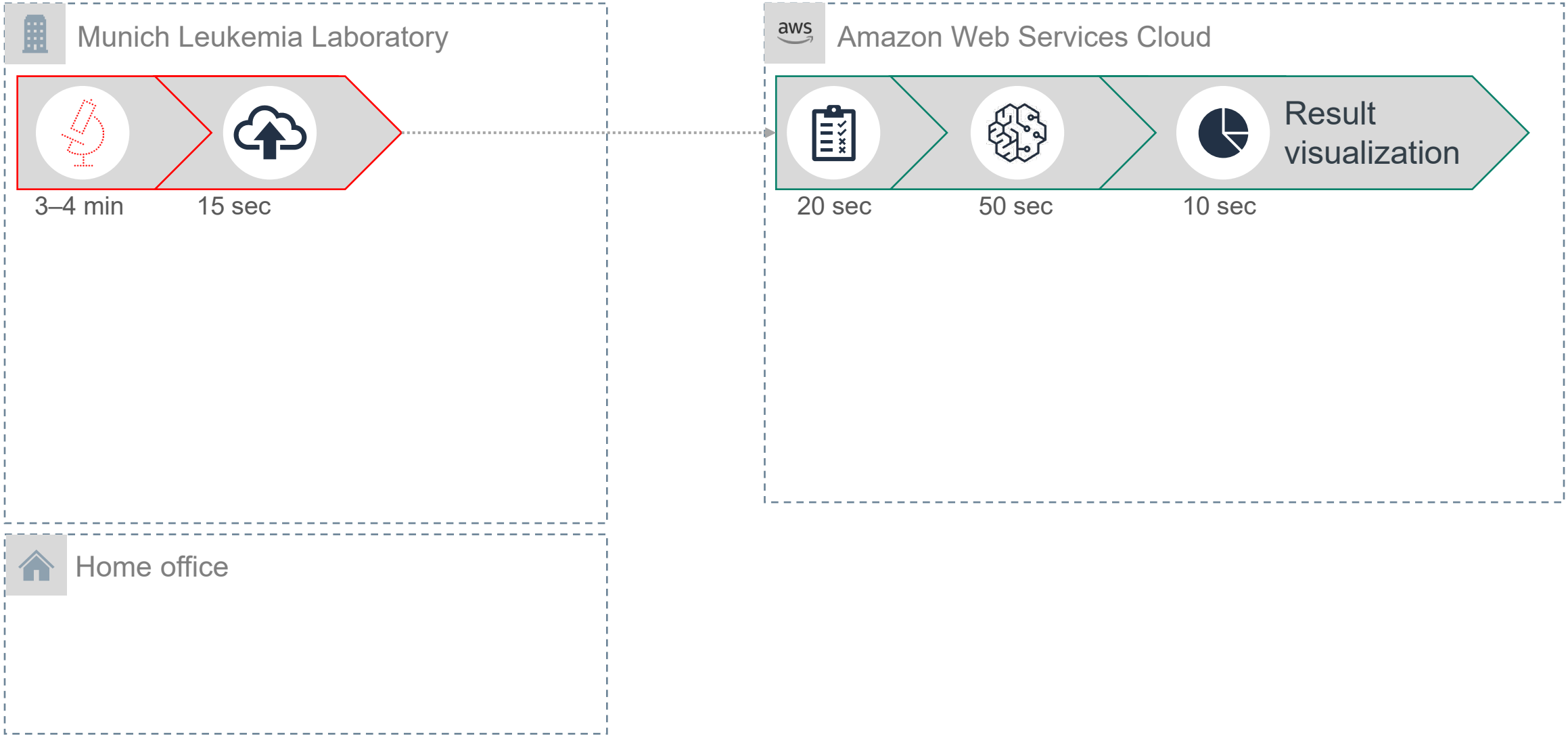
AI, artificial intelligence.

Integration into routine diagnostics workflow



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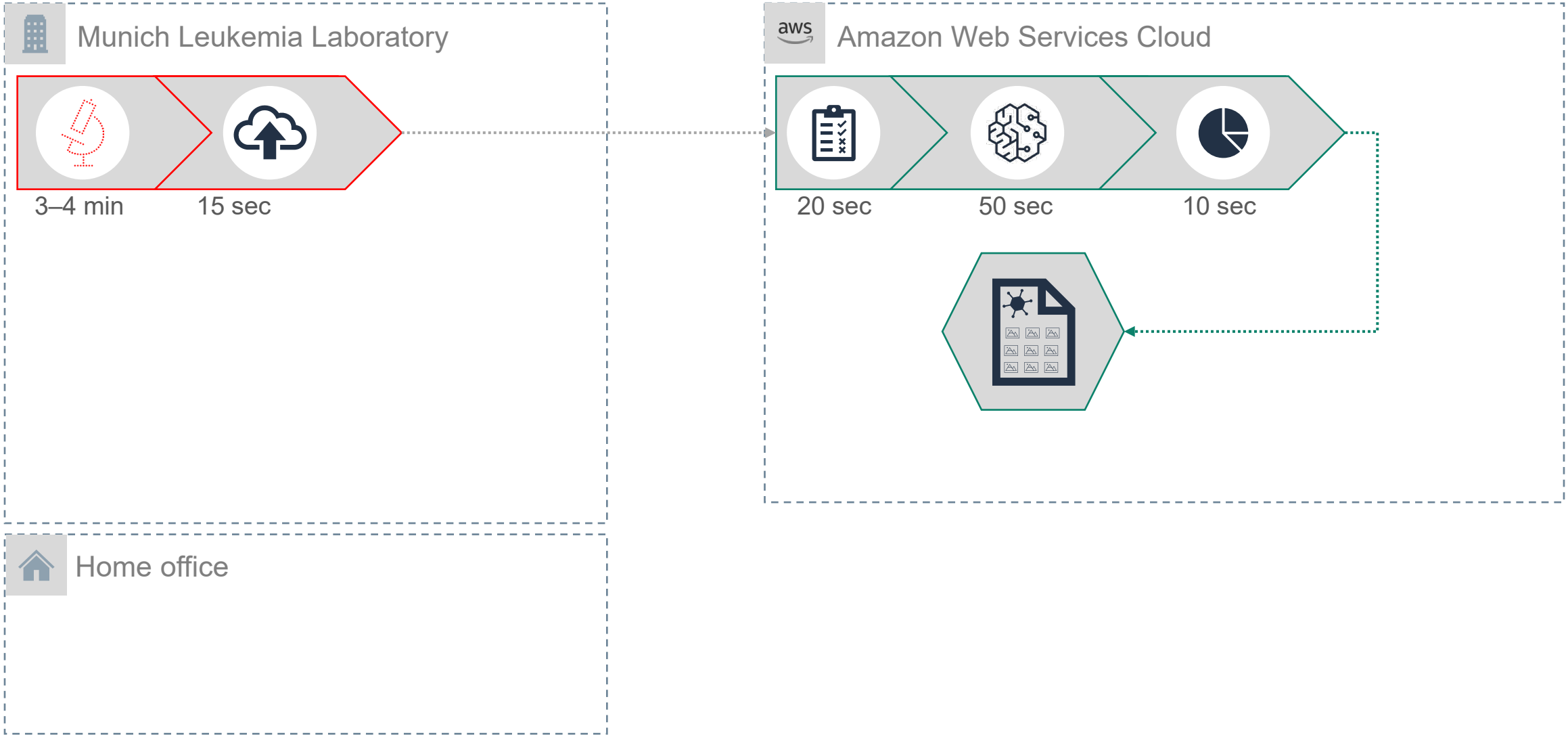

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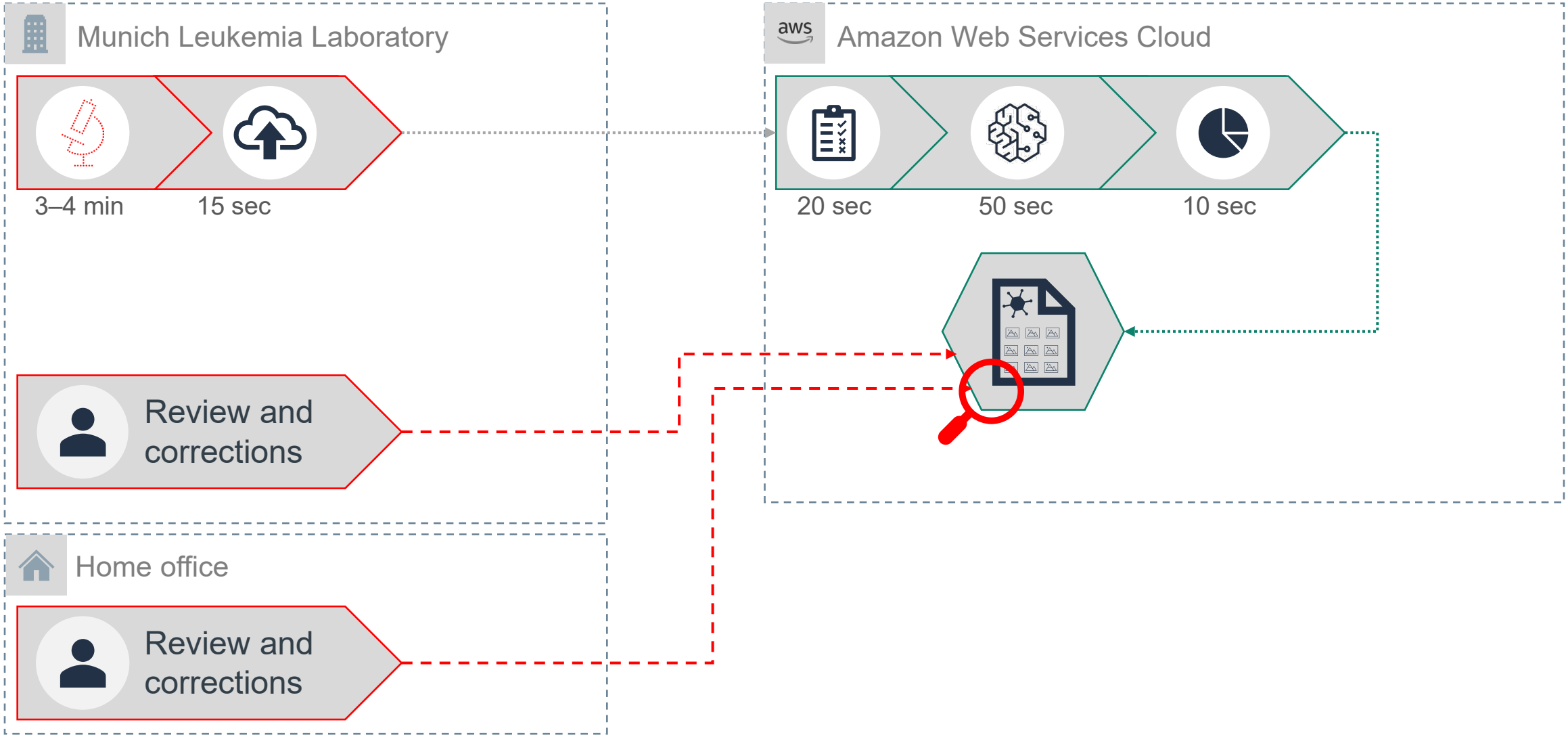

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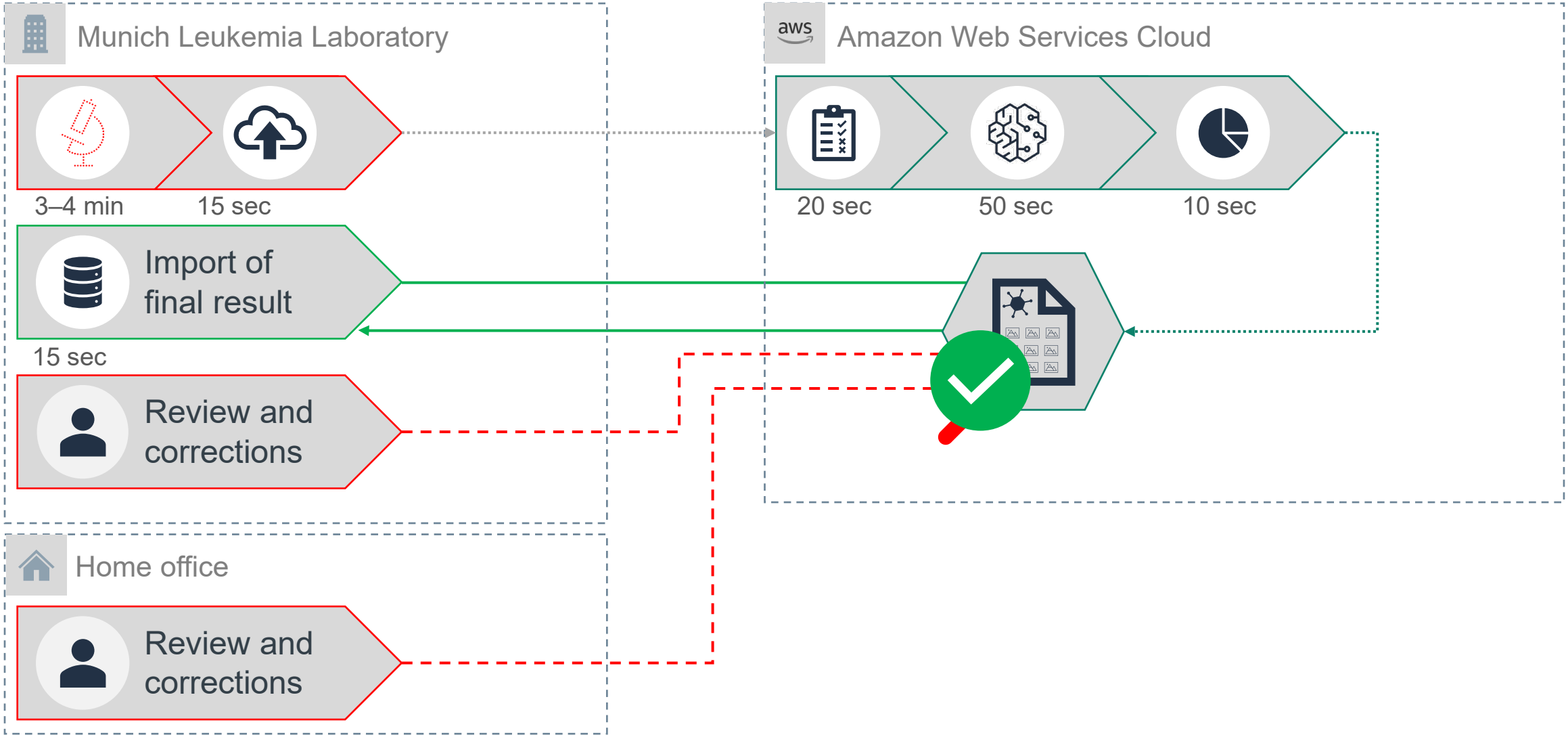
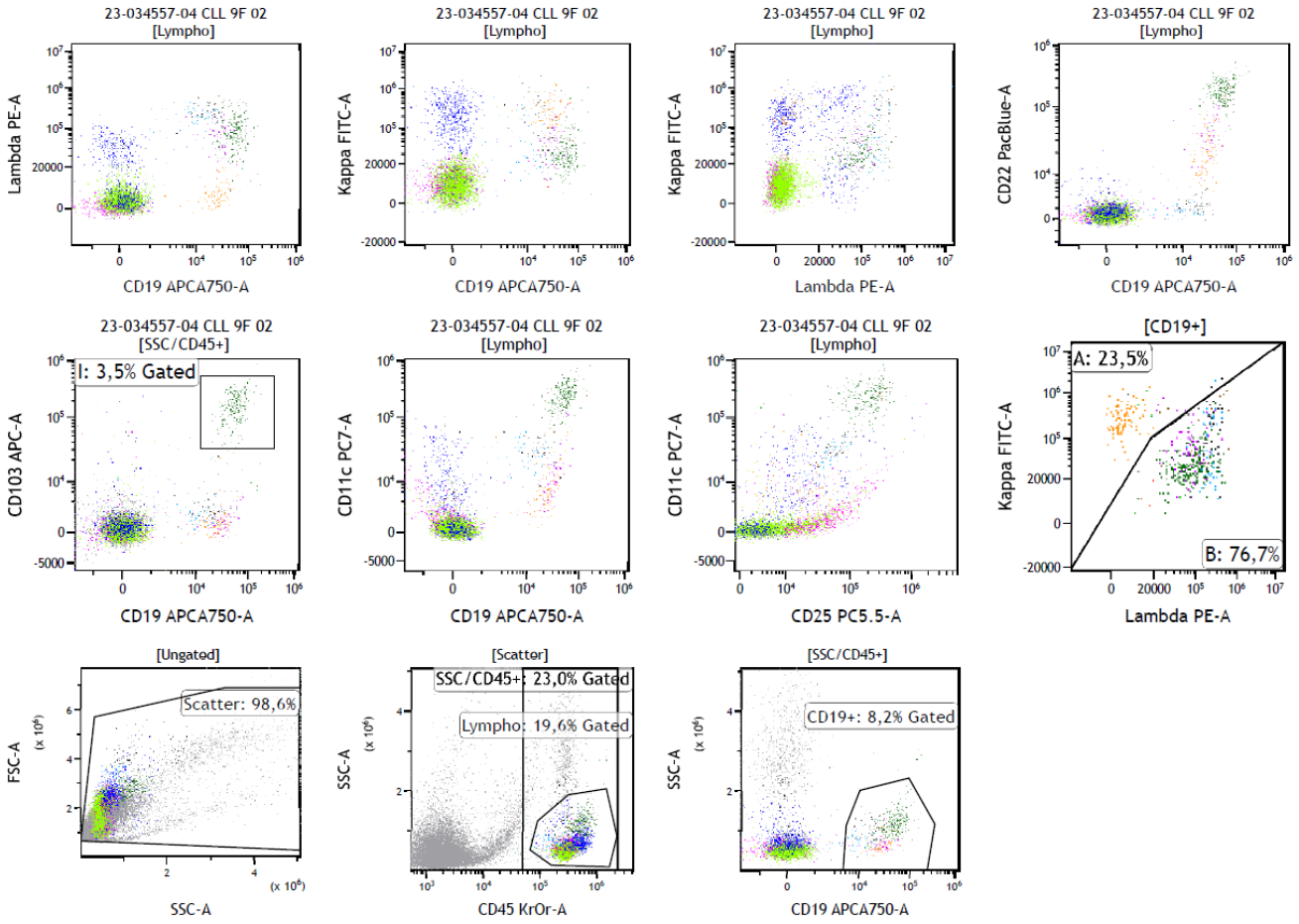
Integration into routine diagnostics workflow

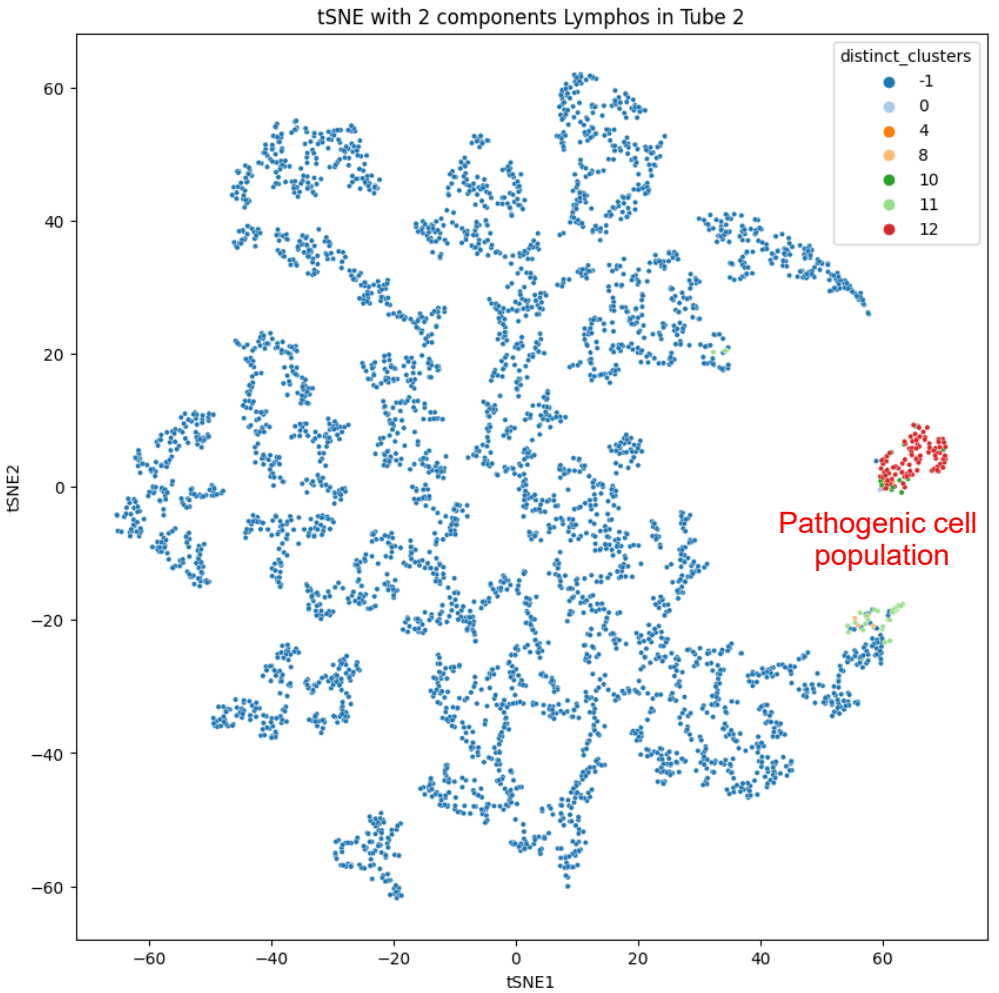


Slide content provided courtesy of Munich Leukemia Laboratory.

Dimensionality reduction



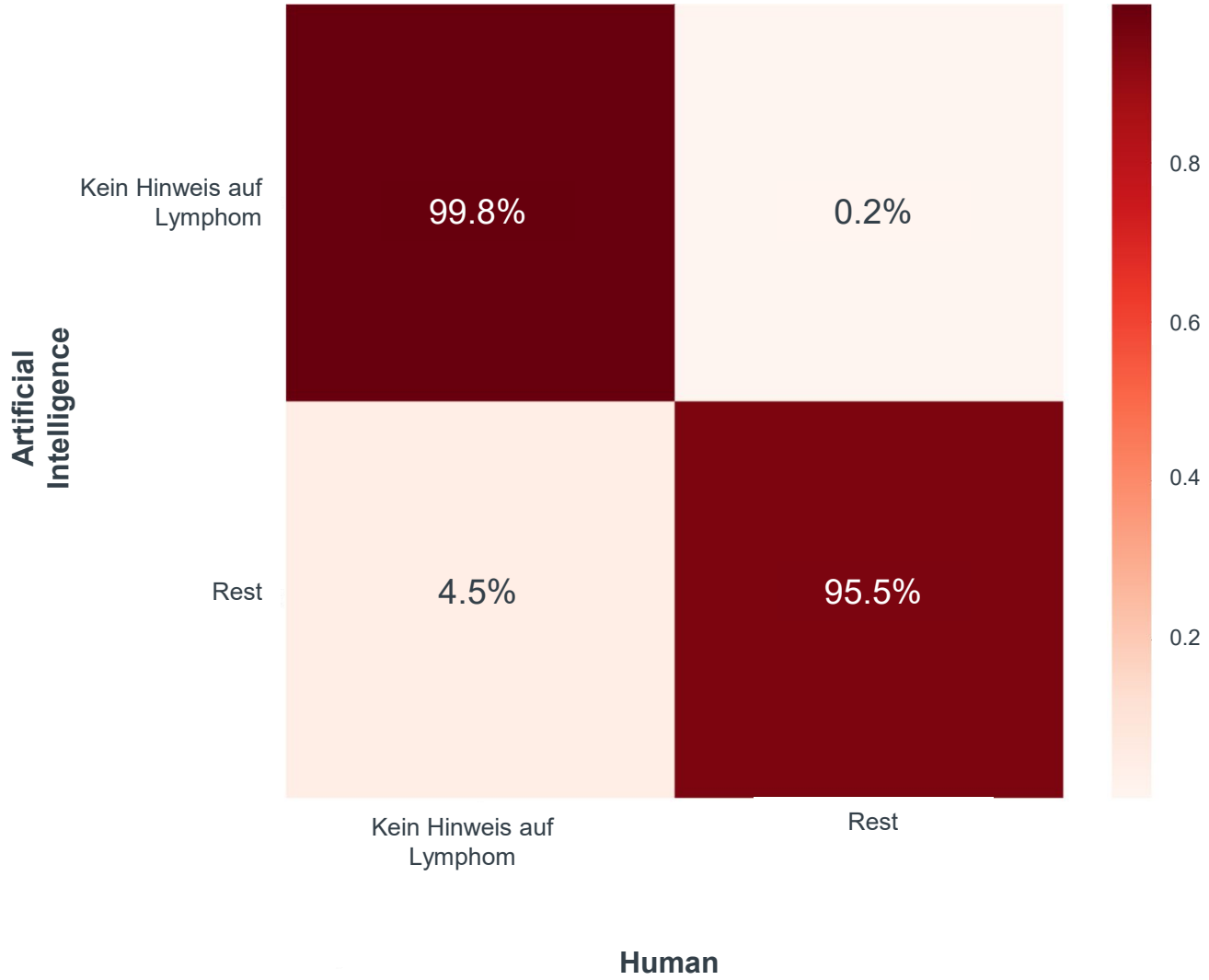
Traditional expert human review
High complexity



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

Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; APC, allophycocyanin; APCA, APC-Alexa Fluor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; FITC, fluorescein isothiocyanate; KrOr, krome orange; Lympho, lymphocytes; PacBlue, Pacific Blue®; PC, phycoerythrin-cyanine; PE, phycoerythrin; SSC, side scatter; tSNE, t-distributed stochastic neighbor embedding.

