AI Promise to the Practice of Hematopathology

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MAYO CLINIC

Disclosures

- Serve on the board of directors and have stock options with Techcyte Inc.

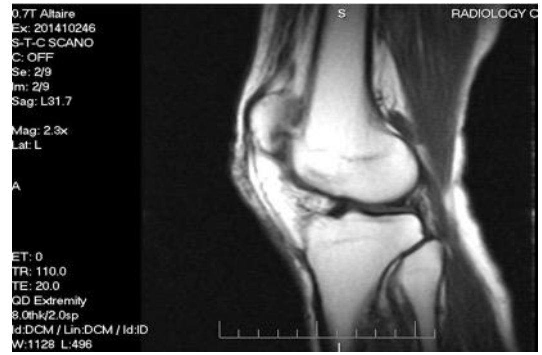
Digital imaging makes pathology a quantitative science

The promise of digital imaging & AI

- Every “image-based” pathologist will use computer-assisted analytic tools
- Digital Pathology enables AI
- AI extending beyond imaging
- Increased reliance on pathology
- Integration of E-management systems with LIS, and EMR, will revolutionize our workflow

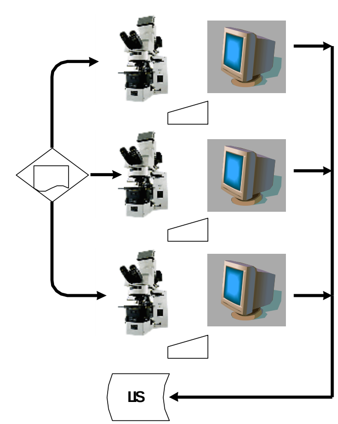
Why switch to digital?

- Image quality, access and consistency and work flow can be greatly improved.