Binary classifier performance: No lymphoma vs. lymphoma



Training set:
52,381*

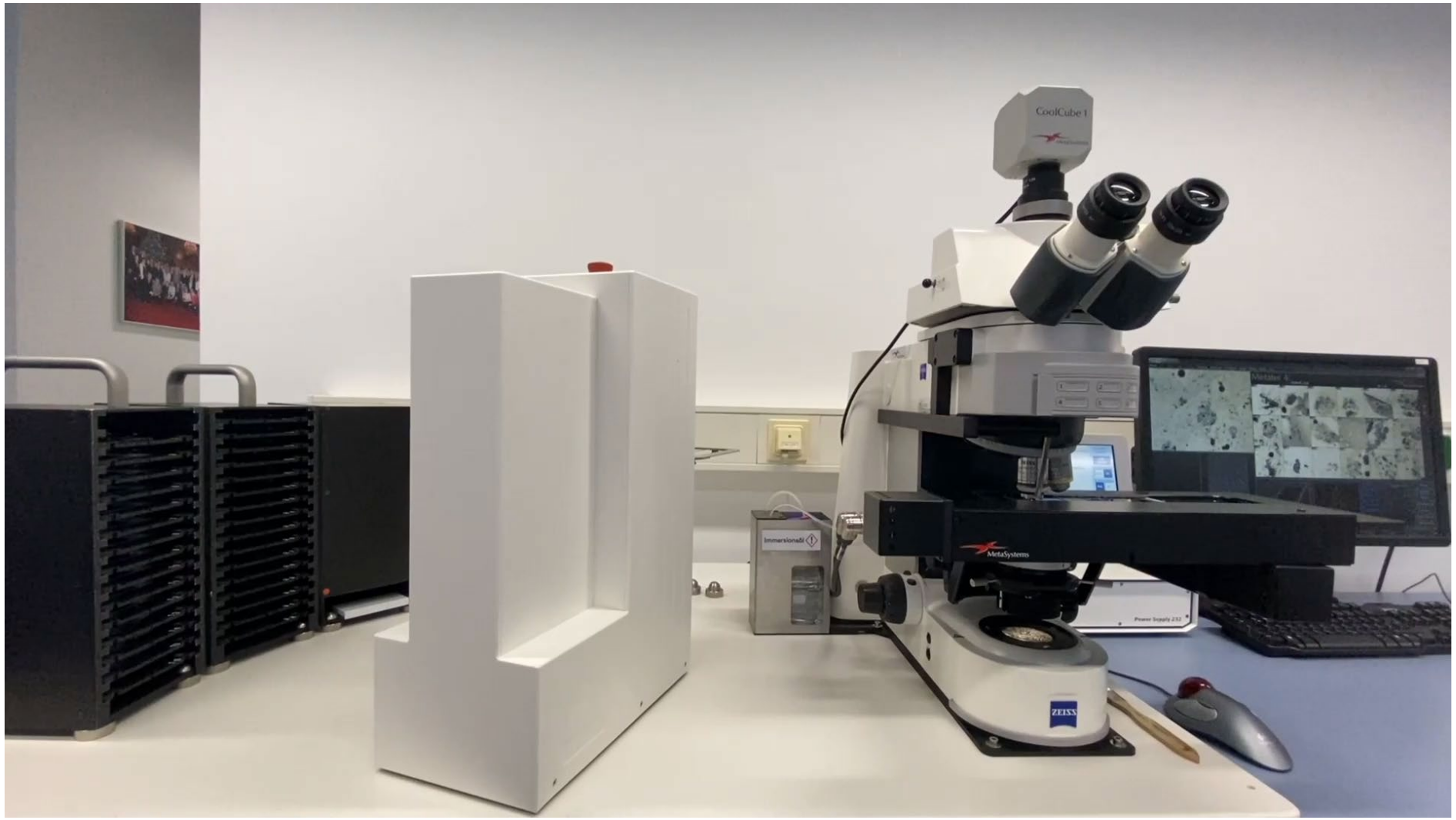
Test set:
1,246 cases

Accuracy of
98.0%

*Upsampled with SMOTE (synthetic data) from 11,206 cases to balance all classes (6 lymphoma subtypes and 1 no evidence of lymphoma)

Slide content provided courtesy of Munich Leukemia Laboratory.

Automated metaphase finder

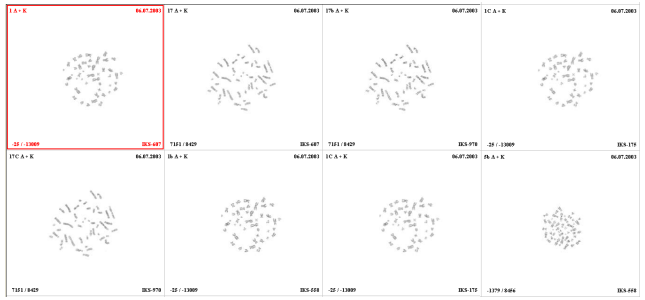


Slide content provided courtesy of Munich Leukemia Laboratory.

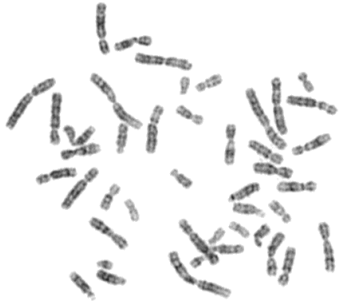
Chromosome banding analysis

Labor-intensive technique requiring advanced experience in the lab and in interpretation

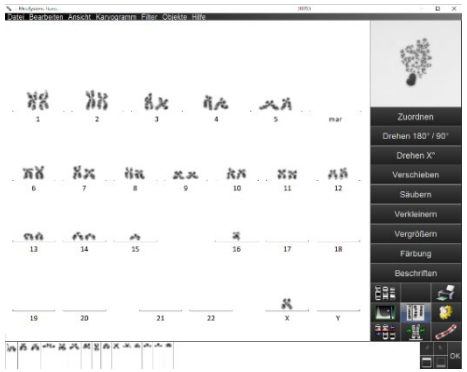
Selection of ≥20 metaphases



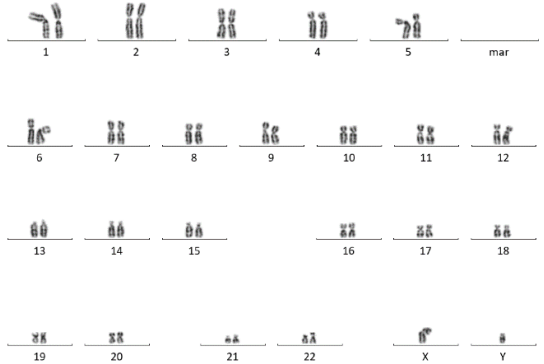
Editing
(separation of objects/contrast, etc.)



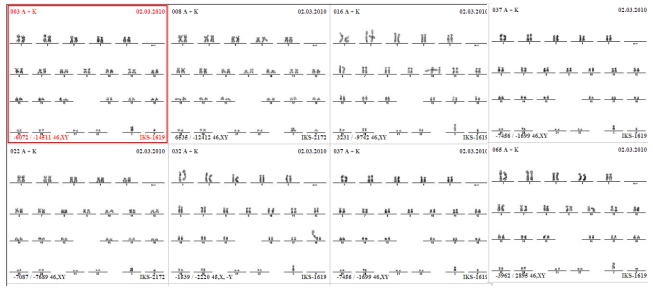
Karyotyping



Analysis of karyograms



Final karyotype
based on ≥20 karyograms



46,XY [20]

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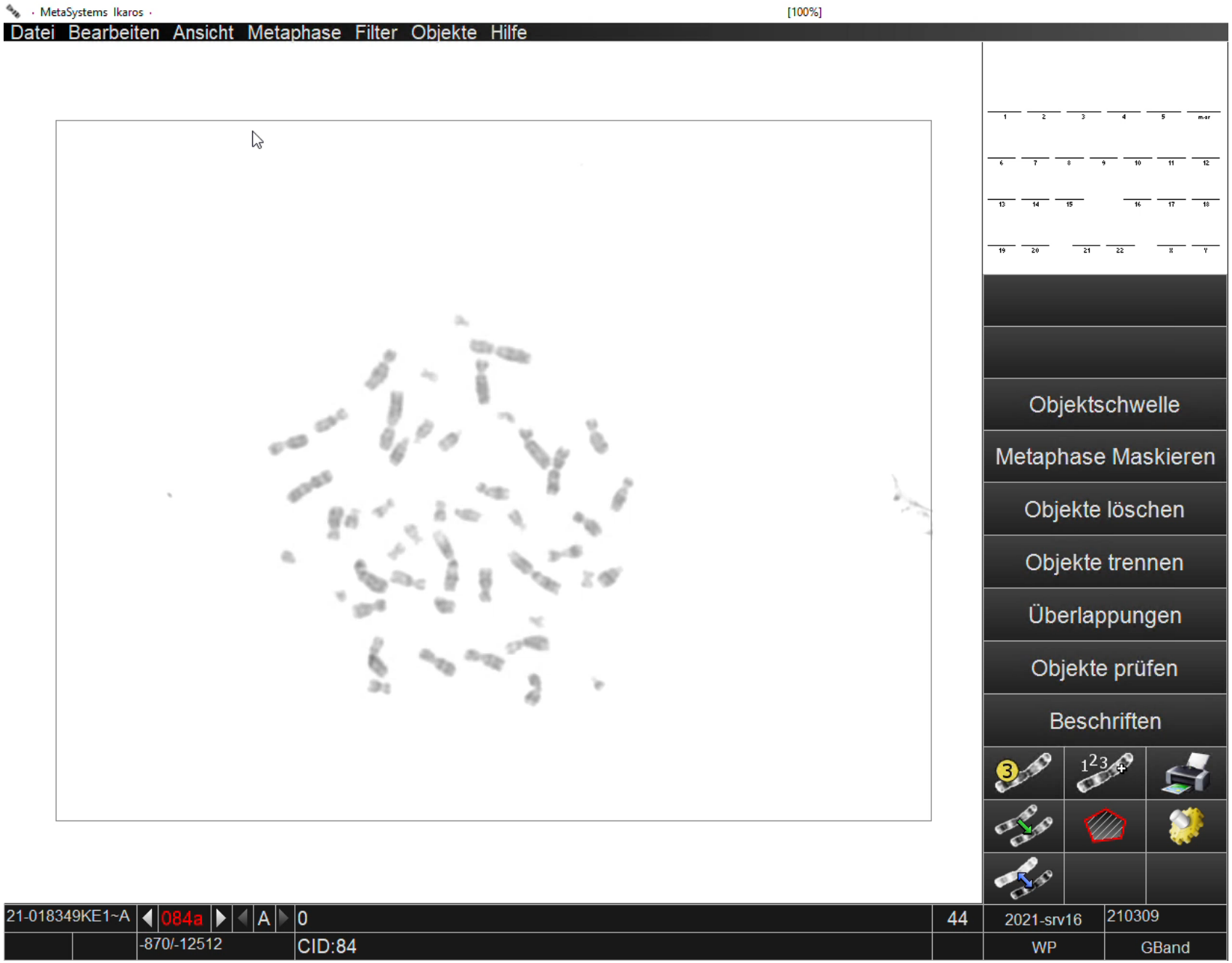
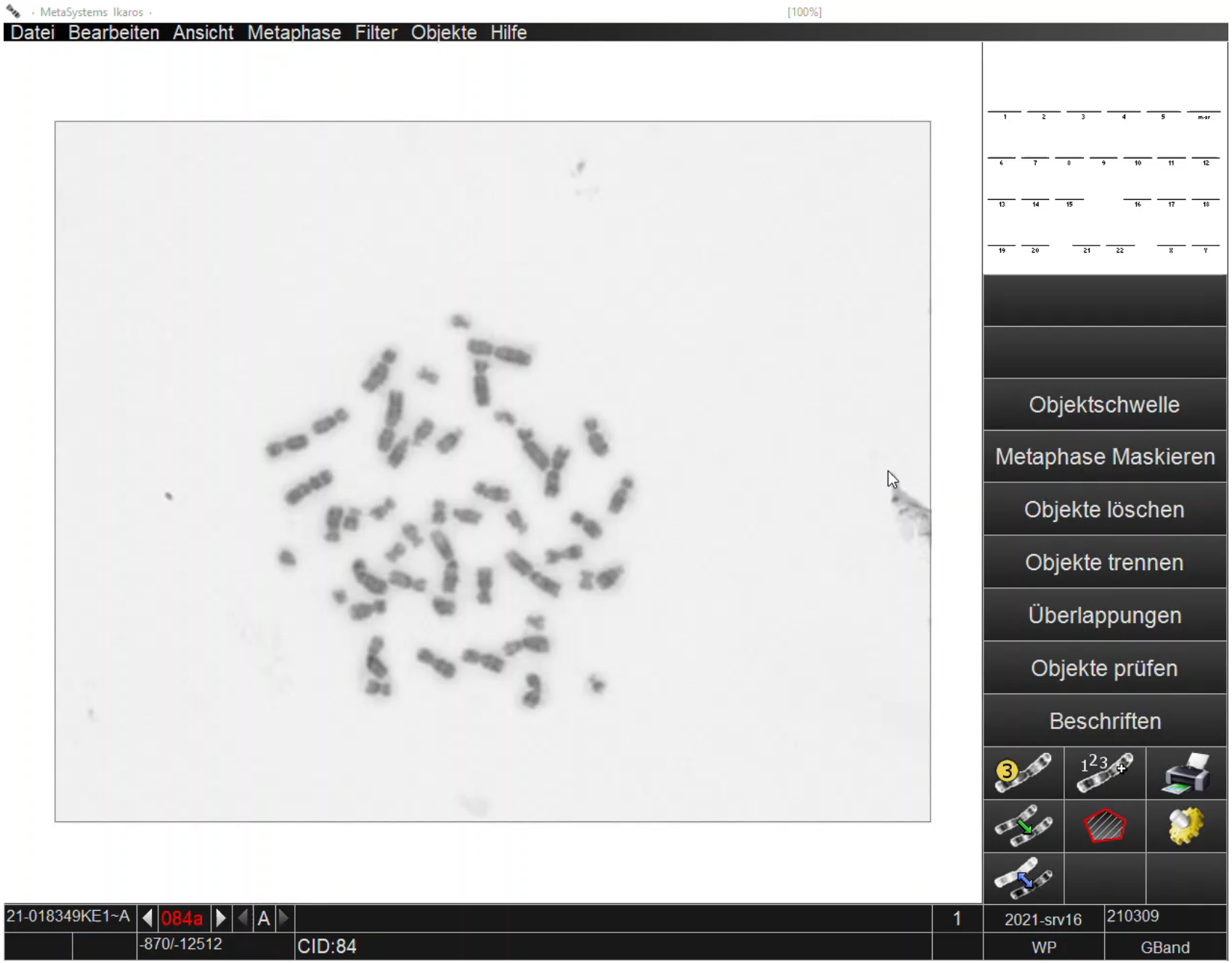
Manual classification



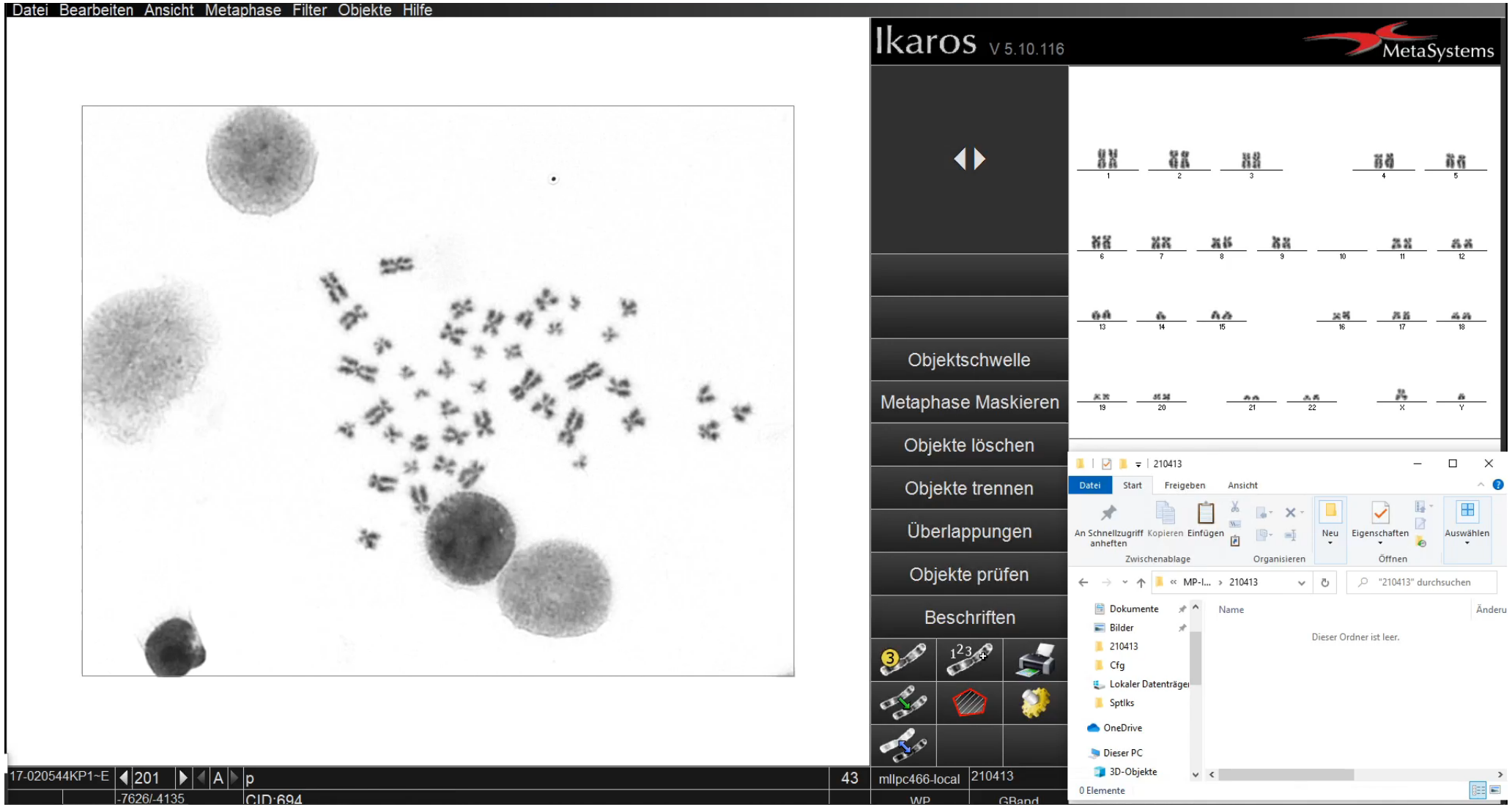
Slide content provided courtesy of Munich Leukemia Laboratory.

AI-based classification

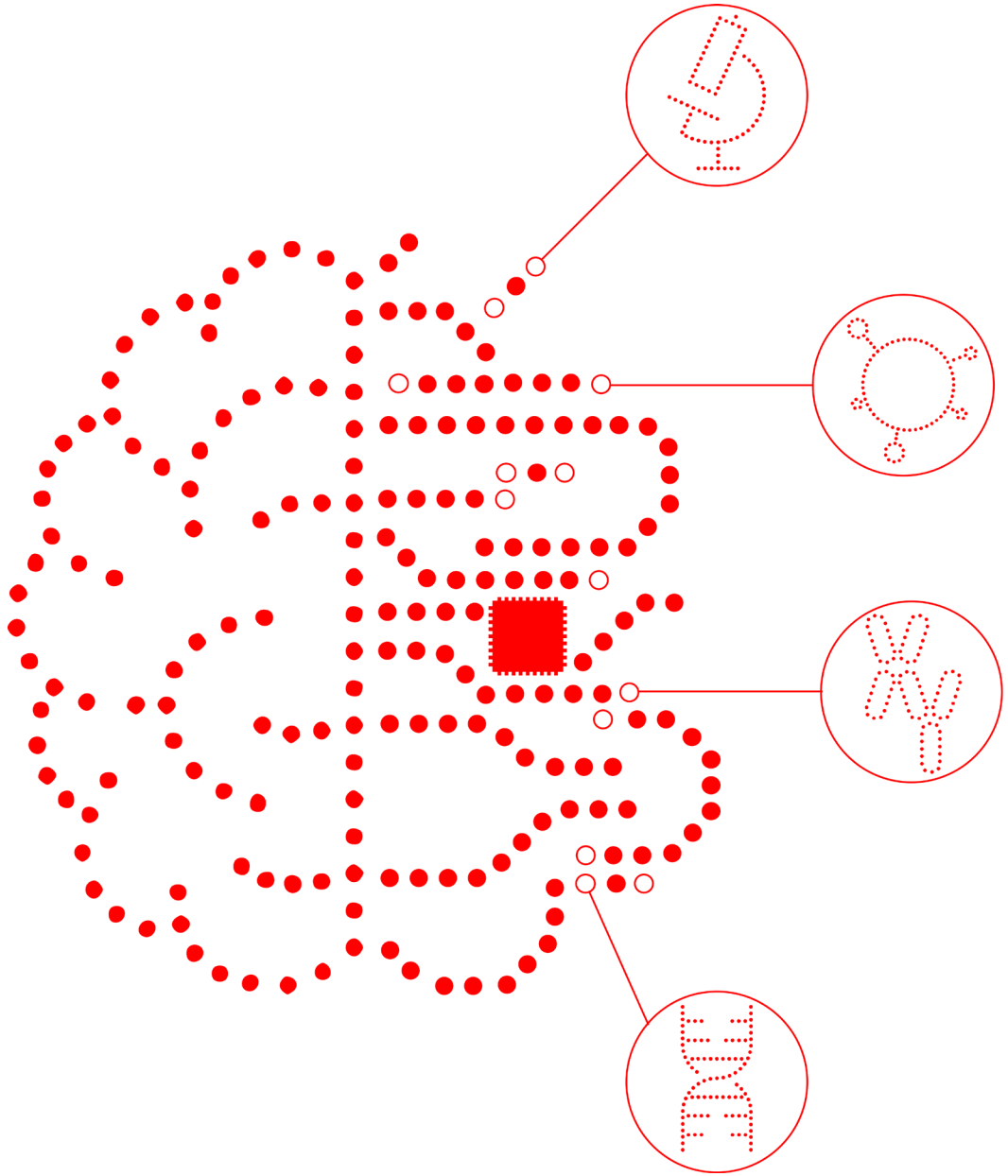


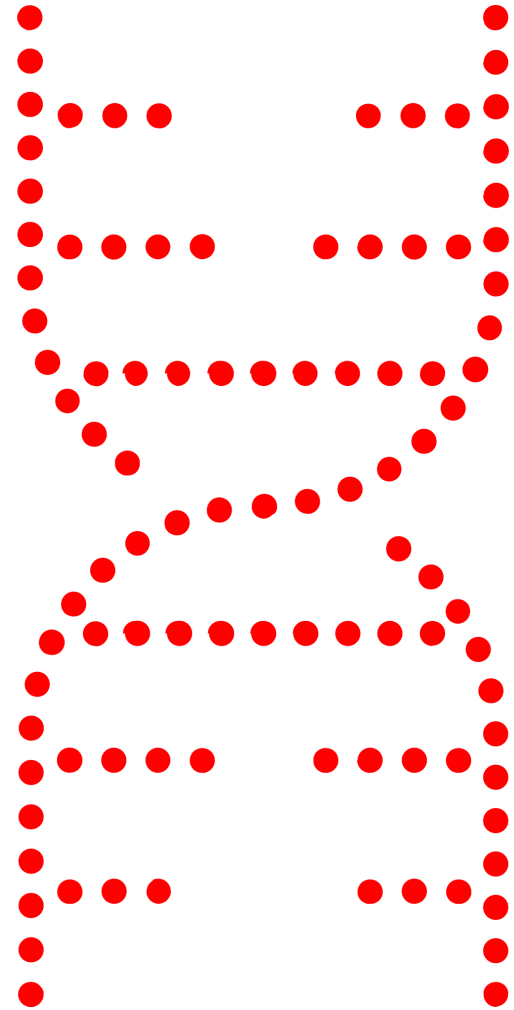
Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.

AI-based batch karyotyping (20 metaphases)



Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.





Molecular methods: Panel sequencing

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

myeloid panel

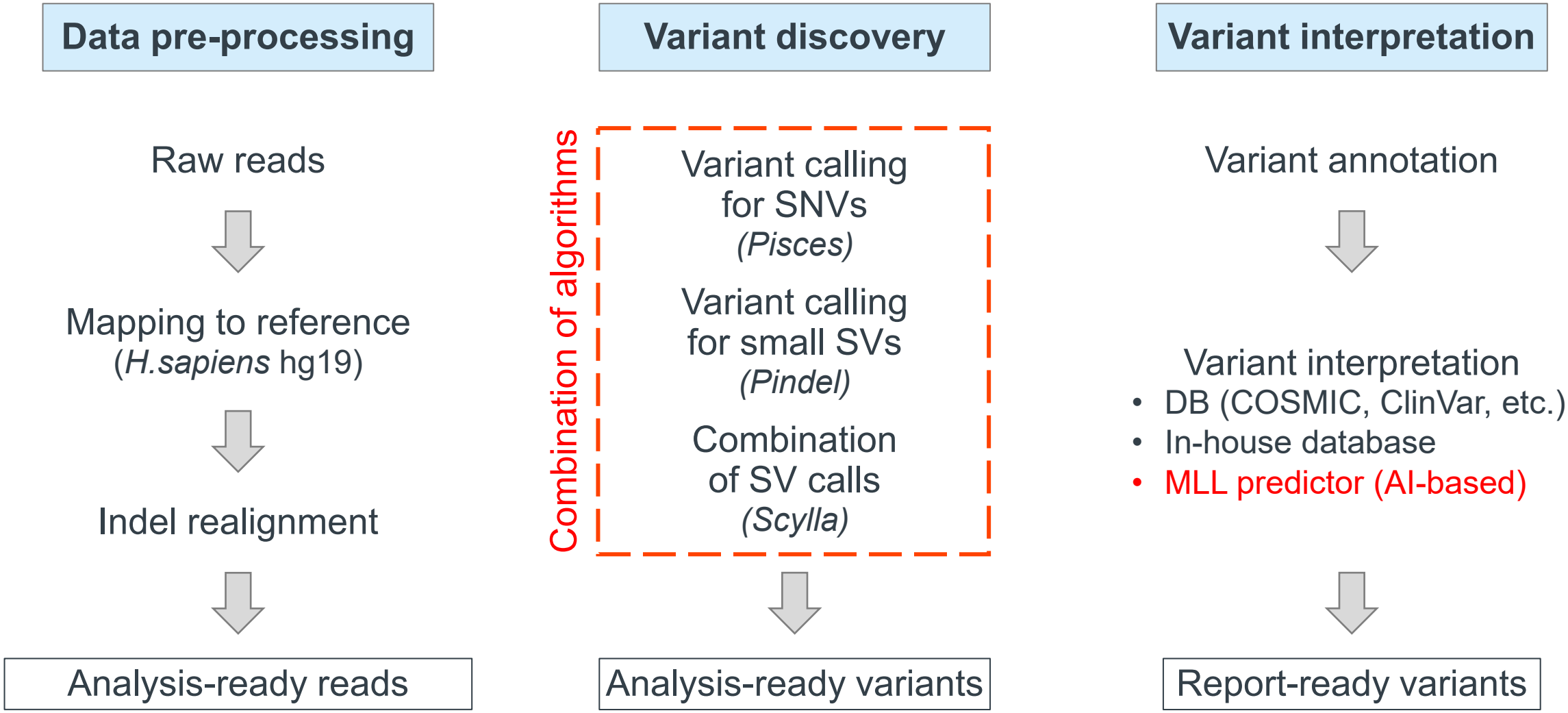
Gene	ROI
ARID1A	CCS
ATM	CCS
ATR	CCS
BCL10	CCS
BCL2	CCS
BIRC3	CCS
BRAF	CCS
BTK	E15
CARD11	CCS
CCL22	CCS
CCND1	UTR+CCS
CD28	CCS
CD79B	CCS
CREBBP	CCS
CXCR4	CCS
DIS3	CCS
DNMT3A	CCS
EGR1	CCS
EP300	CCS
ETV6	CCS
EZH2	CCS
FBXW7	CCS
FLT3	E14-E20
FOXO1	CCS
FYN	CCS
ID3	CCS
IDH2	E04, E07
IKZF1	CCS
IL7R	CCS
IRF4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

lymphoid panel

Slide content provided courtesy of Munich Leukemia Laboratory.
ROI, region of interest.

Data interpretation: NGS

Variant annotation and interpretation



Slide content provided courtesy of Munich Leukemia Laboratory.

AI, artificial intelligence; COSMIC, Catalogue of Somatic Mutations in Cancer; DB, database; MLL, Munich Leukemia Laboratory; NGS, next-generation sequencing; SNV, single nucleotide variant; SV, structural variant.

Data interpretation: NGS

Variant annotation and 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

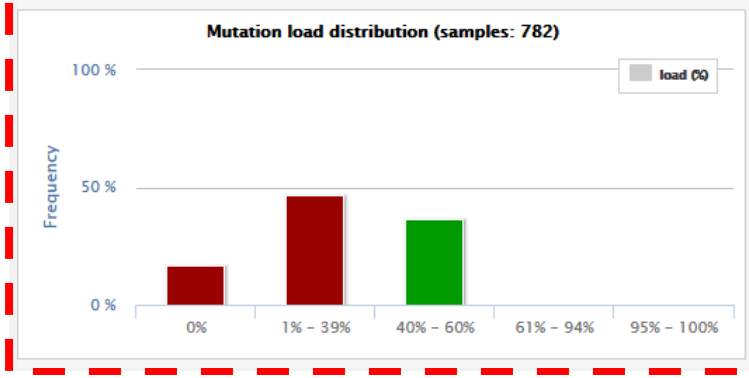
ID	HGVS	Type	Clinical Significance	Origin	ReviewStatus	Number Submitters	Last Evaluated	dbSNP	Cytogenetics	Guidelines	PhenotypeIDs
362761	c.2644C>T (p.Arg882Cys)	single nucleotide variant	Pathogenic/Likely pathogenic	somatic	no assertion criteria provided	1	May 31, 2016	rs377577594	2p23.3		MedGen MedGen 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

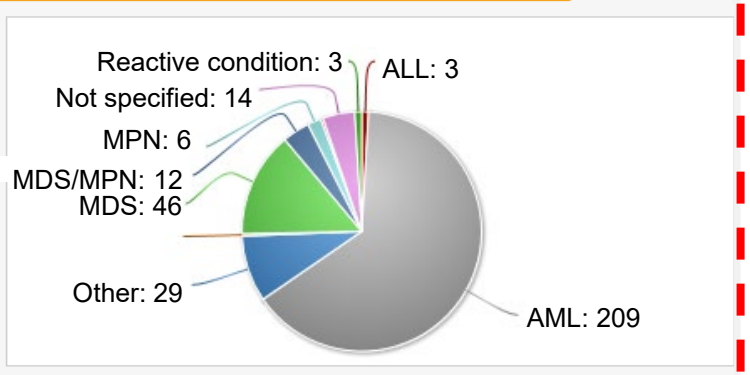
DNA pos. may differ, as different transcripts are used. Query based on chromosomal coordinates.

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 addtional information.





Variant interpretation

Variant annotation

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

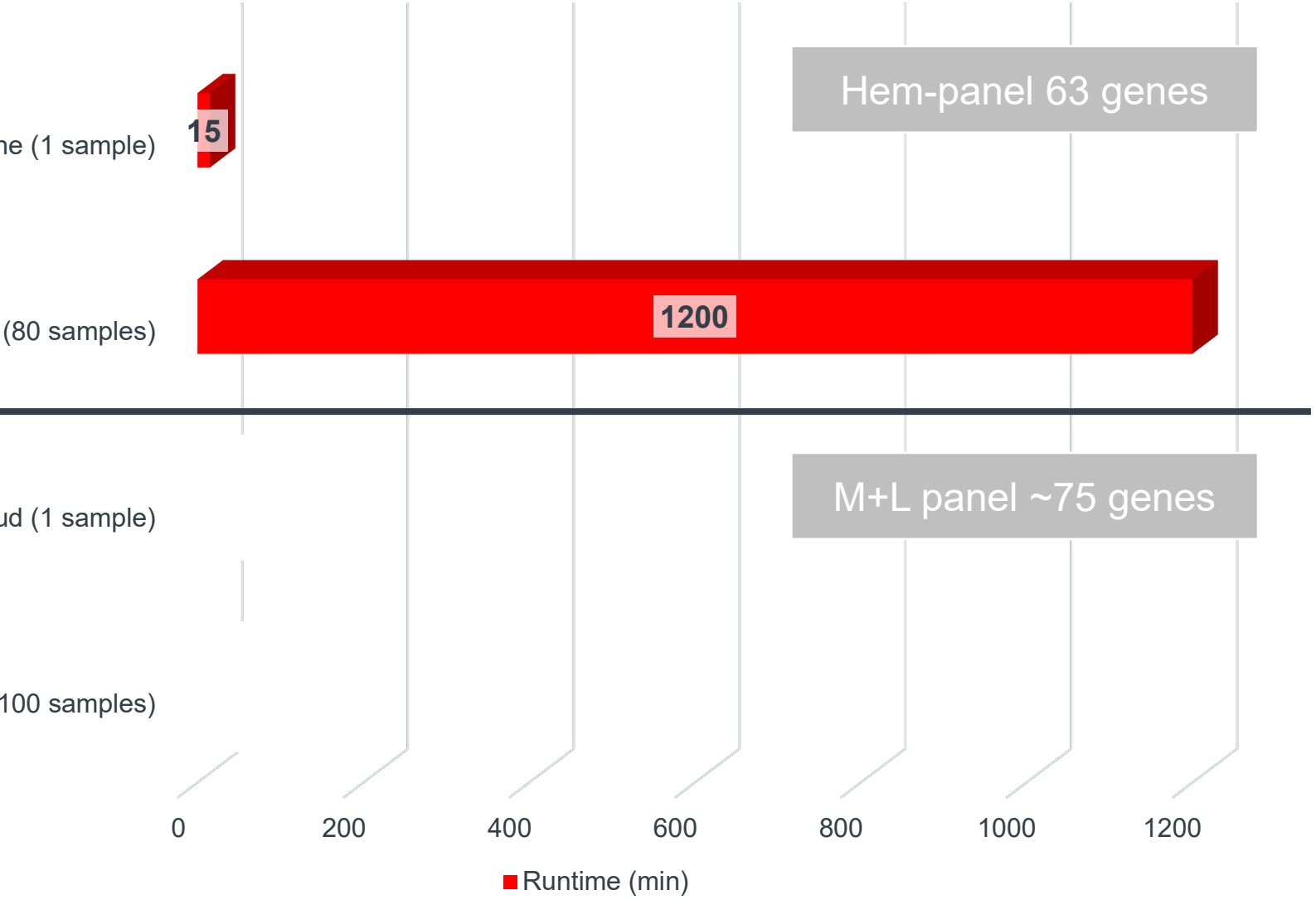
Report-ready variants

Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; COSMIC, Catalogue of Somatic Mutations in Cancer; DB, database; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; MLL, Munich Leukemia Laboratory; NGS, next-generation sequencing; SNOMED CT, Systematized Nomenclature of Medicine – Clinical Terms; SNP, single nucleotide polymorphism.

Scaling by cloud computing

Slide content provided courtesy of Munich Leukemia Laboratory.

Scaling by cloud computing



Slide content provided courtesy of Munich Leukemia Laboratory.

Scaling by cloud computing

Slide content provided courtesy of Munich Leukemia Laboratory.

Scaling by cloud computing

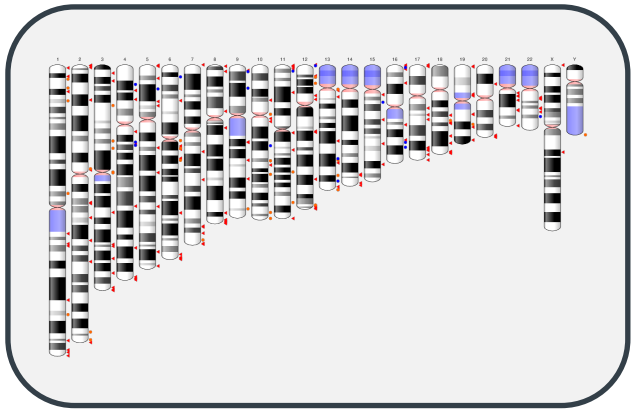
Slide content provided courtesy of Munich Leukemia Laboratory.

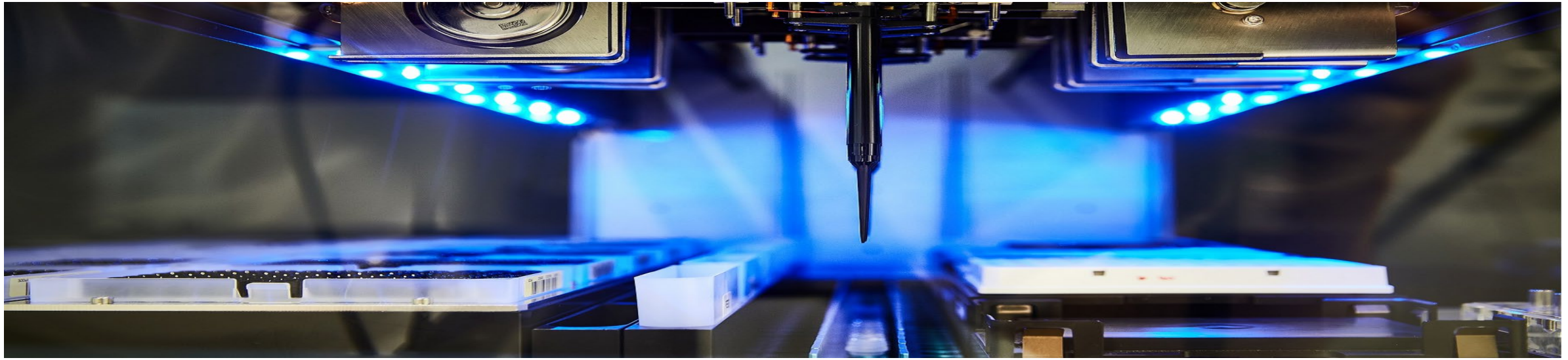
MLL 5k genomes project

PML-RARA
CEBPA
FLT3
ASXL1
TP53
NPM1

From: panels

To: genomes



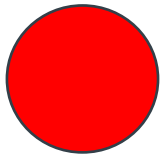


Slide content provided courtesy of Munich Leukemia Laboratory.

Next-generation sequencing

Targeted sequencing

- Gene panels or individual genes
- Up to a few 100 kb region



Whole-exome sequencing

- Coding regions
- ~60 Mb region

Slide content provided courtesy of Munich Leukemia Laboratory.

Workflow in 2024

WTS
(1.5 d)

WGS
(~6 hr)

WGS (~48 hr)
100× coverage
2×151 cycles

WTS (~24 hr)
50 mio reads
2×101 cycles

Library preparation

Sequencing

Data analysis

Turnaround time
5–7 days

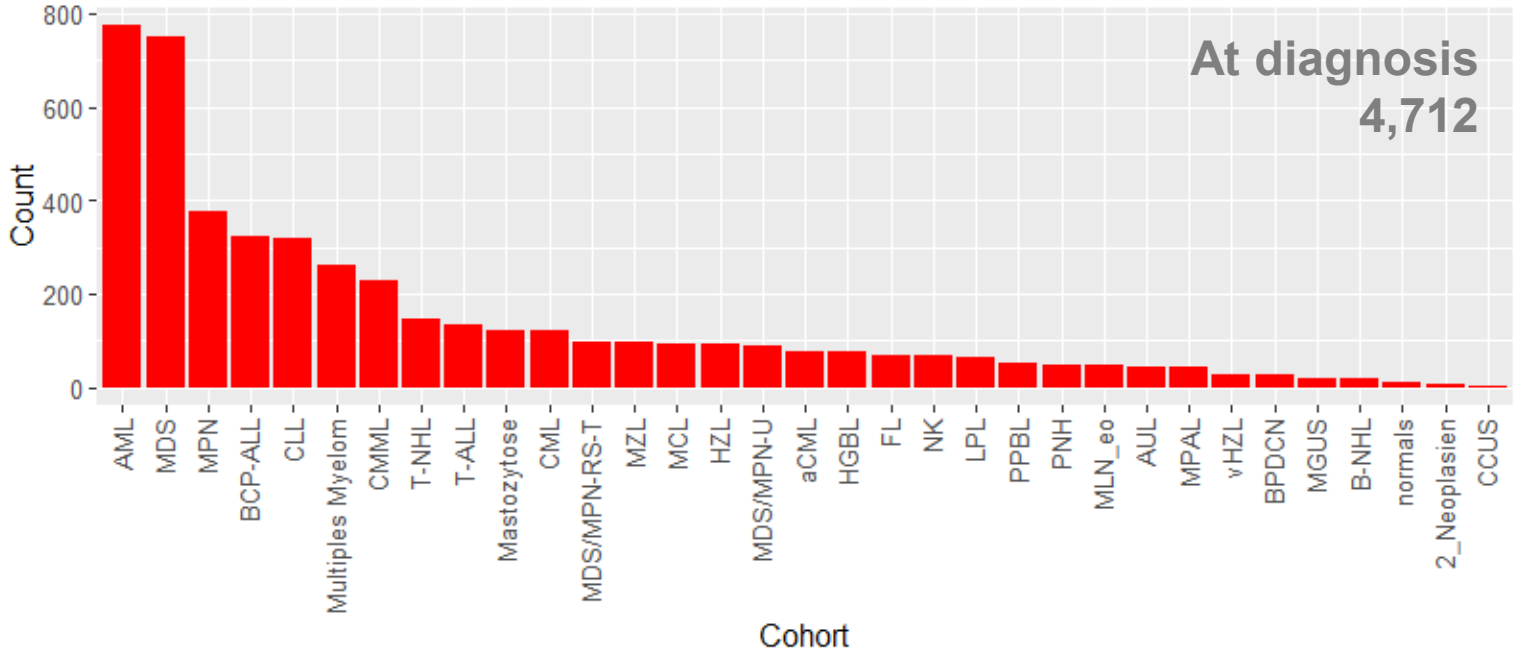
Processing steps
- Fragmentation
- End repair
- Adapter ligation
- Amplification (RNA)

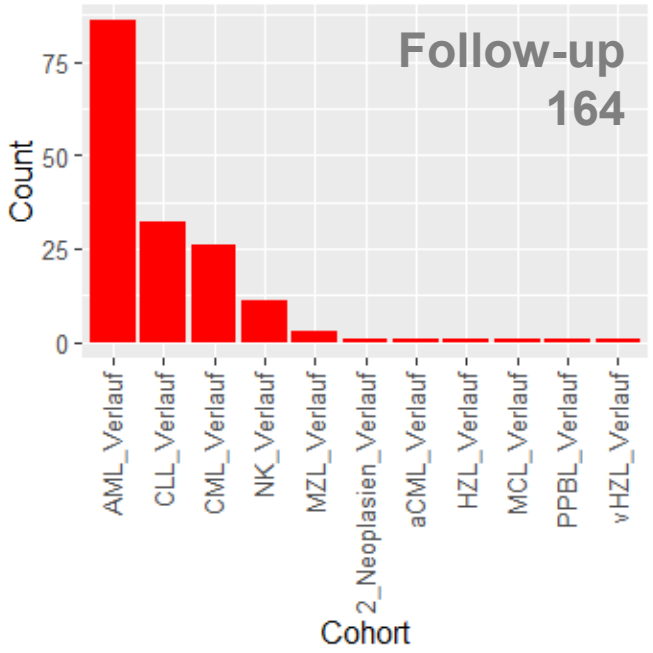
Data preprocessing (~4 hr)
- FASTQ generation
- Alignment
- Variant calling (SV, SNV)

Data analysis
- Variant interpretation
- Gene expression
- CNV analysis
- SV analysis

Slide content provided courtesy of Munich Leukemia Laboratory.
CNV, copy number variation; SNV, single nucleotide variant; SV, structural variant; WGS, whole-genome sequencing; WTS, whole-transcriptome sequencing.

The MLL5K project – and beyond





MLL5K WTS

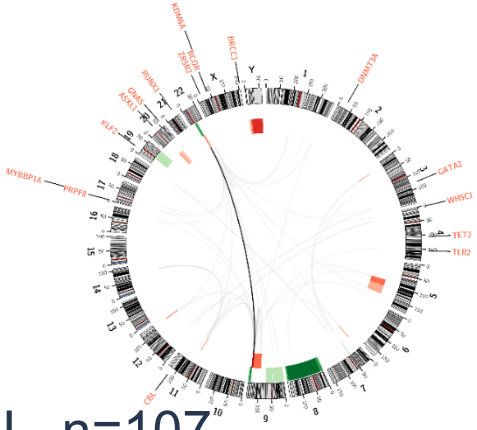
- 4,772 matched transcriptomes
- Number of reads: ~68 mio
- Mapped reads: 92%

As of 14.01.2025

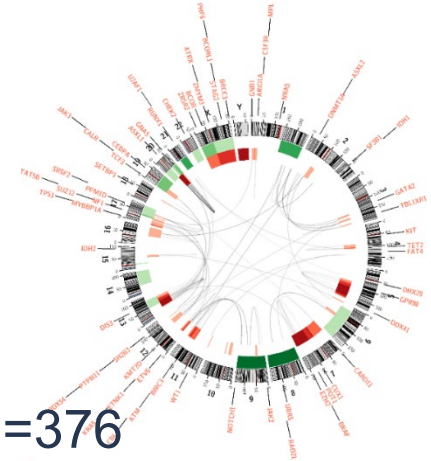
- **WGS: 6,742 cases**
- **WTS: 7,801 cases**

Slide content provided courtesy of Munich Leukemia Laboratory.
Abbreviated terms are defined in slide notes.