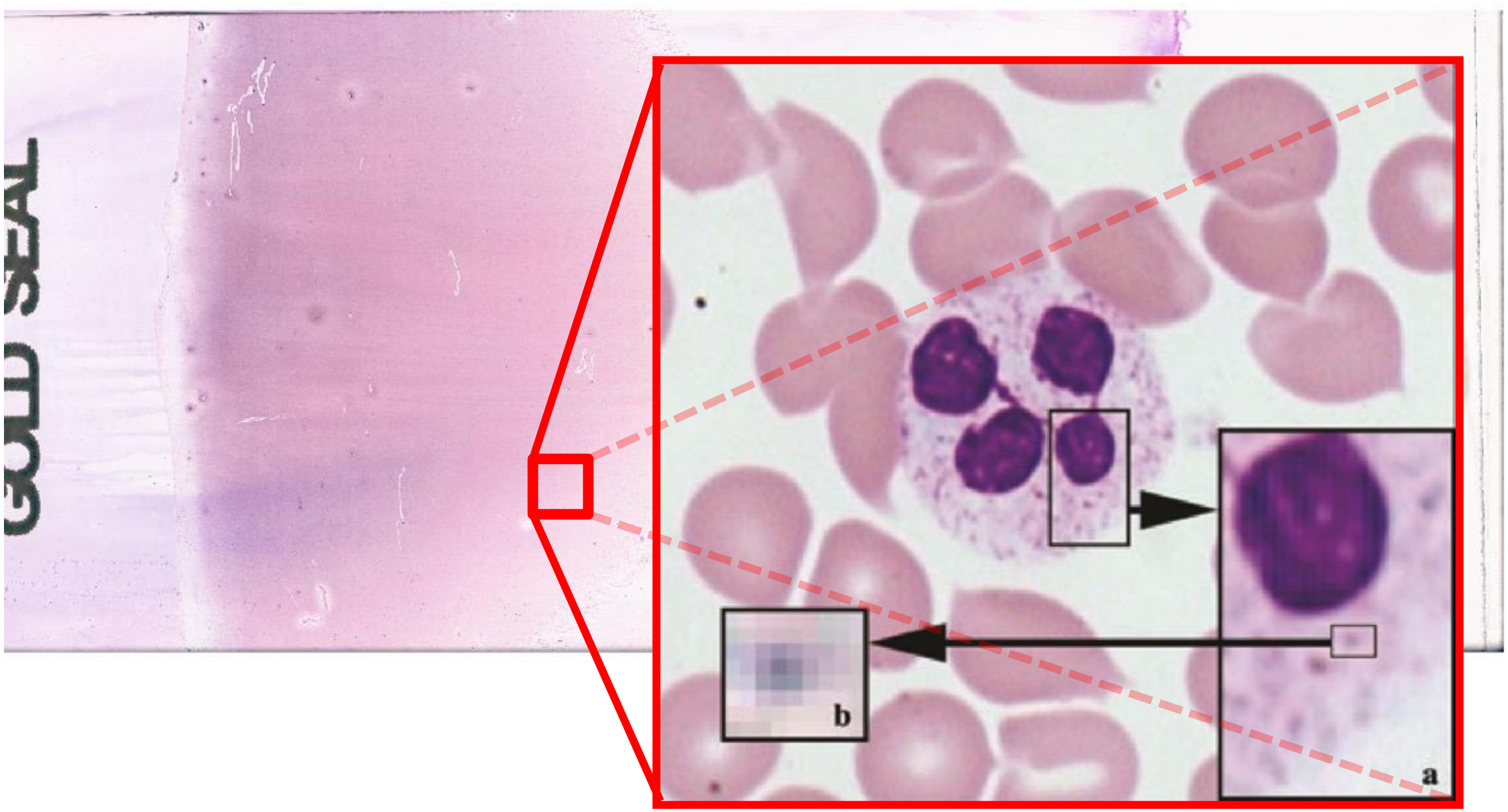


Problems with Manual Microscopy in the hematology lab

- Labor intensive
- Not standardized
- Difficult to train
- No historical images
- Limited consultation
- No traceability

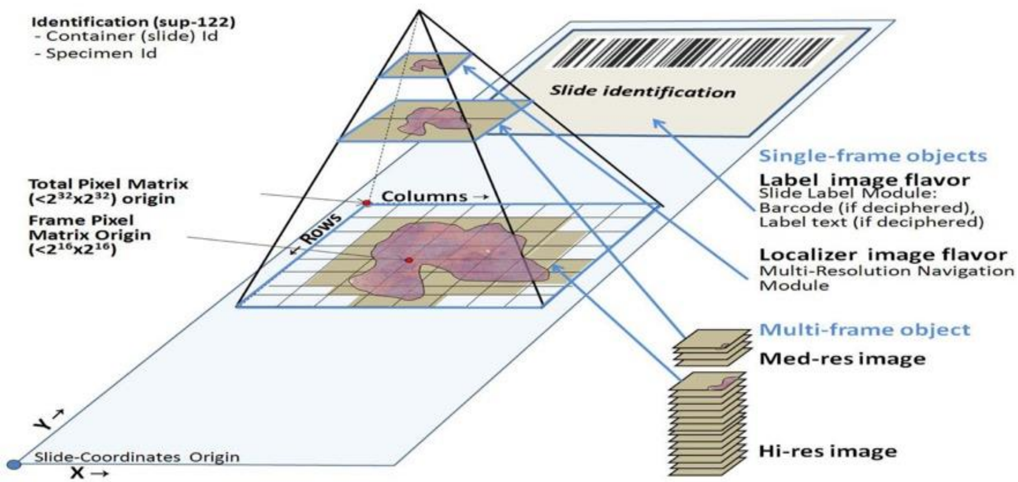


How viewing digital images differs from the viewing of glass slides through a microscope?