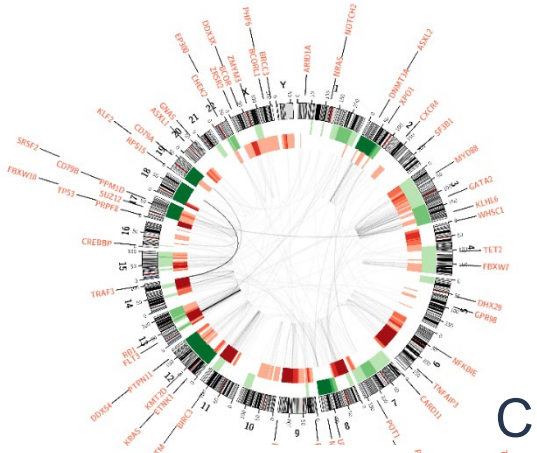
Genomic profiles in 5k cohort



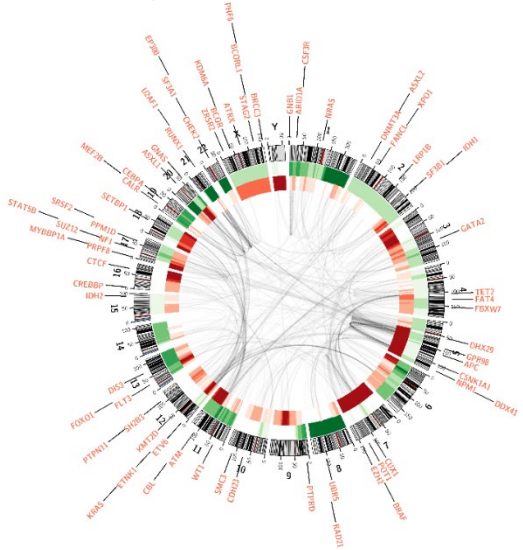
CML, n=107



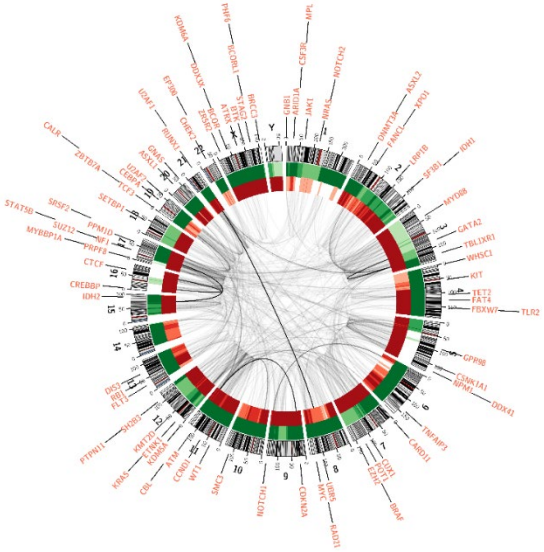
MPN, n=376



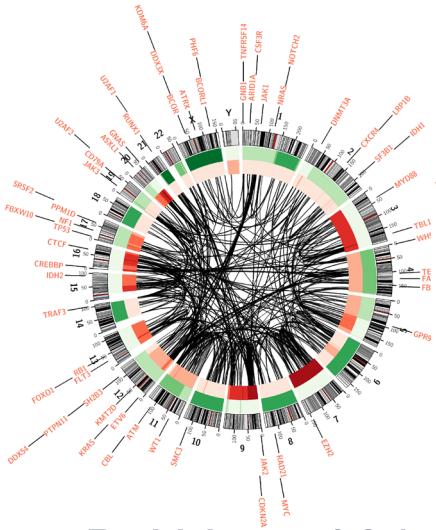
CLL, n=317



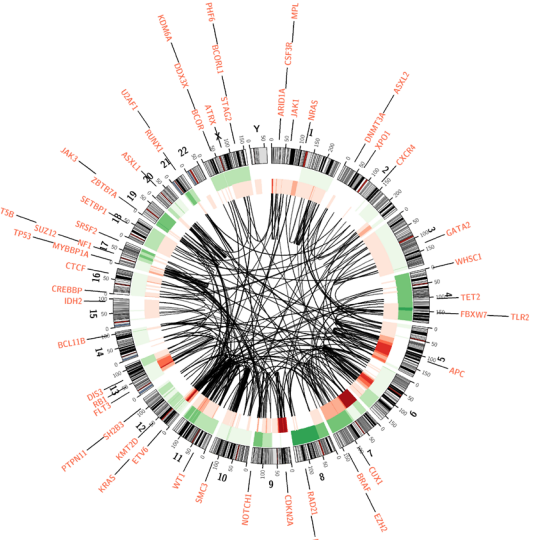
MDS, n=783



AML, n=614



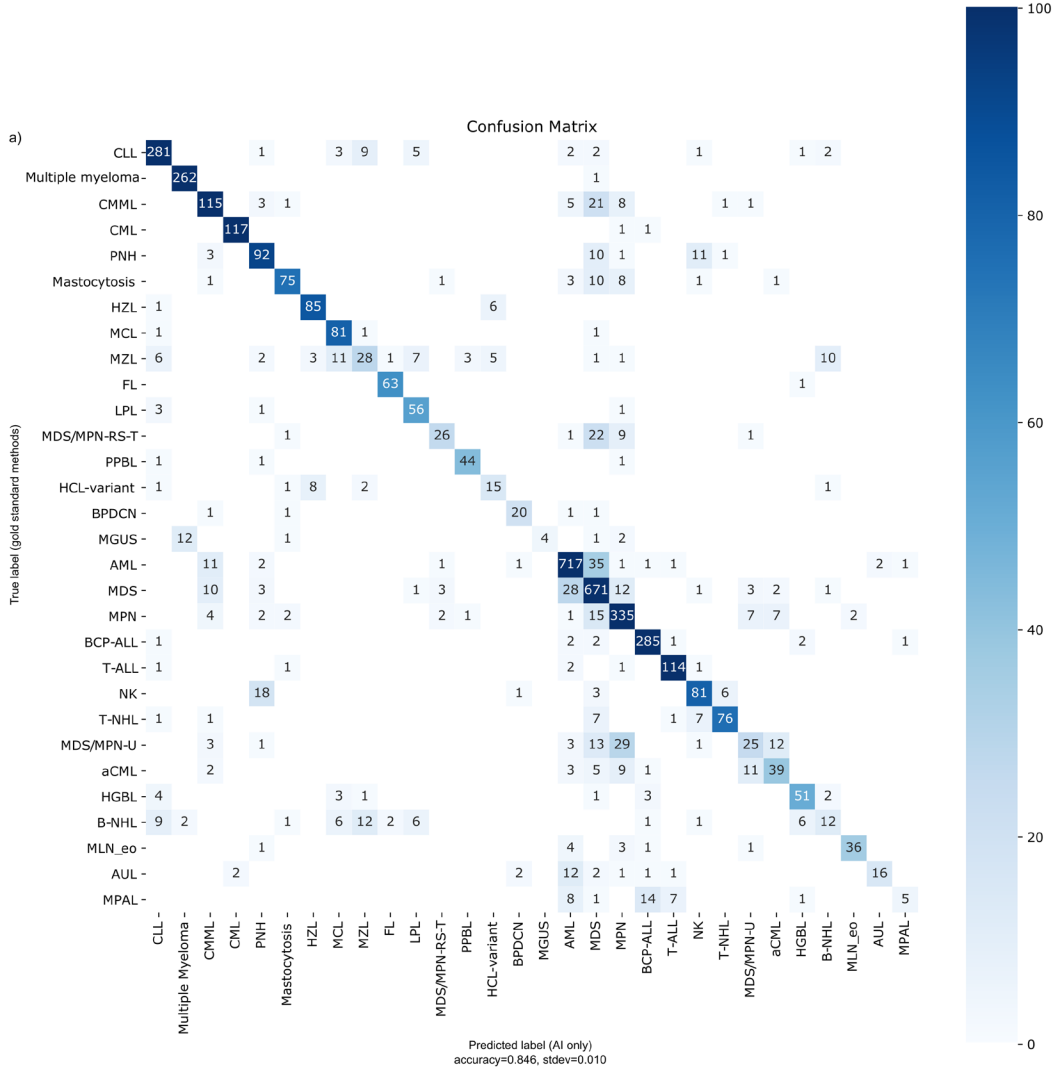
B-ALL, n=324



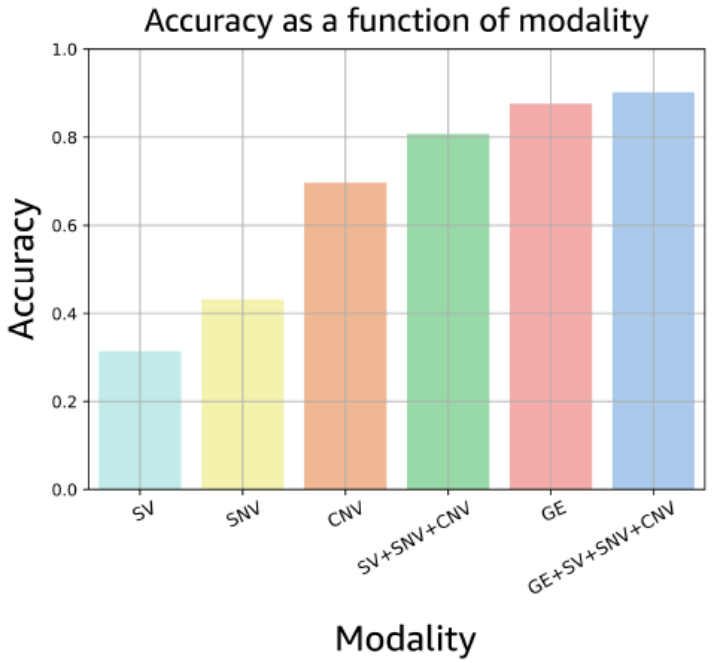
T-ALL, n=133

Slide content provided courtesy of Munich Leukemia Laboratory.
(B-/T-)ALL, (B-cell precursor / T-cell) acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

Confusion matrix of model performance

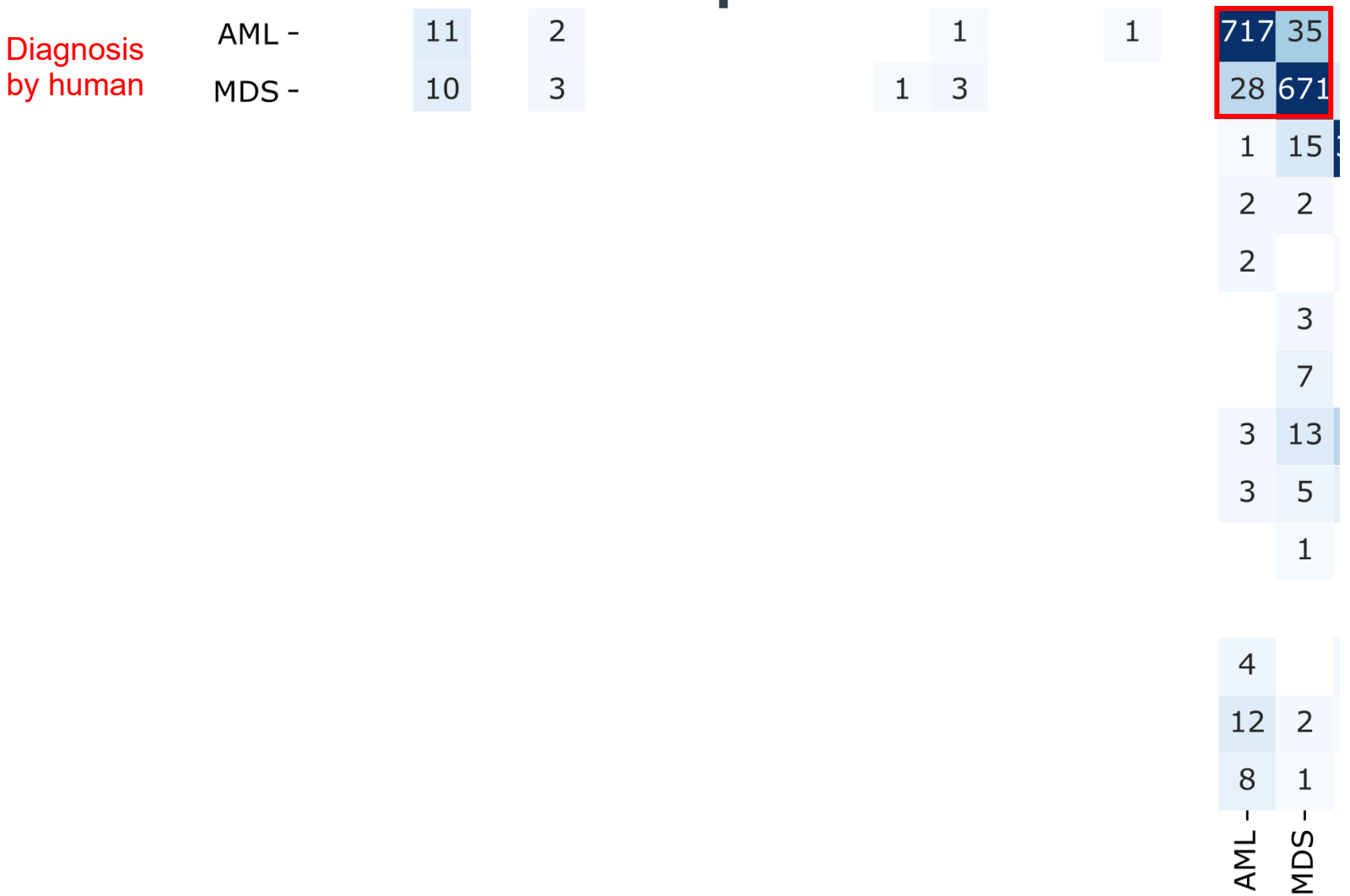


- Multi-mode classifier trained on 4,689 cases with 32 different hematologic neoplasms and normal category
- Dataset was unbalanced (20–773 cases)



Images provided courtesy of Munich Leukemia Laboratory.
Abbreviated terms are defined in slide notes.
Nadarajah N *et al*. Abstract #790 from ASH 2022; New Orleans, LA, USA, December 10–13, 2022.

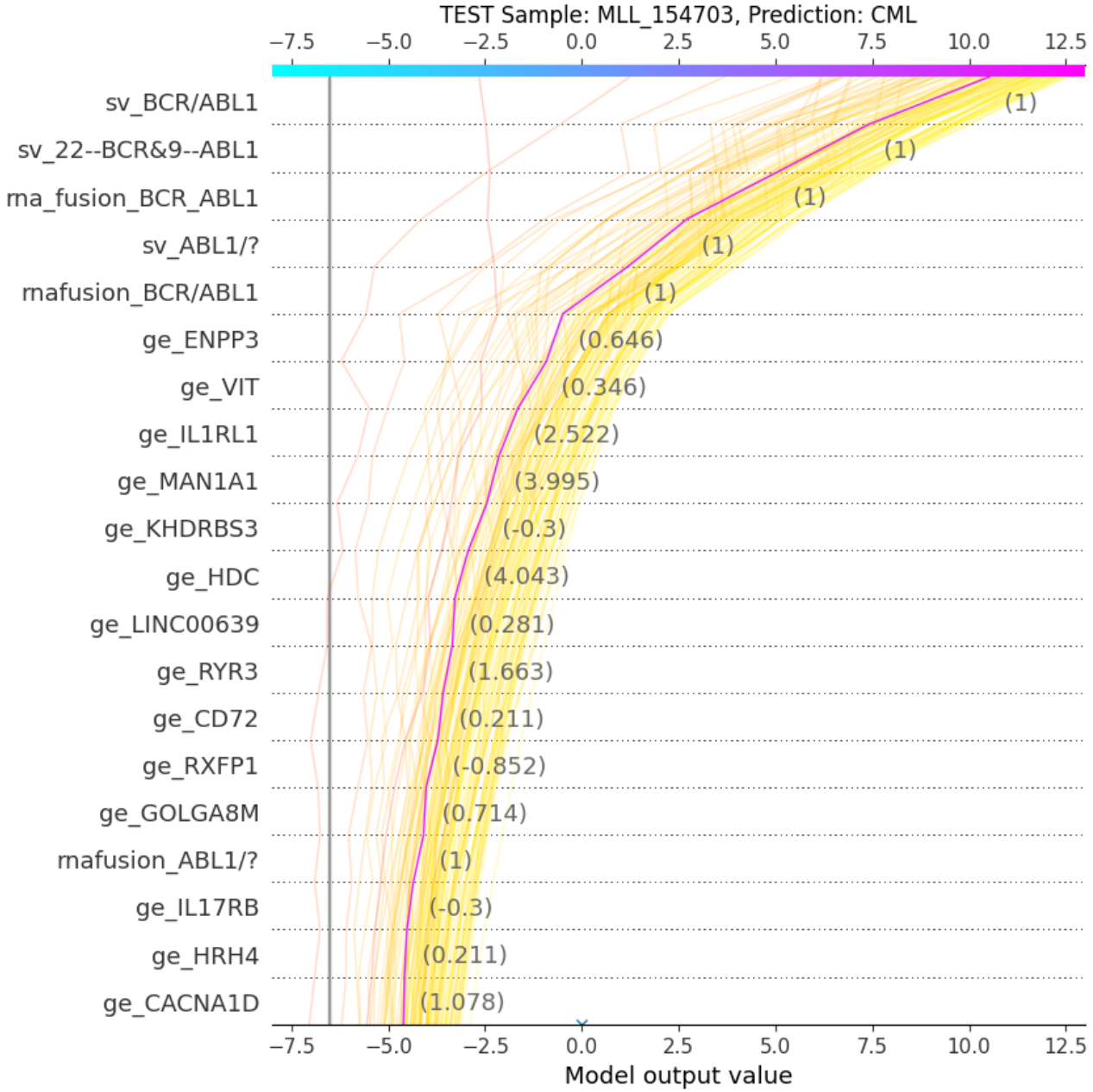
Confusion matrix of model performance



1,451 cases
1,388 concordant
63 non-concordant = 4.3%

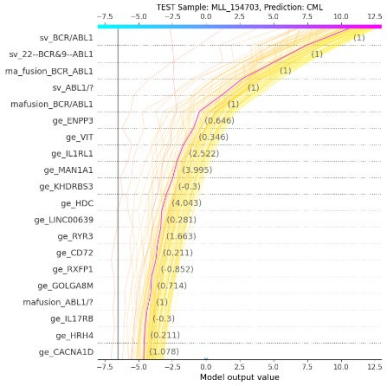
Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome.

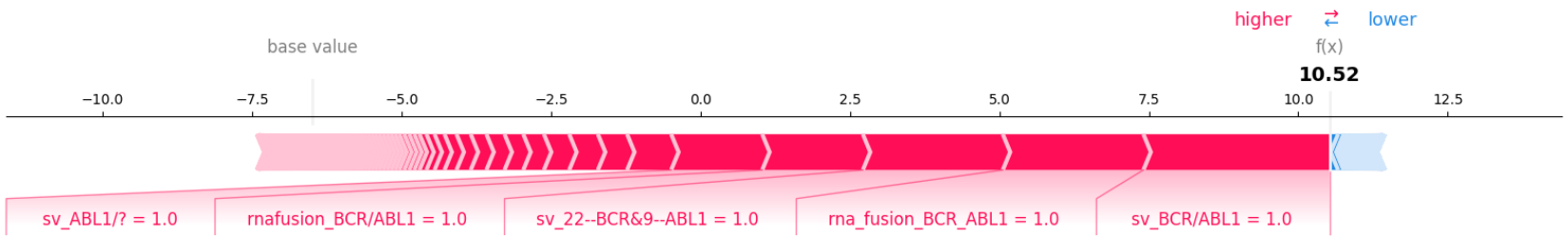
Explainable AI



Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; CML, chronic myeloid leukemia.

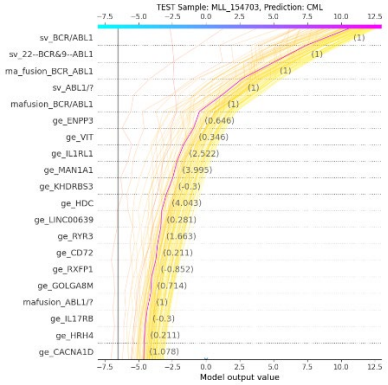
Explainable AI

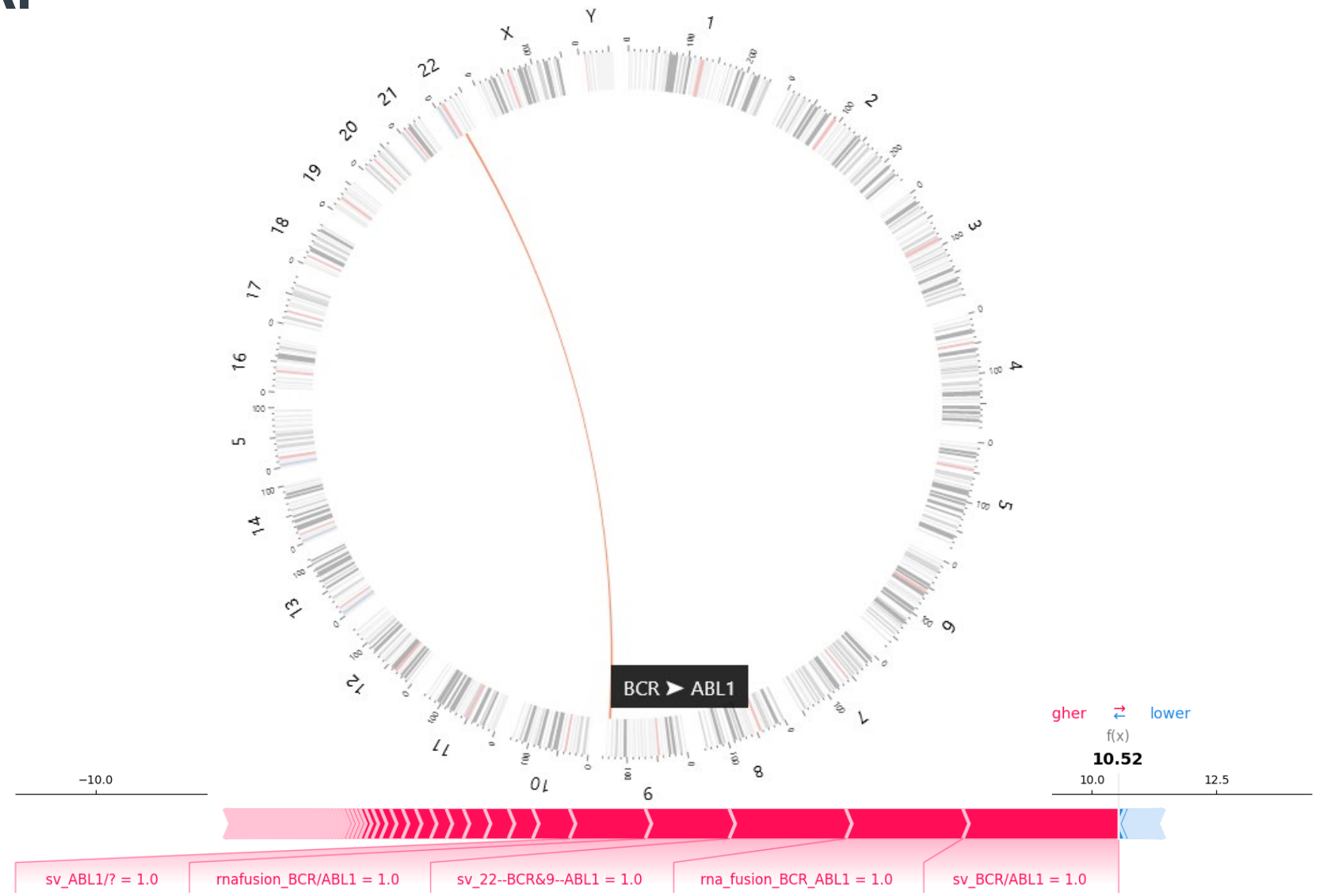




Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.

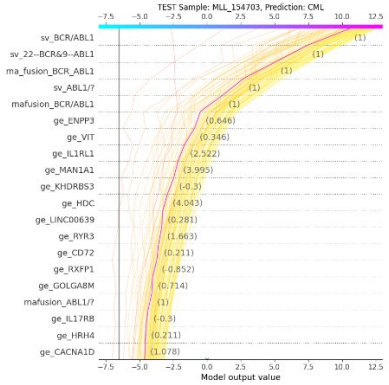
Explainable AI

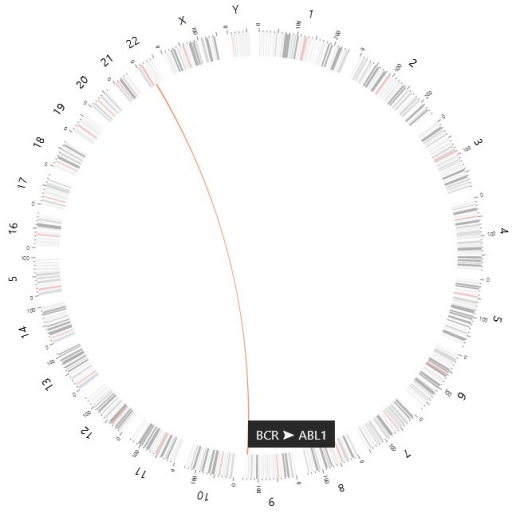


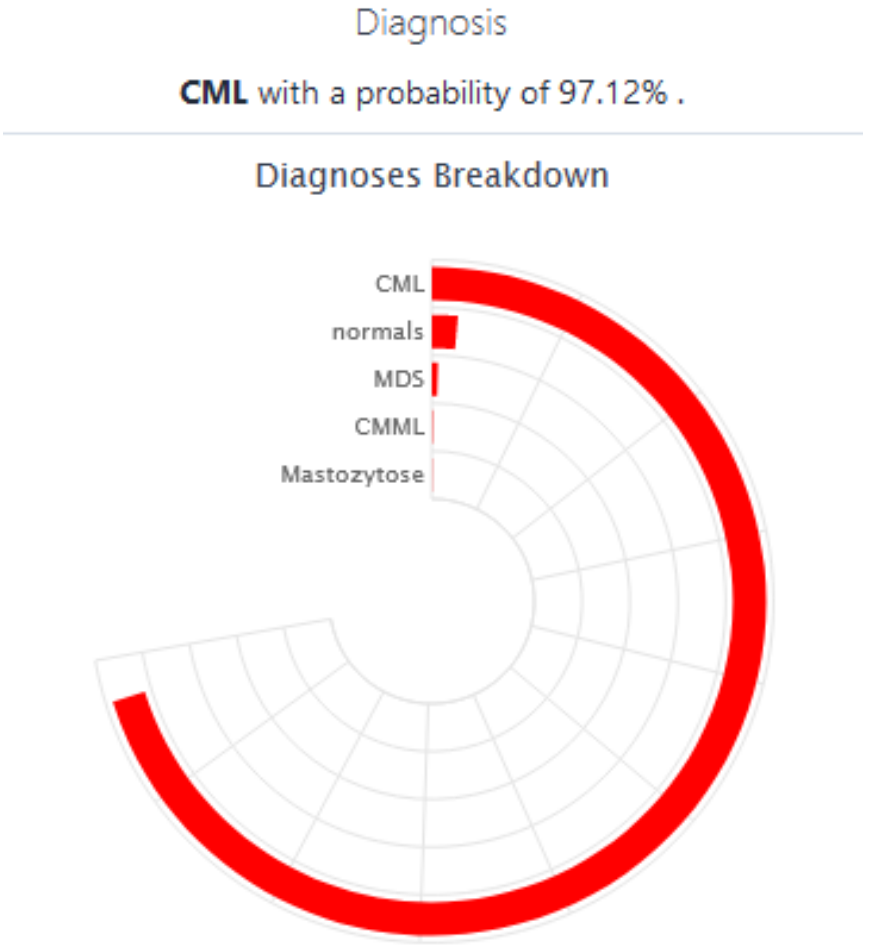


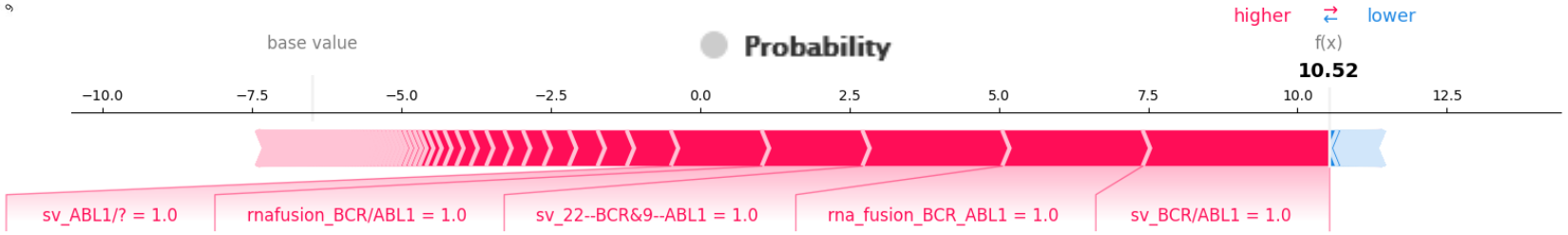
Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.

Explainable AI









Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome.

Explainable AI (XAI)

Data visualization

Diagnosis breakdown

AML with a probability of 96.6%

PacMAP projection of data from 32 leukemia subtypes

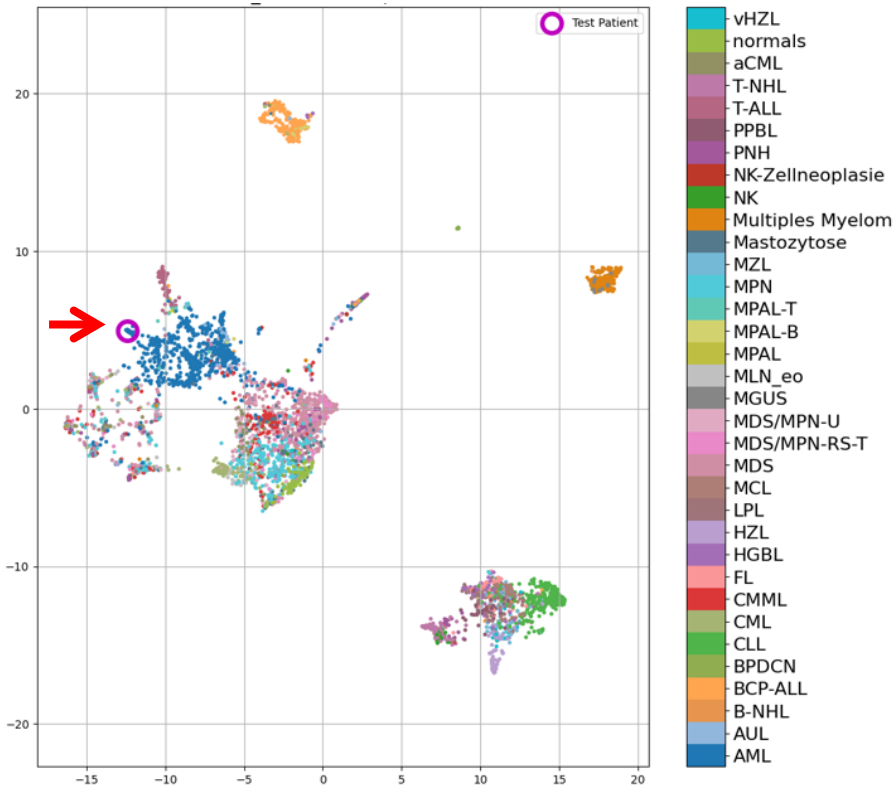
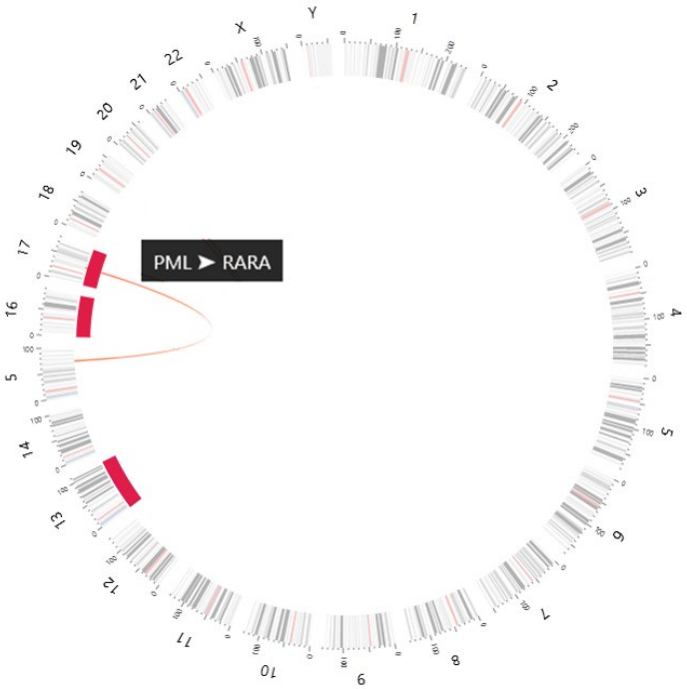
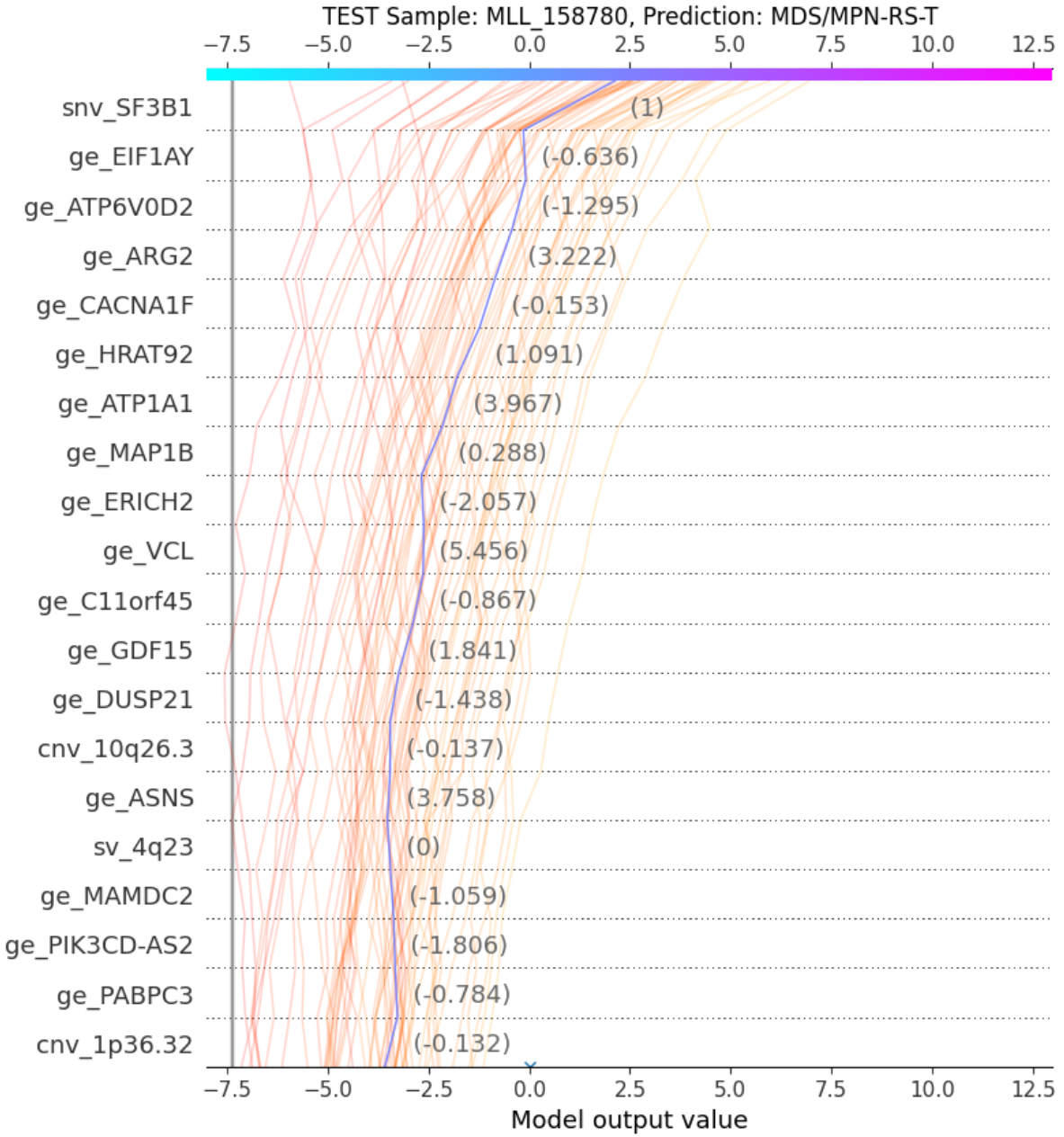


Illustration of genetic findings



Slide content provided courtesy of Munich Leukemia Laboratory.
Abbreviated terms are defined in slide notes.

Explainable AI

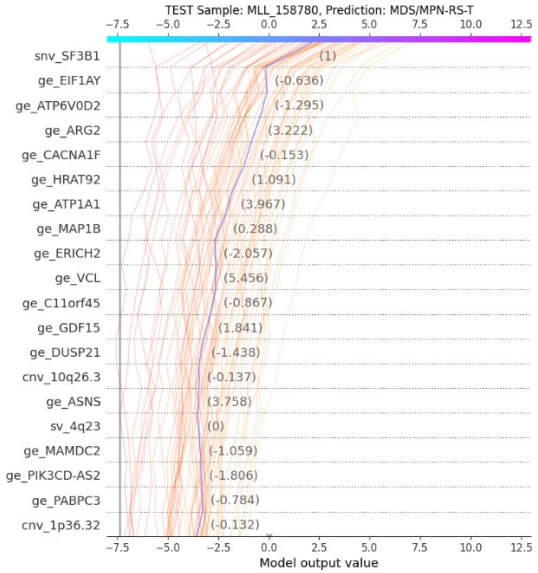


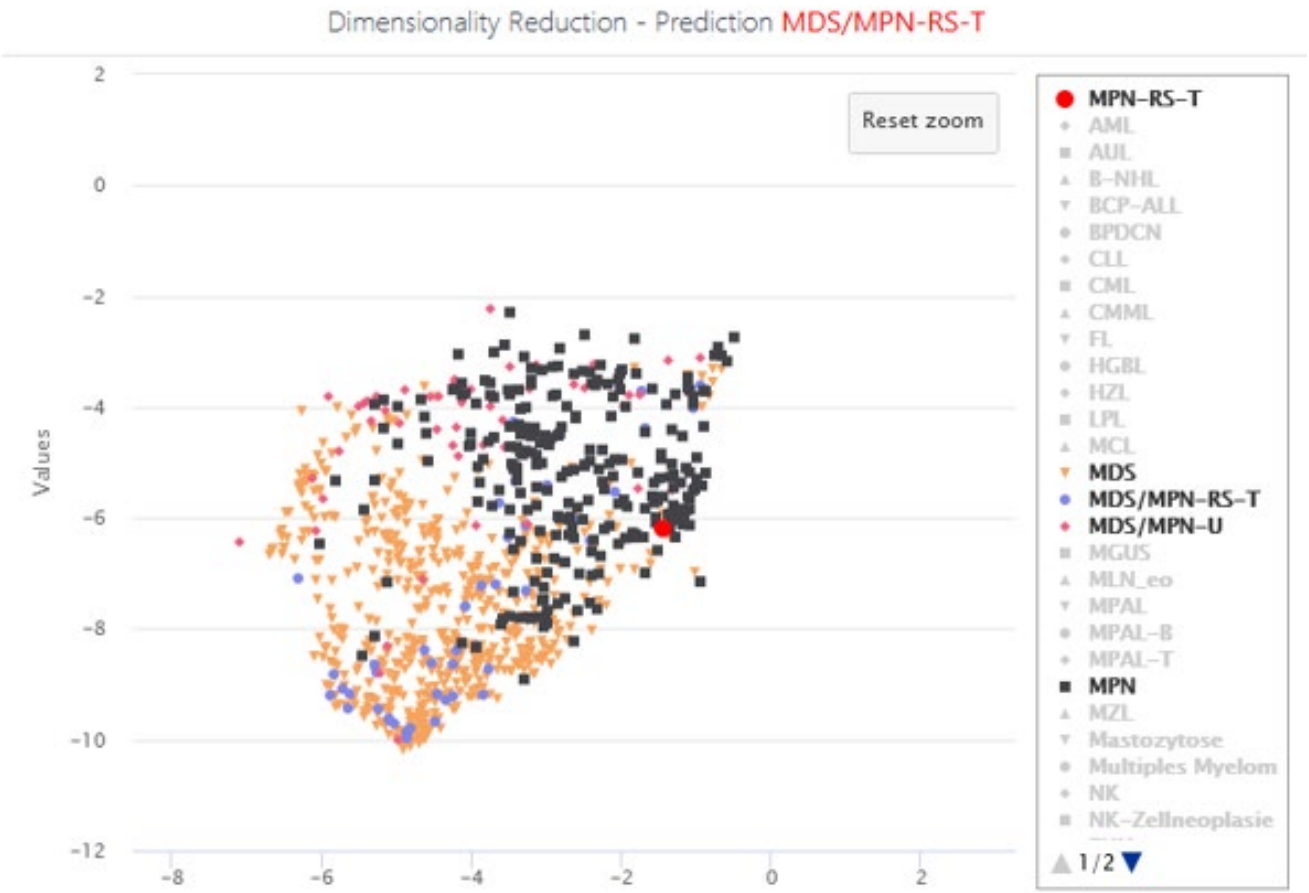
Current sample

MDS/MPN-*SF3B1*-T samples in training set (n=109)

Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm.

Explainable AI





Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; MDS, myelodysplastic syndrome; MDS/MPN-RS-T, myelodysplastic syndrome / myeloproliferative neoplasm with ring sideroblasts and thrombocytosis; MDS/MPN-U, myelodysplastic syndrome / myeloproliferative neoplasm, unclassifiable; MPN, myeloproliferative neoplasm.

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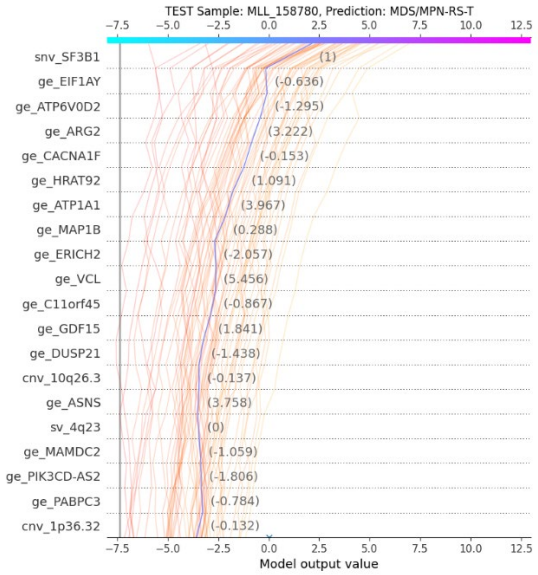