Clin. Lab. Haem. 2005, 27, 357–362

Challenges implementing WSI for Hematopathology

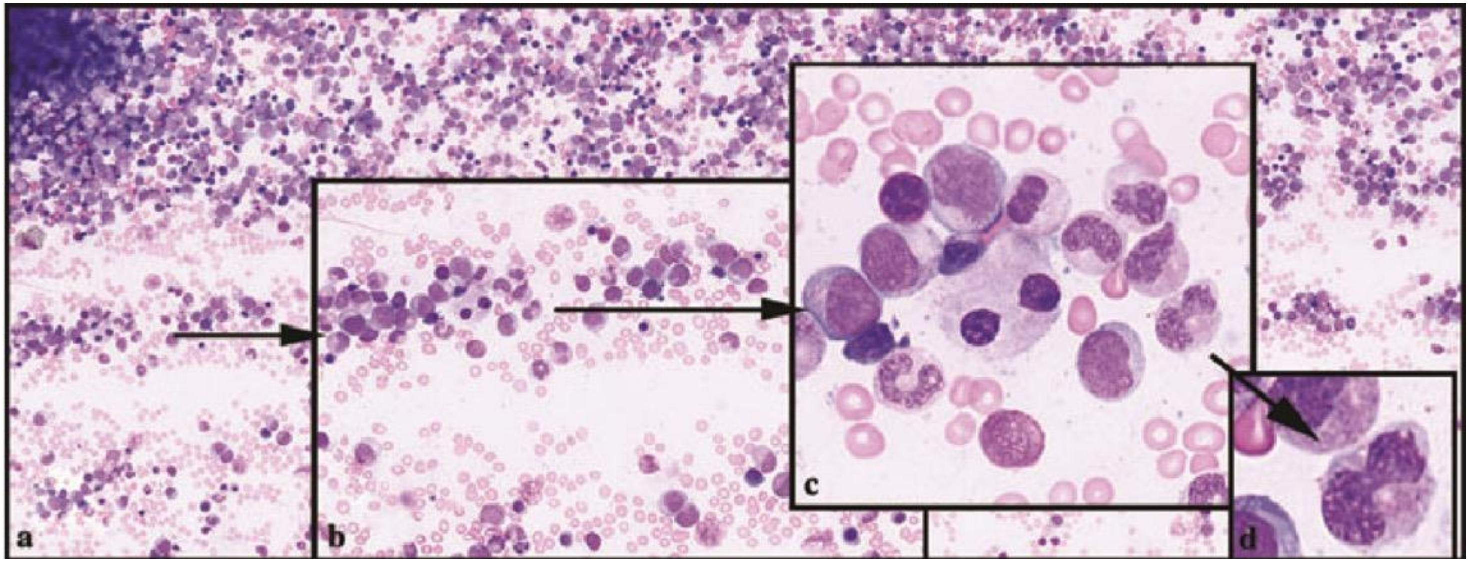


Scanning magnifications /time

•100X oil immersion (blood and marrow smear slides)

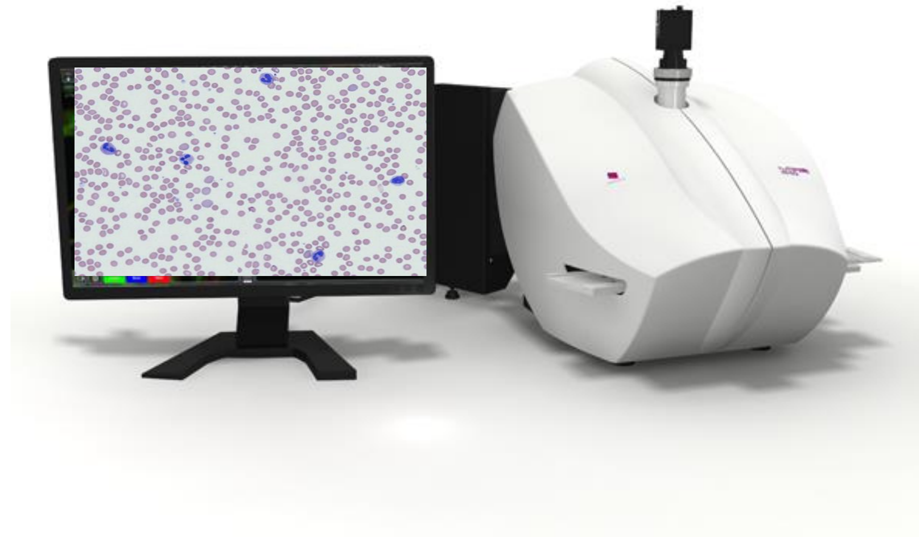
- –2x2 mm scan area: 8.4 min
- –5x5 mm: 11 min
- –7x7 mm: 13.5 min
- –9x9 mm: 16.6 min

J Pathol Inform. 2014 Oct 21;5(1):41.