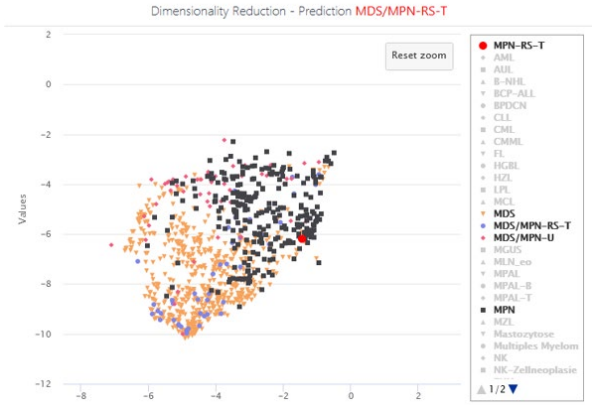

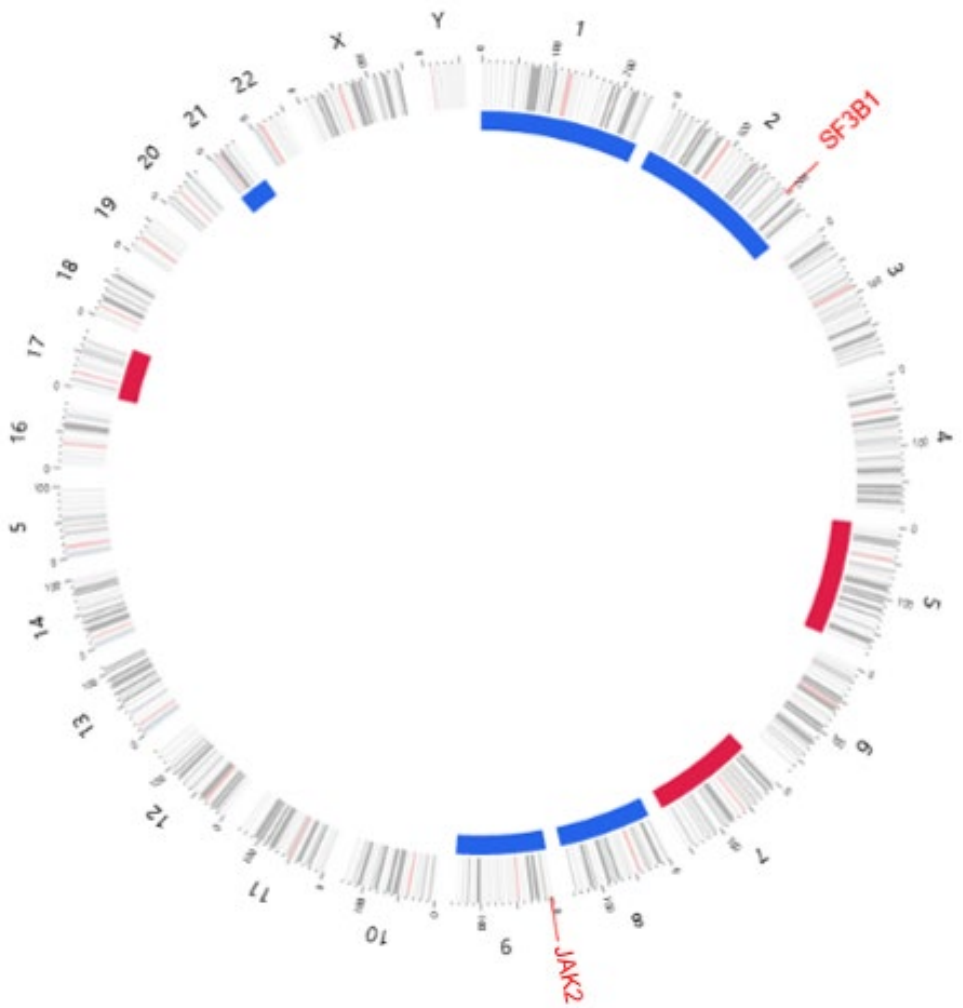

Slide content provided courtesy of Munich Leukemia Laboratory.
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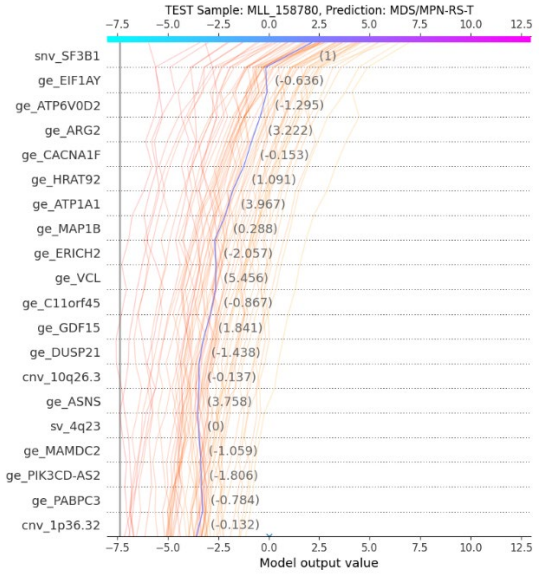
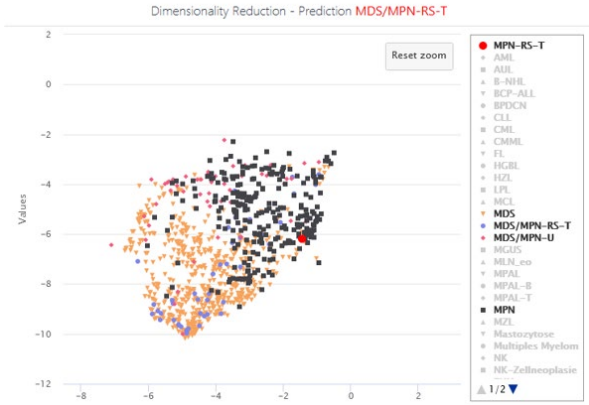
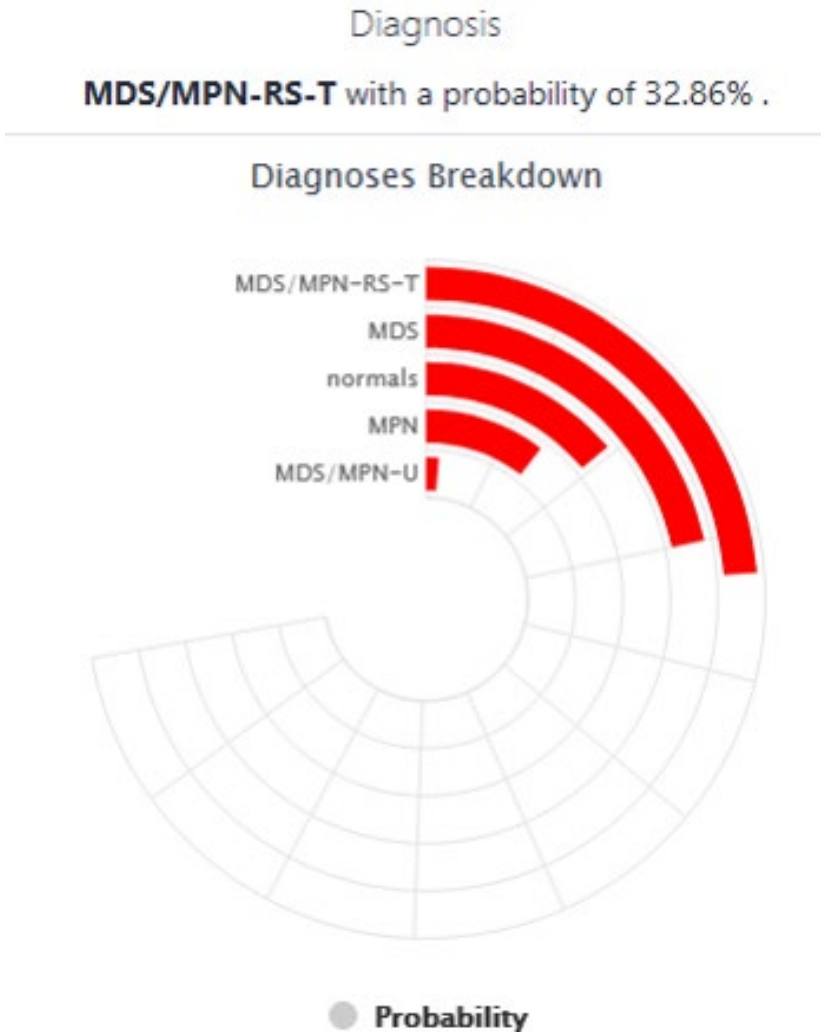
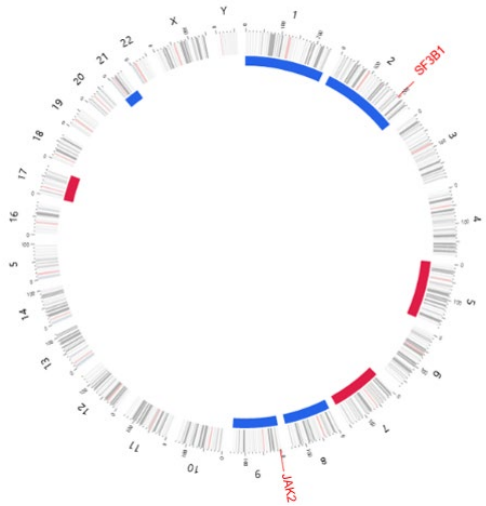
Explainable AI – MDS/MPN-*SF3B1*-T









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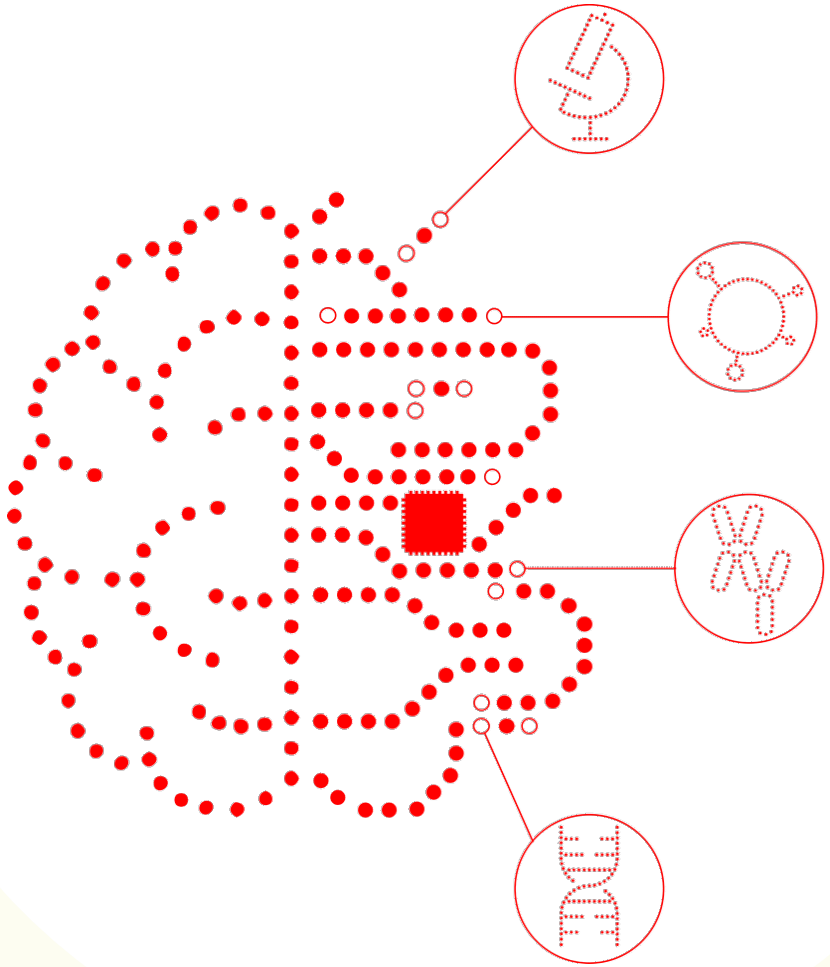
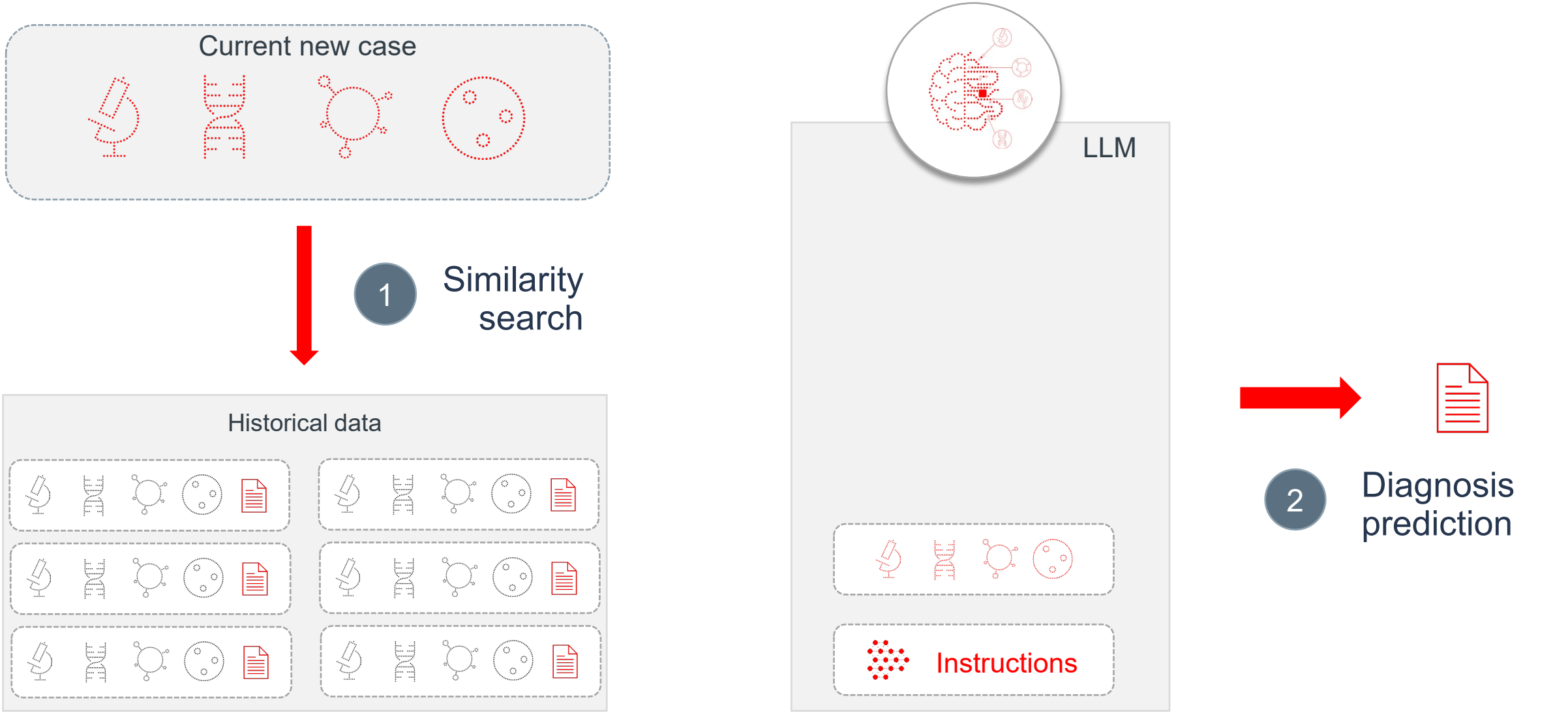


Large language models

AI offers tremendous utility for quickly summarizing large volumes of information

AI, artificial intelligence.

Automated diagnosis with LLMs



Slide content provided courtesy of Munich Leukemia Laboratory.
LLM, large language model.

LLM as a judge for LLM-created reports – before human review

Generated by AI

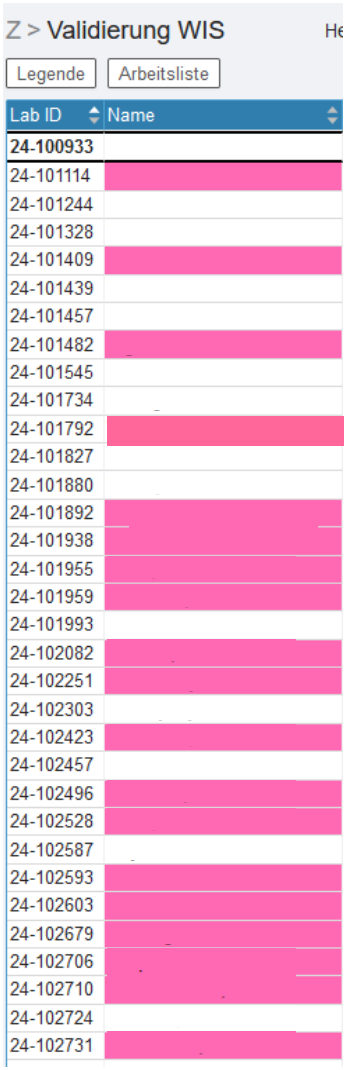
Generated by human (historical data)

1. Is the AI output coherent and grammatically correct?
2. Does the AI output mention all diagnostic criteria which are present in the human response?
3. Does the AI output mention any diagnostic criteria which are not present in the human response? (hallucinations)
4. Does the AI output mention any irrelevant information?

Returns a score from 1–10 and a short reasoning in bullet points

Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence; LLM, large language model.

With or without LLMs, this is the question



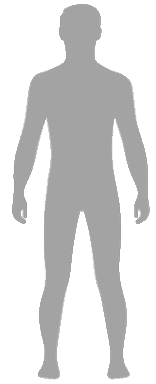
Report text created from adapted text modules

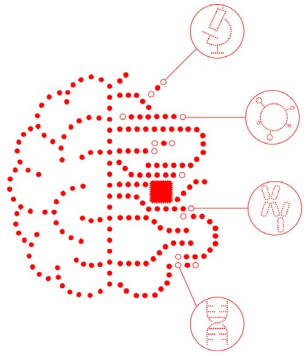
Report text initially created by LLM and then ‘corrected’ by a human

Report possible as created by LLM without changes in

75.5%

Modell: MLL internes Modell
(adaptiert von Mistral-7B-v0.1)





Slide content provided courtesy of Munich Leukemia Laboratory.
LLM, large language model.

Comprehensive information processing

ICC

PubMed

NCCN

WHO

Clinicaltrials.gov

Up-to-date

Reimbursement

Side effects

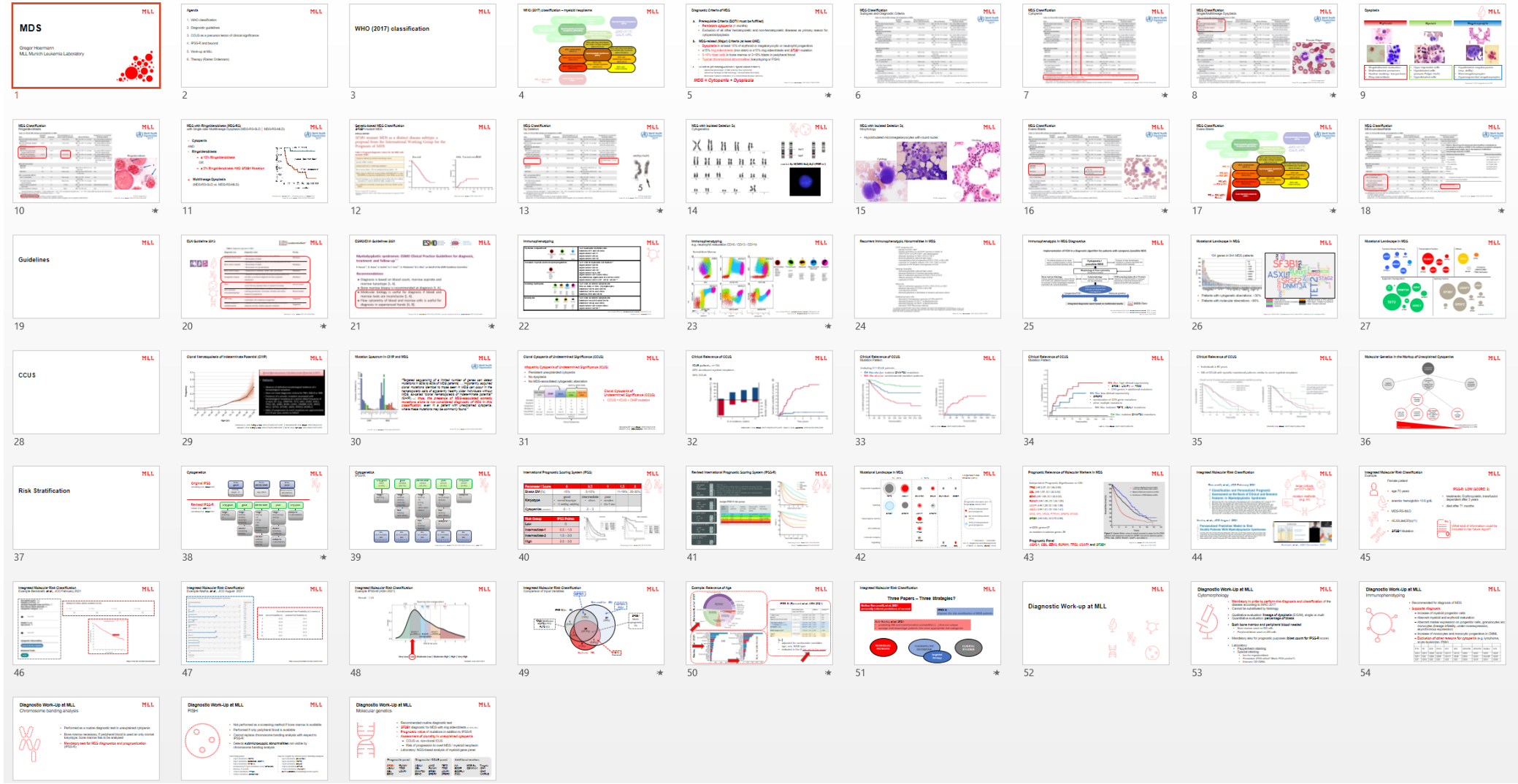
FDA approval

AI as an Agent

Slide content provided courtesy of Munich Leukemia Laboratory. Graphic generated with Dall-E.

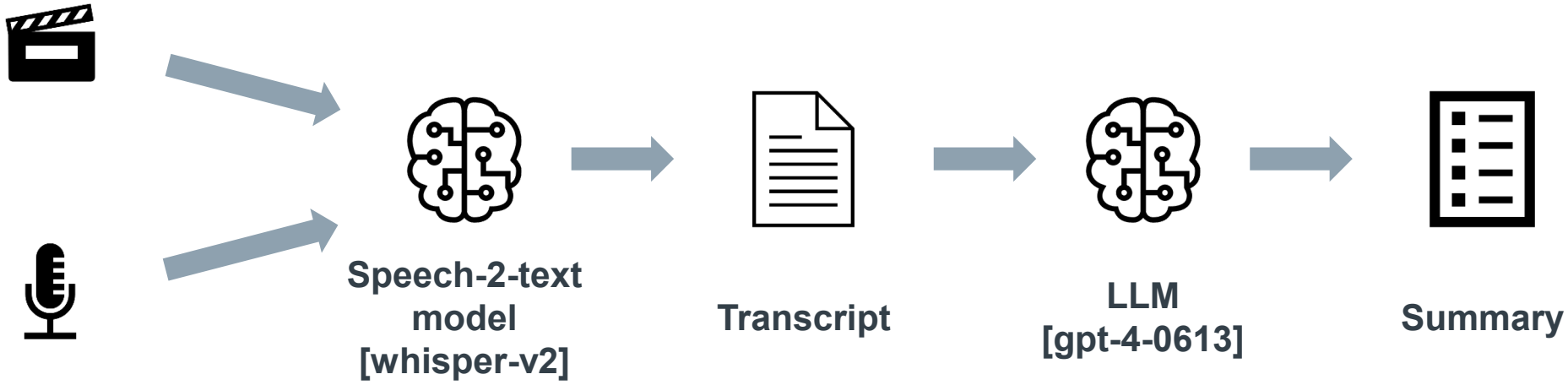
AI, artificial intelligence; FDA, US Food and Drug Administration; ICC, International Consensus Classification; NCCN, US National Comprehensive Cancer Network; WHO, World Health Organization.

Knowledge summarization



Slide content provided courtesy of Munich Leukemia Laboratory.

Knowledge summarization



Slide content provided courtesy of Munich Leukemia Laboratory.
LLM, large language model.

Standardising acute myeloid leukaemia classification systems: a perspective from a panel of international experts (Shallis RM *et al. Lancet Haematol* 2023; 10 (9): E767–E776)

Standardising acute myeloid leukaemia classification systems: a perspective from a panel of international experts

Rory M Shallis, Naval Daver, Jessica K Altman, Rami S Komrokji, Daniel A Pollyea, Talha Badar, Jan P Bewersdorf, Vijaya R Bhatt, Stéphane de Botton, Adolfo de la Fuente Burguera, Hetty E Carraway, Pinkal Desai, Richard Dillon, Nicolas Duployez, Firas El Chaer, Amir T Fathi, Sylvie D Freeman, Ivana Gojo, Michael R Grunwald, Brian A Jonas, Marina Konopleva, Tara L Lin, Gabriel N Mannis, John Mascarenhas, Laura C Michaelis, Alice S Mims, Pau Montesinos, Olga Pozdnyakova, Keith W Pratz, Andre C Schuh, Mikkael A Sekeres, Catherine C Smith, Maximilian Stahl, Marion Subklewe, Geoffrey L Uy, Maria Teresa Voso, Roland B Walter, Eunice S Wang, Joshua F Zeidner, Andrius Žučenka, Amer M Zeidan

The existence of two acute myeloid leukaemia classification systems—one put forth by WHO and one by the International Consensus Classification in 2022—is concerning. Although both systems appropriately move towards genomic disease definitions and reduced emphasis on blast enumeration, there are consequential disagreements between the two systems on what constitutes a diagnosis of acute myeloid leukaemia. This fundamental problem threatens the ability of heath-care providers to diagnose acute myeloid leukaemia, communicate with patients and other health-care providers, and deliver appropriate and consistent management strategies for patients with the condition. Clinical trial eligibility, standardised response assessments, and eventual drug development and regulatory pathways might also be negatively affected by the discrepancies. In this Viewpoint, we review the merits and limitations of both classification systems and illustrate how the coexistence, as well as application of both systems is an undue challenge to patients, clinicians, hematopathologists, sponsors of research, and regulators. Lastly, we emphasise the urgency and propose a roadmap, by which the two divergent classification systems can be harmonised.

Introduction

Our understanding of the genetic landscape of acute myeloid leukaemia and how its underlying pathobiology links to clinical phenotype and patient outcomes has greatly improved over the last 20 years. Albeit slowly, therapeutic successes have followed with multiple new drugs approved since 2017. Concurrently, there has been an important and continued effort to integrate genetic data into day-to-day clinical decision making, to develop a personalised management approach for acute myeloid leukaemia treatment. However, the rapidly increasing quantity and complexity of genetic, pathological, and clinical variables to be integrated into optimal therapy and risk-based decision making is complicating an already multilayered and rapidly evolving management schema. A new challenge to the creation of such a data-driven consensus approach to personalised acute myeloid leukaemia treatment is the emerging disagreement among experts about what should constitute a diagnosis of the condition (ie, the absence of a shared consensus regarding the classification criteria for acute myeloid leukaemia). In 2022, WHO[1] and the International Consensus Classification (ICC)[2] offered distinct frameworks, through which myeloid neoplasms can be classified and approached diagnostically. Furthermore, the European LeukemiaNet (ELN),[3] which largely aligns with the ICC, has provided updated risk stratification and response criteria for acute myeloid leukaemia that might further influence clinical management and treatment decisions. However, the discordance between these well intended systems introduces great variability in diagnostic terminology, acute myeloid leukaemia management, patients' clinical trial eligibility, and clinical outcome assessments. Eventually, this issue might delay clinical drug development, lead to heterogeneity in populations enrolled onto clinical trials, and affect the regulatory pathway of emerging drugs. In this Viewpoint, we review the potential impetus for the development of the contemporary acute myeloid leukaemia classification systems, their inherent limitations (particularly as they relate to risk stratification for routine clinical practice and clinical drug development), and how divergent classification systems complicate diagnosis and management decisions, and confuse clinicians and patients. We offer an opinion on how to move forward in patient care and clinical research.

Regressing myeloblast thresholds

Classification systems for myeloid neoplasms have evolved to rationally incorporate genetics and biology. Under the previous, widely used French–American–British classification from 1976, patients with myelodysplastic syndromes and 20–29% blasts were included in a subcategory of myelodysplastic syndromes, known as refractory anaemia with excess blasts in transformation.[4] The subsequent recognition that patients with 20–29% blasts and those with at least 30% blasts had similar clinical outcomes prompted WHO in 2001, to eliminate refractory anaemia with excess blasts in transformation as a myelodysplastic syndromes category, and to reduce the arbitrary acute myeloid leukaemia-defining marrow or peripheral blood blast threshold to at least 20%. This change did not affect the core-binding factor (CBF) acute myeloid leukaemia and acute promyelocytic leukaemia, which continued to be defined based on the identification of an acute myeloid leukaemia-defining genetic abnormality, irrespective of the blast count.[5] The 20% marrow or blood blast threshold, at which morphologically defined acute myeloid leukaemia is diagnosed, has been retained in both the

Lancet Haematol 2023; 10: e767–76

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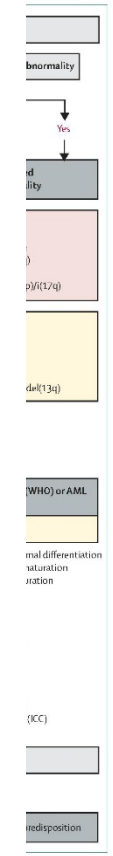

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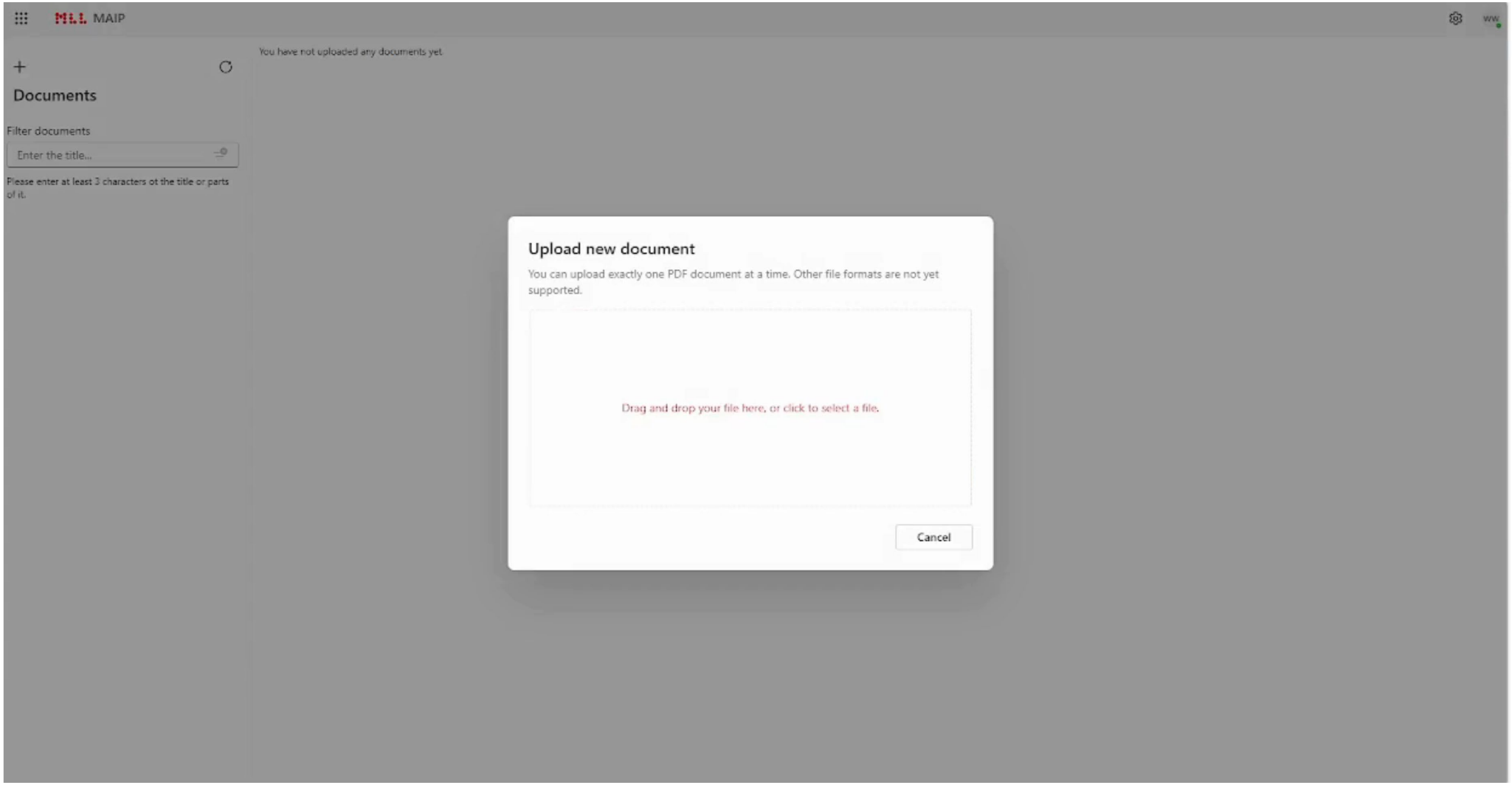
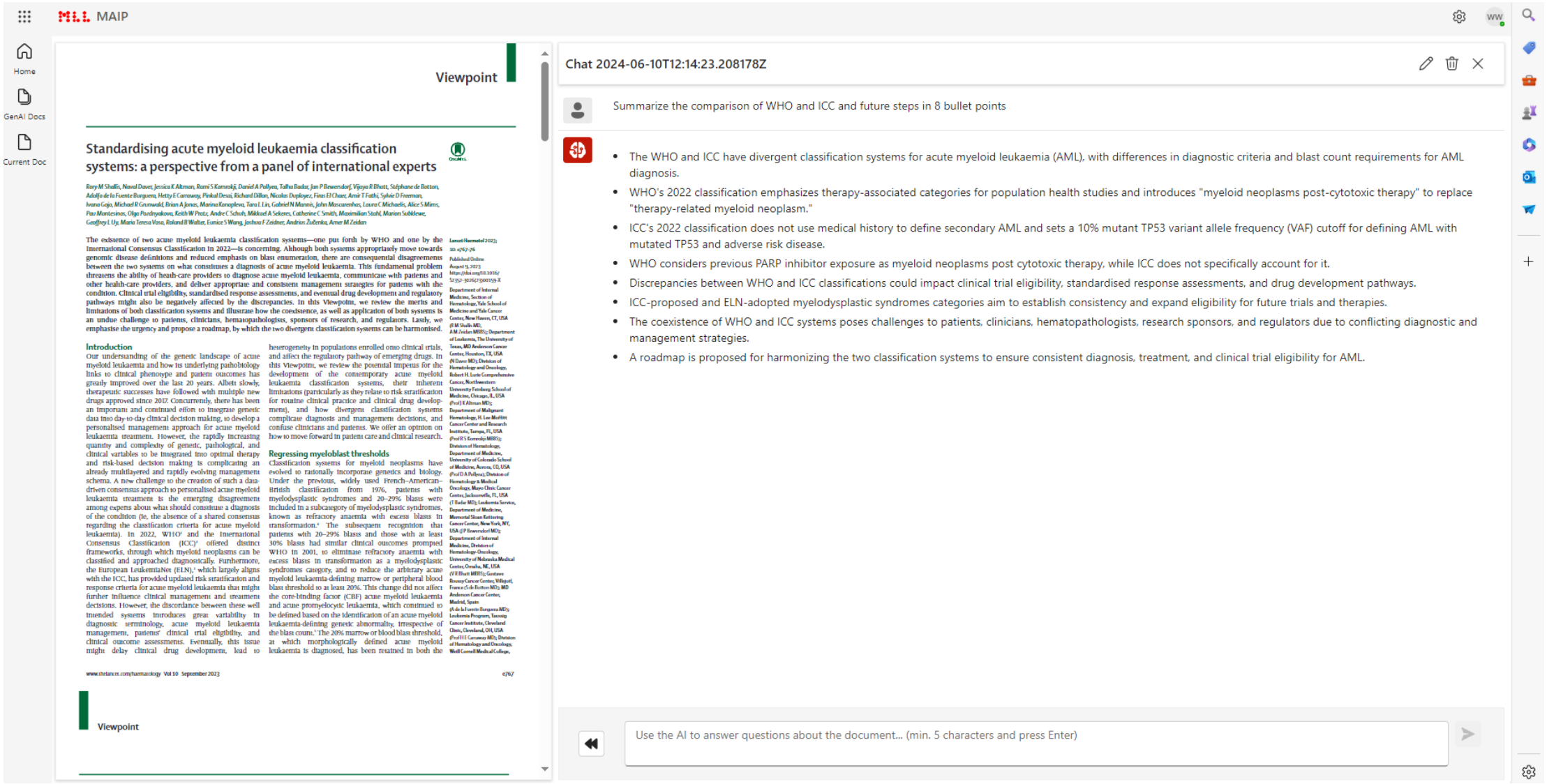
AI for literature research and extraction



Slide content provided courtesy of Munich Leukemia Laboratory.
AI, artificial intelligence.

AI for literature research



AI, artificial intelligence.

AI for literature research

Chat 2024-06-10T12:14:23.208178Z

Summarize the comparison of WHO and ICC and future steps in 8 bullet points

- The WHO and ICC have divergent classification systems for acute myeloid leukaemia (AML), with differences in diagnostic criteria and blast count requirements for AML diagnosis.
- WHO's 2022 classification emphasizes therapy-associated categories for population health studies and introduces "myeloid neoplasms post-cytotoxic therapy" to replace "therapy-related myeloid neoplasm."
- ICC's 2022 classification does not use medical history to define secondary AML and sets a 10% mutant TP53 variant allele frequency (VAF) cutoff for defining AML with mutated TP53 and adverse risk disease.
- WHO considers previous PARP inhibitor exposure as myeloid neoplasms post cytotoxic therapy, while ICC does not specifically account for it.
- Discrepancies between WHO and ICC classifications could impact clinical trial eligibility, standardised response assessments, and drug development pathways.
- ICC-proposed and ELN-adopted myelodysplastic syndromes categories aim to establish consistency and expand eligibility for future trials and therapies.
- The coexistence of WHO and ICC systems poses challenges to patients, clinicians, hematopathologists, research sponsors, and regulators due to conflicting diagnostic and management strategies.
- A roadmap is proposed for harmonizing the two classification systems to ensure consistent diagnosis, treatment, and clinical trial eligibility for AML.

AI, artificial intelligence; ELN, European LeukemiaNet; ICC, International Consensus Classification; WHO, World Health Organization.

A patient's medical history

AI can improve patient–physician conversations, and help personalize patient care

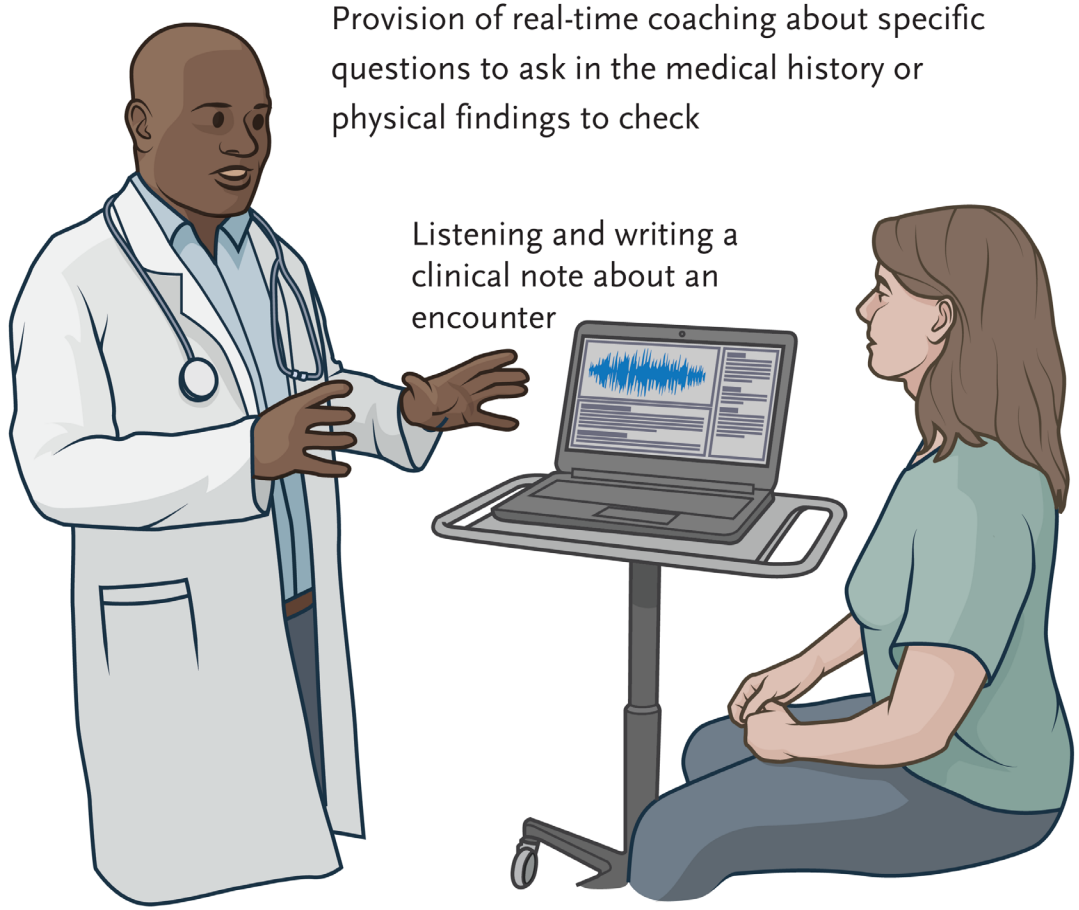
AI, artificial intelligence.

For better and more efficient conversations

B Future

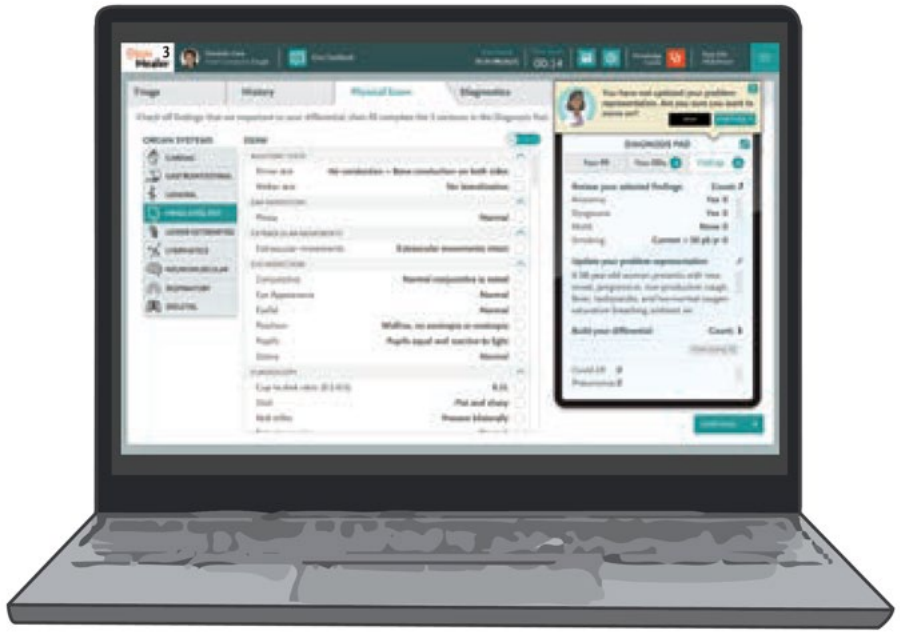
Provision of real-time coaching about specific questions to ask in the medical history or physical findings to check

Listening and writing a clinical note about an encounter



Serving as a teacher and an assessor in medical education

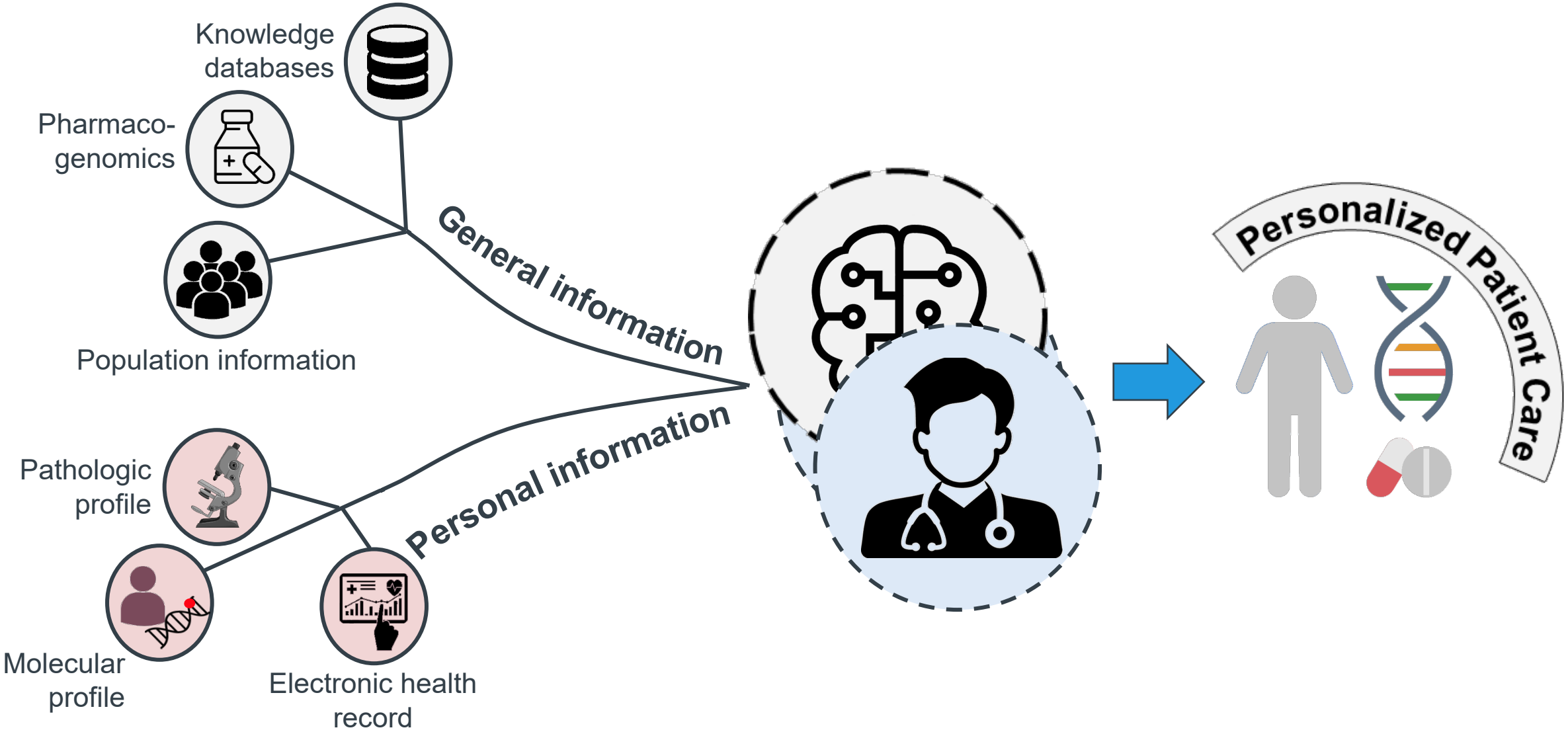
Creating realistic "flight simulators" for simple and complex patient encounters



Haug CJ and Drazen JM. *N Engl J Med* 2023; 388 (13): 1201–1208.

Personalize treatment plans

Comprehensive information processing



Slide content provided courtesy of Munich Leukemia Laboratory.

FDA-approved targeted drugs

Acalabrutinib Daratumumab Bortezomib Brentuximab vedotin Nilotinib Tretinoin Pirtobrutinib

Crizotinib Belinostat Bosutinib Eculizumab Carfilzomib Denileukin diftitox Bexarotene Ravulizumab

Olutasidenib Isatuximab Panobinostat Copanlisib Elotuzumab Ixazomib Gemtuzumab ozogamicin Duvelisib

Pacritinib Moxetumomab pasudotox Lenalidomide Dasatinib Obinutuzumab Glasdegib Venetoclax Tagraxofusp

Vorinostat Gilteritinib Ciltacabtagene autoleucel Enasidenib Ofatumumab Ruxolitinib Blinatumomab Zanubrutinib

Mosunetuzumab Inotuzumab ozogamicin Nivolumab Ibrutinib Rituximab Idelalisib Tafasitamab Avapritinib

Sorafenib Siltuximab Ivosidenib Imatinib Alemtuzumab Axicabtagene ciloleucel Polatuzumab vedotin

Brexucabtagene autoleucel Dabrafenib Ibritumomab tiuxetan Midostaurin Tisagenlecleucel Vemurafenib Mogamulizumab

Pembrolizumab Asciminib Tazemetostat Idecabtagene vicleucel Belantamab mafodotin Pomalidomide

Ponatinib Selinexor Lisocabtagene maraleucel Fedratinib Loncastuximab tesirine Romidepsin Pemigatinib

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Kinase inhibitor **Enzyme inhibitor** **Monoclonal antibody** **Histone deacetylase inhibitor**

Immunotoxin/-conjugate **Proteasome inhibitor** **Immunomodulatory** **Checkpoint inhibitor**

CAR-T cell **Retinoid** **Apoptosis inducer** **T-cell engager** **Radioimmunotherapy**

Slide content provided courtesy of Munich Leukemia Laboratory. CAR, chimeric antigen receptor; FDA, US Food and Drug Administration.

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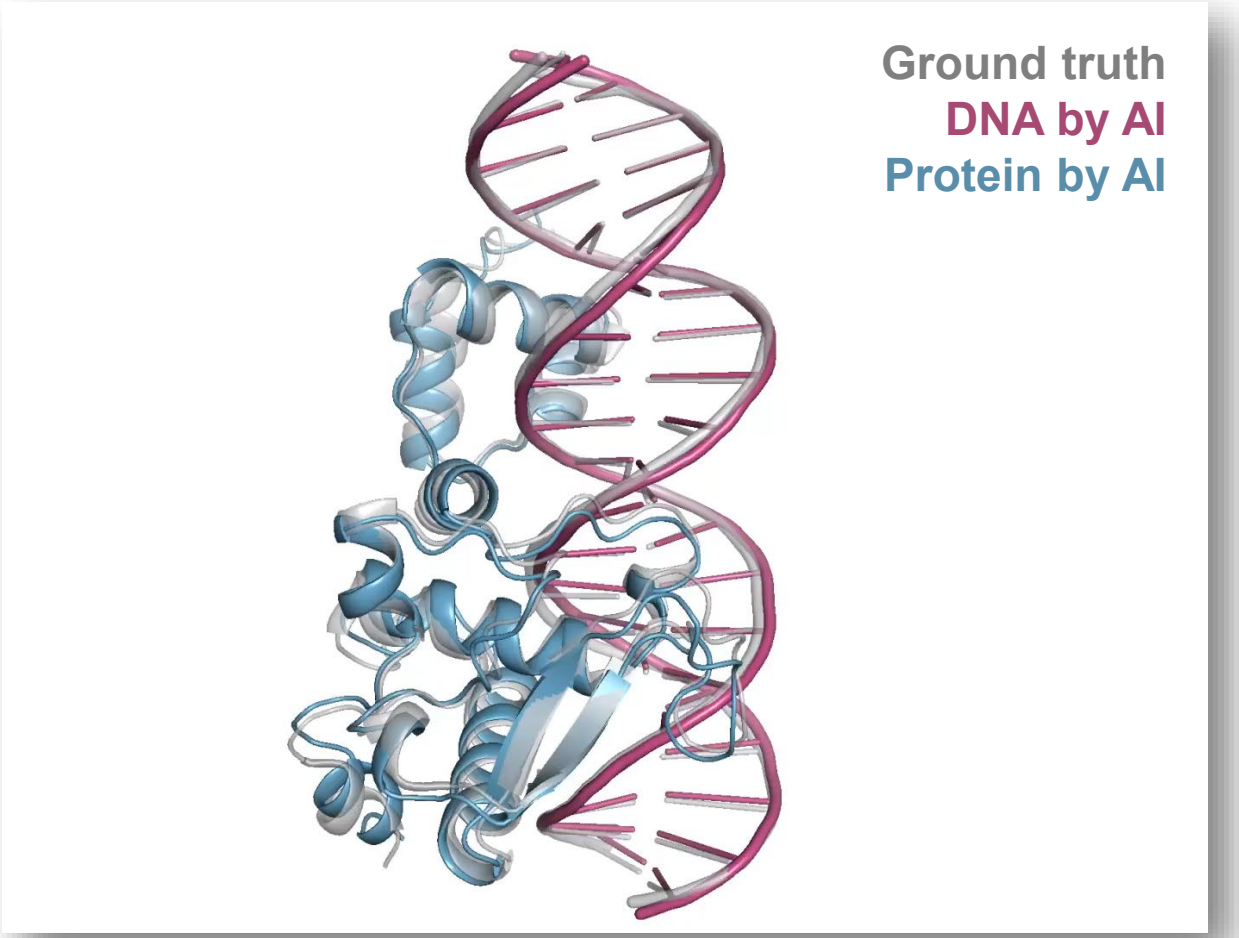
AI for drug development



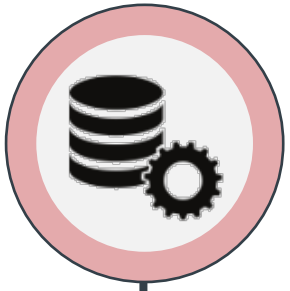
7R6R – DNA-binding protein: AlphaFold 3's prediction for a molecular complex featuring a protein bound to a double helix of DNA is a near-perfect match to the true molecular structure discovered through painstaking experiments.