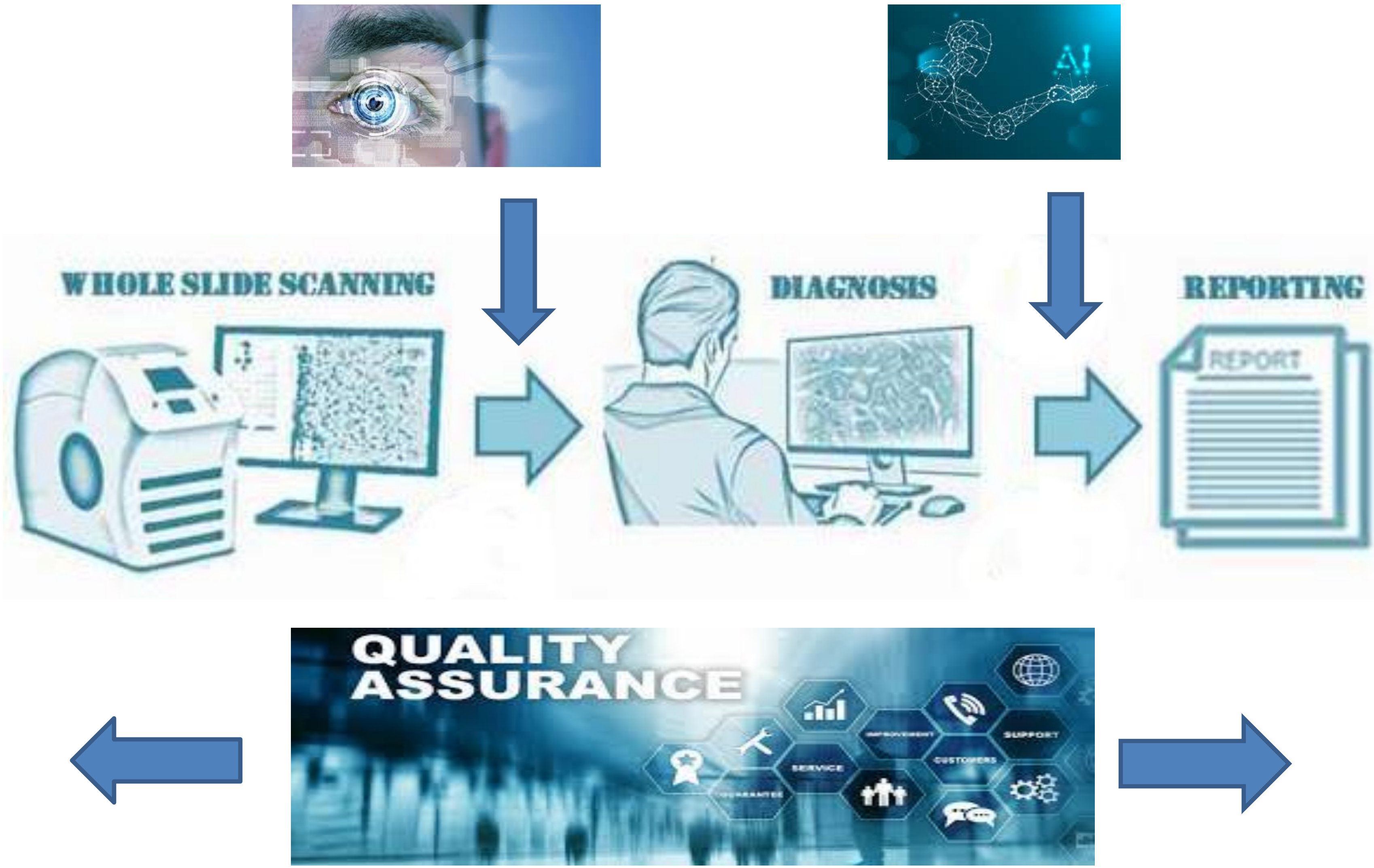
Flavors of Oil based scanners in evolution……..

More vendors …..and faster speed…….



Bionovation
Image cytometry

Pathologist-Centric System



Applications in the clinical hematology lab

Pre-analytical

☞ Pre-diagnosis
- Case assignment
- Screen slides
- Pre-order stain

Analytical

☞ Automated classification of Hematopoietic cells

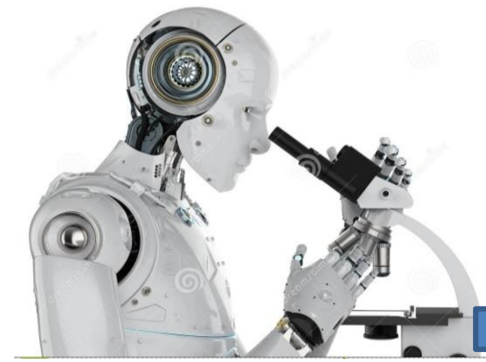
☞ Assist in the disease differential diagnosis

Post-analytical

☞ As directed
- NLP for report generation

Ancillary testing (e.g. flow cytometry)

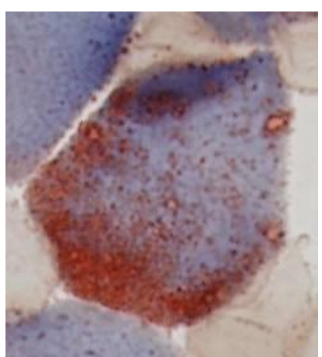
We need to step into the future to chart our course