AI, artificial intelligence.

Google. AlphaFold 3 predicts the structure and interactions of all of life's molecules. Available at: https://blog.google/technology/ai/google-deepmind-isomorphic-alphafold-3-ai-model/#drug-discovery. Accessed February 2025.

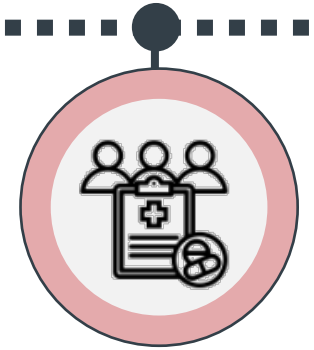
AI support opportunities in clinical trials

Study setup
- eCase report form design
- Database creation

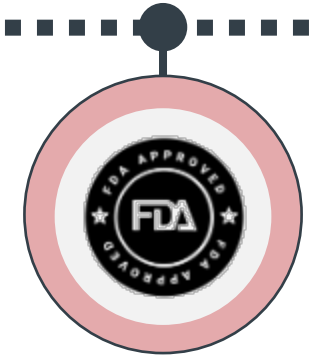


Data analysis
- Medical coding
- Interim/final analysis

Study design
- eProtocol design
- Text translation



Trial management
- Site selection
- Patient enrollment
- Risk-based monitoring



Regulatory submission
- eTrial master files
- Clinical study report automation

Slide content provided courtesy of Munich Leukemia Laboratory.
For further reading see 1. Sharma A *et al*. *Biomed Res Int* 2022; 2022: 7205241. 2. Xue VW *et al*. *Clin Transl Med* 2023; 13 (3): e1216.

Monitoring patient health and supporting patient engagement

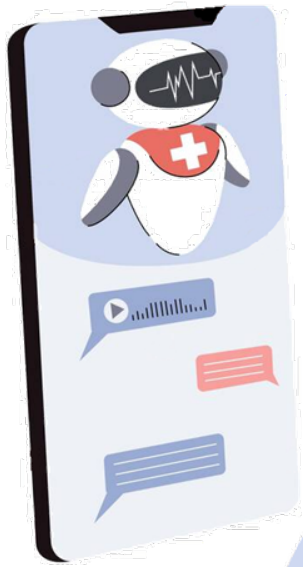
AI can help with patient follow-up and provide opportunities for remote monitoring

AI, artificial intelligence.

Integration of AI to drive patient's engagement

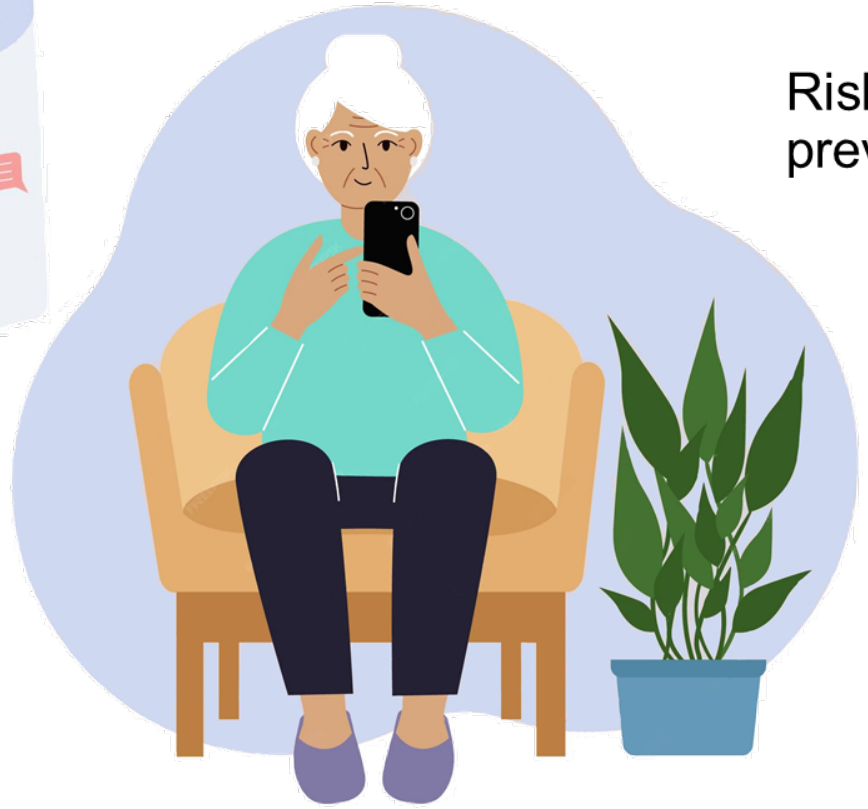
Patient motivation

360-degree view of the patient



AI-powered patient self-service portal

Risk assessments for preventive care



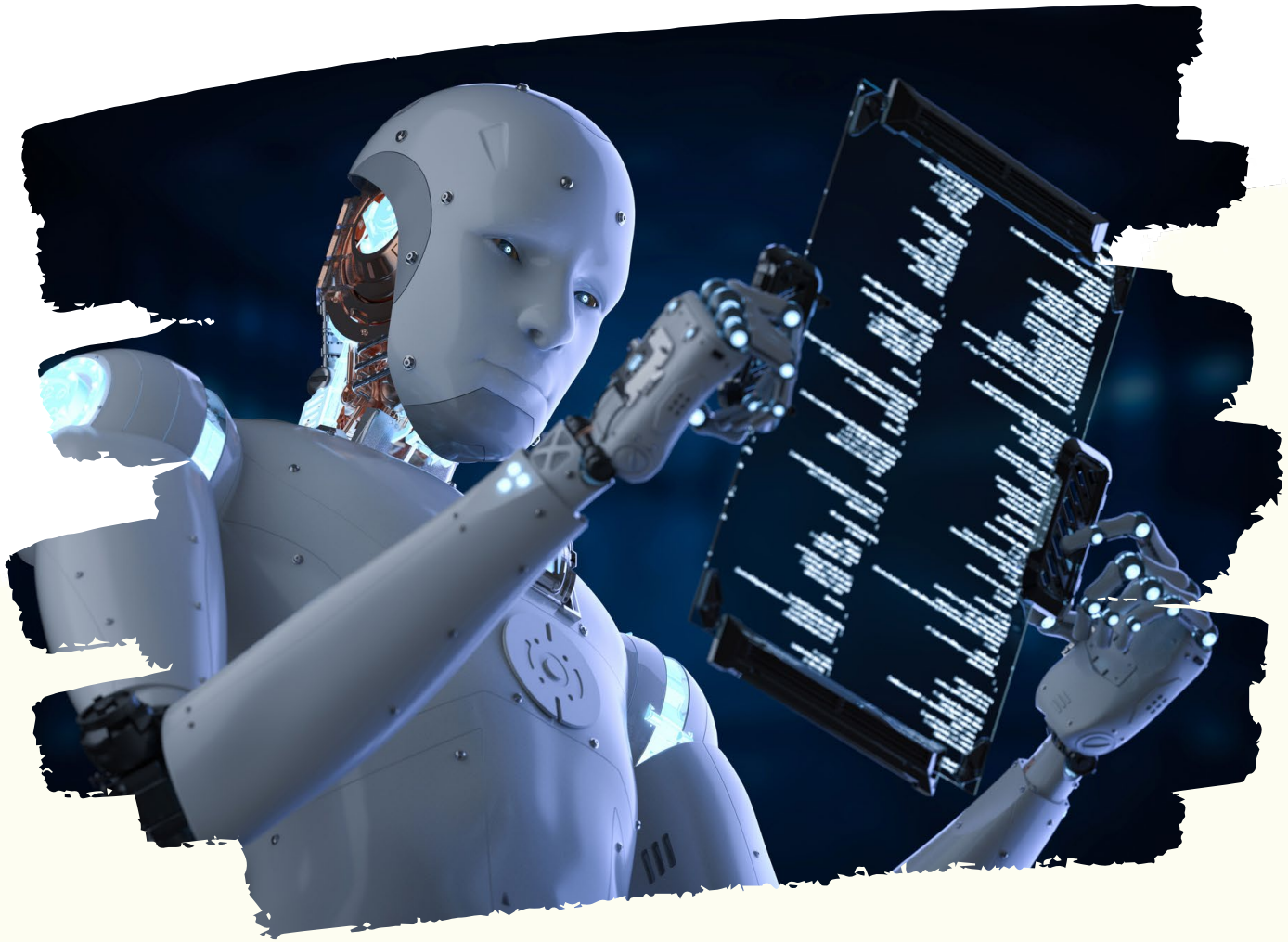
Healthcare virtual assistants

Healthcare workforce optimization

AI, artificial intelligence.

Subramaniam A. Top 8 AI Use Cases in Healthcare for Driving Patient Engagement and Enhancing Patient Experience. Available at: https://kanini.com/blog/how-is-artificial-intelligence-ai-transforming-patient-engagement/. Accessed February 2025.

Will medicine lose its humanity?

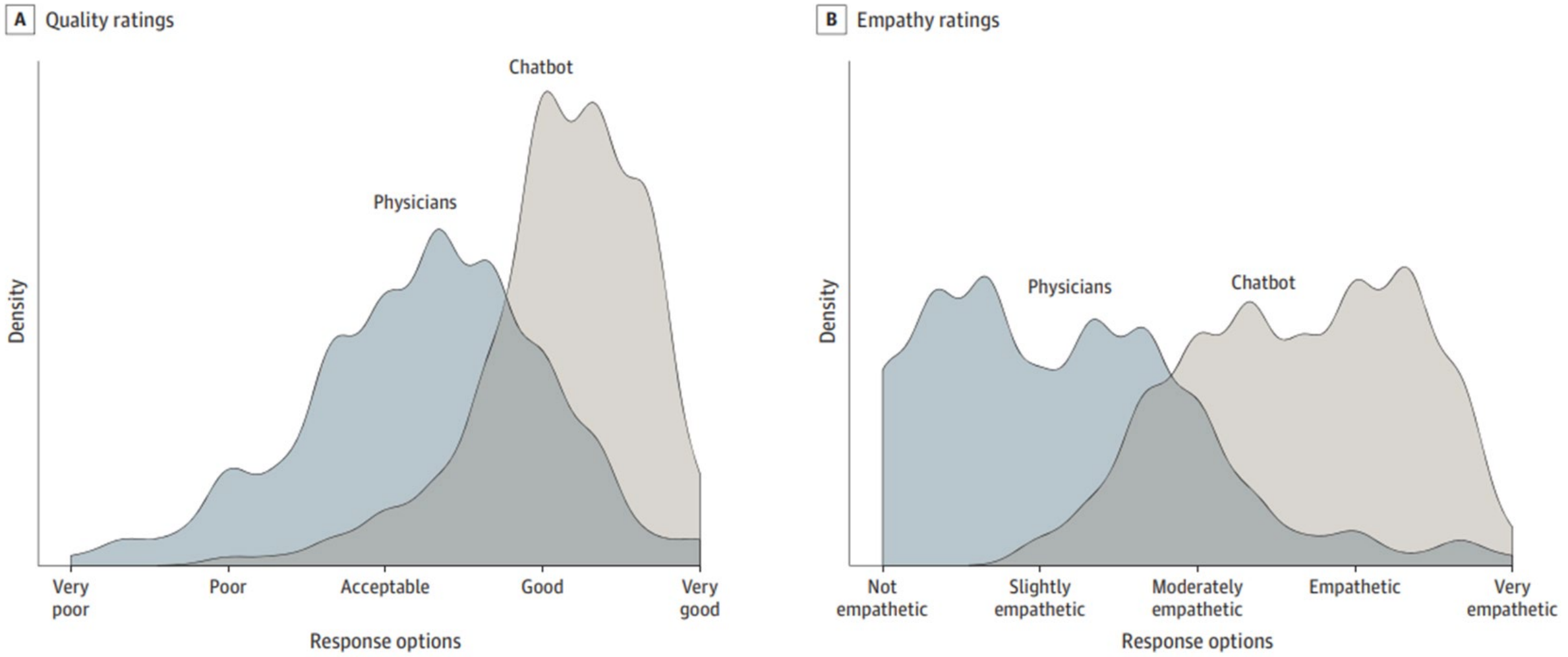


Reduced human interaction?

Loss of empathy?

Physicians compared with ChatGPT-3.5 in online patient survey

Random selection of 195 interactions in which physicians answered patient questions*

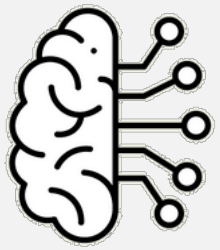


*https://www.reddit.com/r/AskDocs/

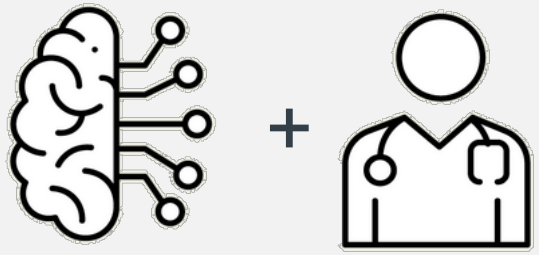
Ayers JW *et al*. *JAMA Intern Med* 2023; 183 (6): 589–596

Why hasn’t AI been able to support physicians better so far?

Median value of diagnostic judgment ability depending on the group:



92%



76%

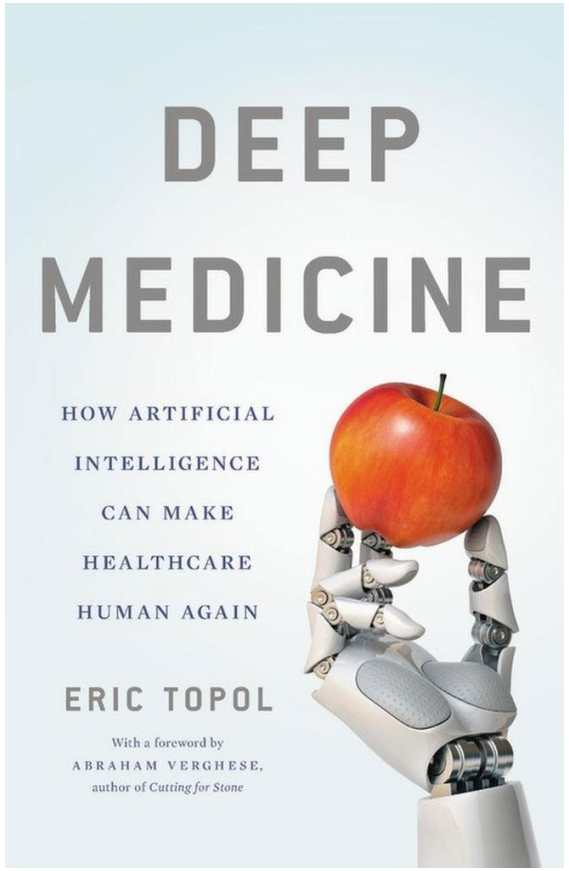
74%

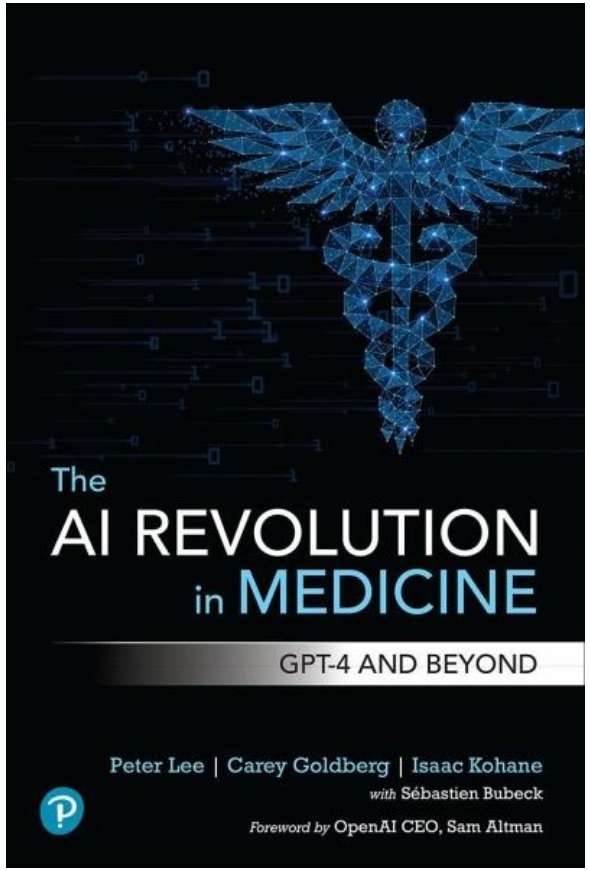
1. Physicians did not give much weight to the second opinion provided by the LLM

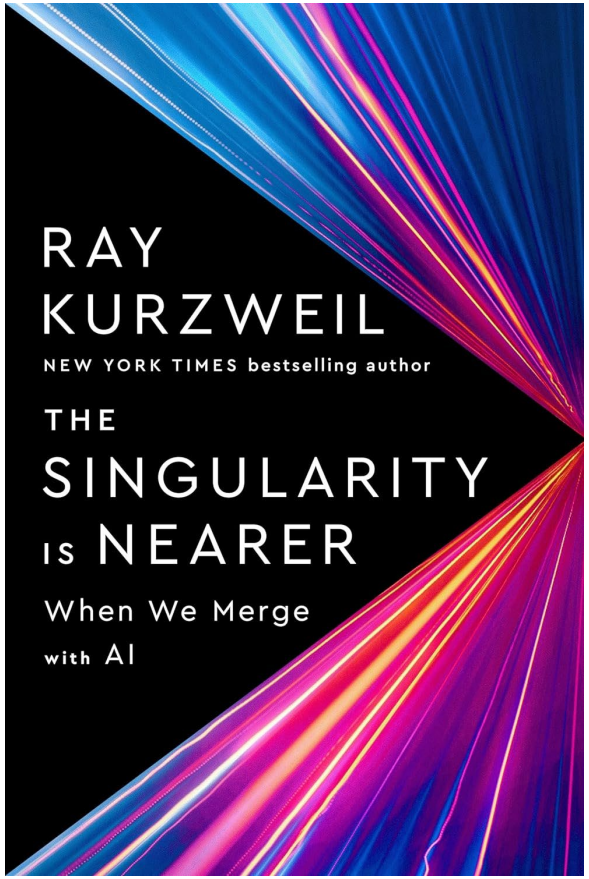
2. Physicians were not sufficiently trained to handle a chatbot/LLM

AI, artificial intelligence; LLM, large language model.
Goh E *et al*. *JAMA Netw Open* 2024; 7 (10): e2440969.

Deep medicine and the future of humans and AI



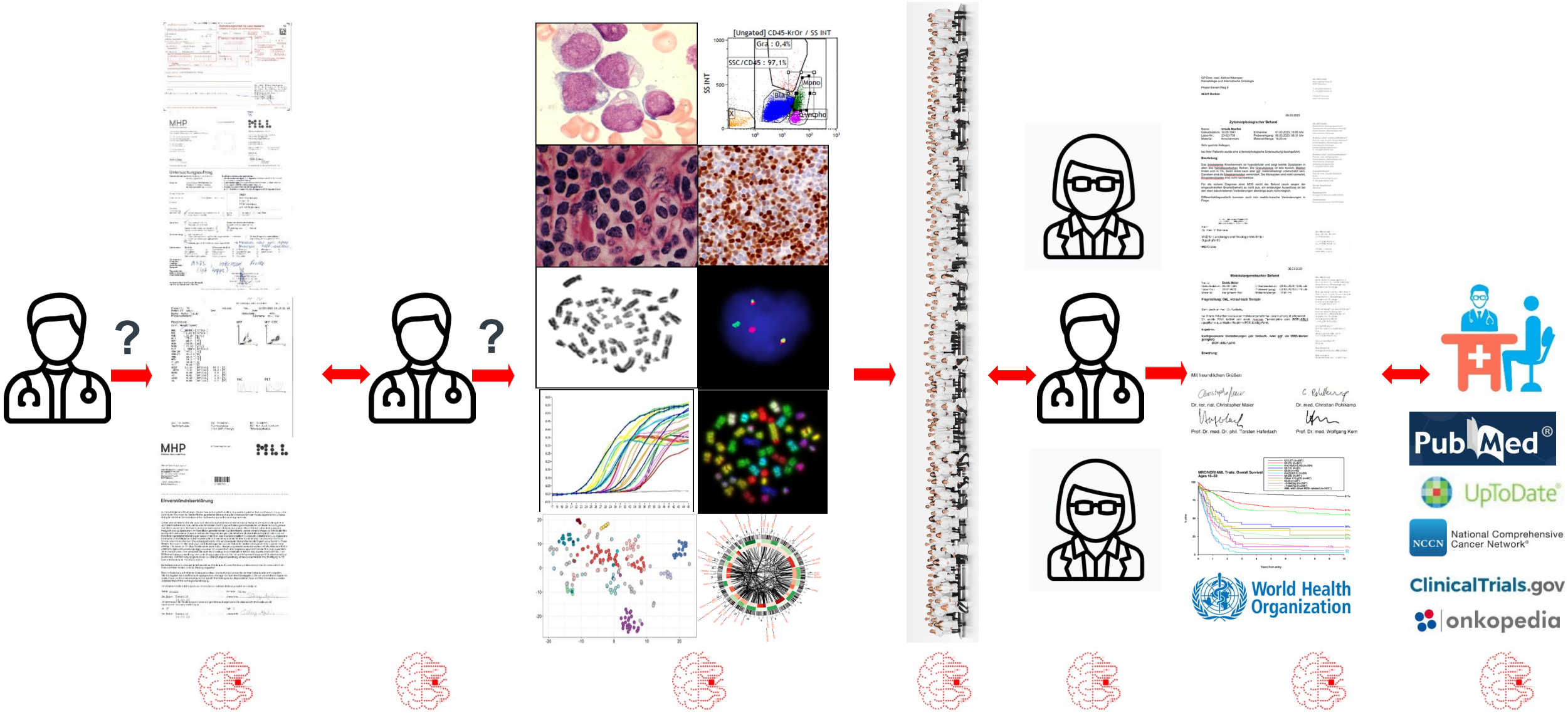




"AI will not replace physicians.
However, physicians who use AI will replace those who don't."

AI, artificial intelligence.

AI-driven diagnostics and treatment advice implementing LLMs



Slide content provided courtesy of Munich Leukemia Laboratory. AI, artificial intelligence; LLM, large language model.

What's next? Artificial General Intelligence (AGI)

- **AGI – Next AI Generation:** Artificial superintelligence will continue to evolve on its own, making human control difficult or unnecessary
- **Gamechanger for technology:** AGI connects digital tools (AI as an Agent), automates processes, and revolutionizes data-intensive industries
- **Workplace in transition:** Initially inefficient, but capable of learning – AGI will quickly solve problems that we have not even recognized until now
- **Between utopia and risk:** Solutions for climate change and diseases are possible, but there is also the danger that AGI may misguide us
- **Politics drives dynamics:** Deregulation and billion-dollar contracts (see US 'Stargate') will accelerate the development of AGI and robotics – with uncertain consequences
- **Danger:** Humans – the greatest threat to the future remains humanity itself, which combines AGI, robotics, and consciousness in an 'uncontrolled' manner

Slide content provided courtesy of Munich Leukemia Laboratory.

What can you do?

Individual-level

1. Start discussions about how AI can be used and accepted within your medical community
   - ➢ Become familiar with regulatory guidance and consider how to address these regulations
2. Use AI to stay abreast of latest developments
   - ➢ AI tools can quickly summarize huge quantities of information

Hospital-level

1. Implement AI systems for entering and organizing patient data to free up capacity
2. Use imaging-based AI tools for initial diagnostic procedures before human input

AI, artificial intelligence.

See behind – go beyond