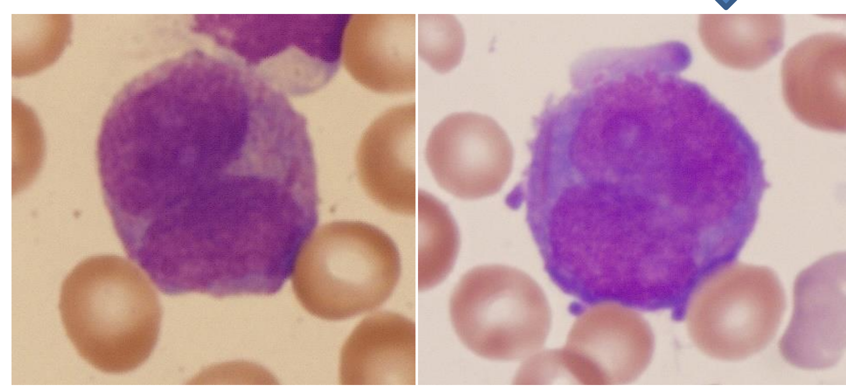


APL Diagnosis

Flow cytometry
FISH t(15;17)

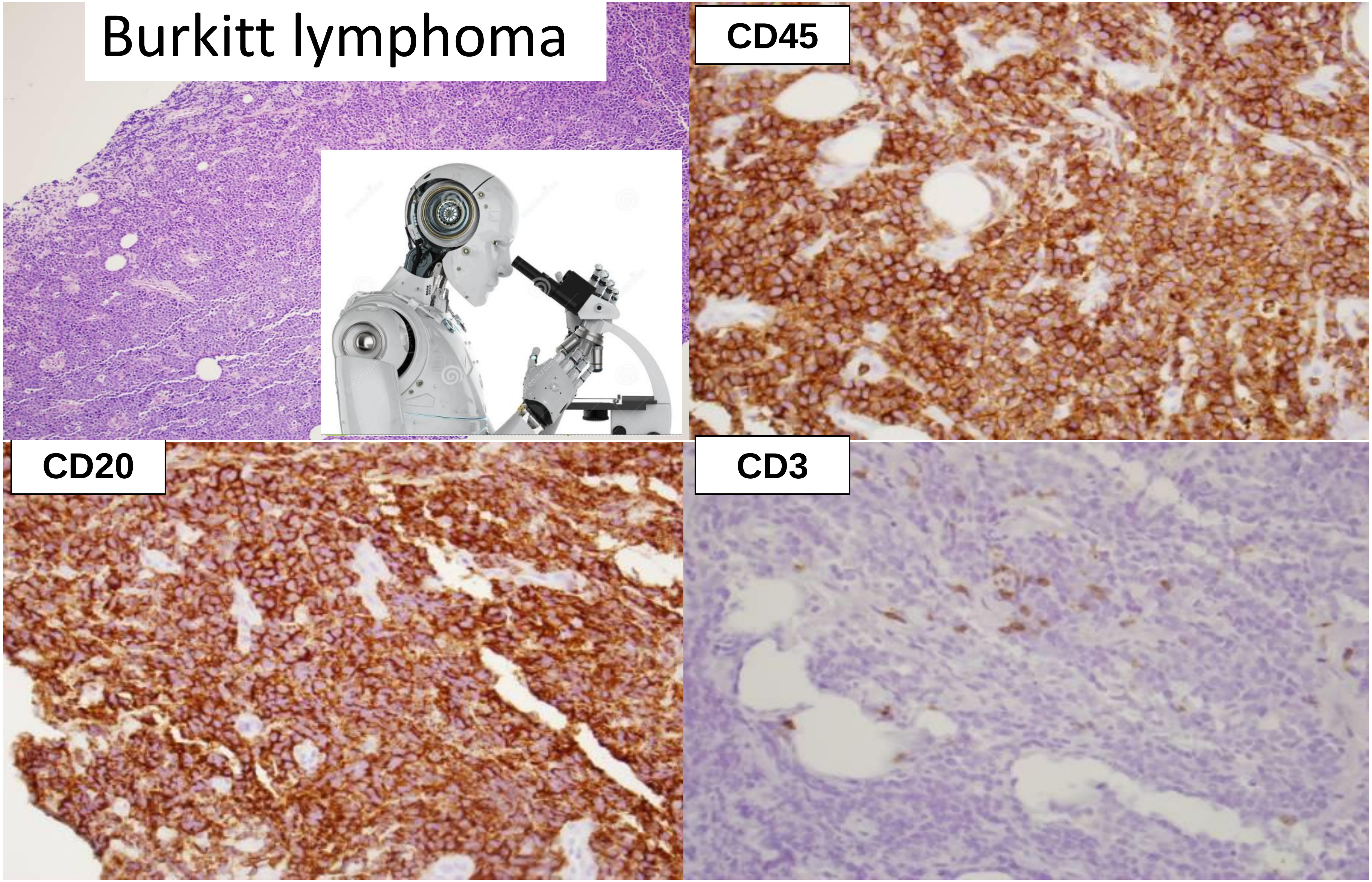
MPO stain





Promyelocytes

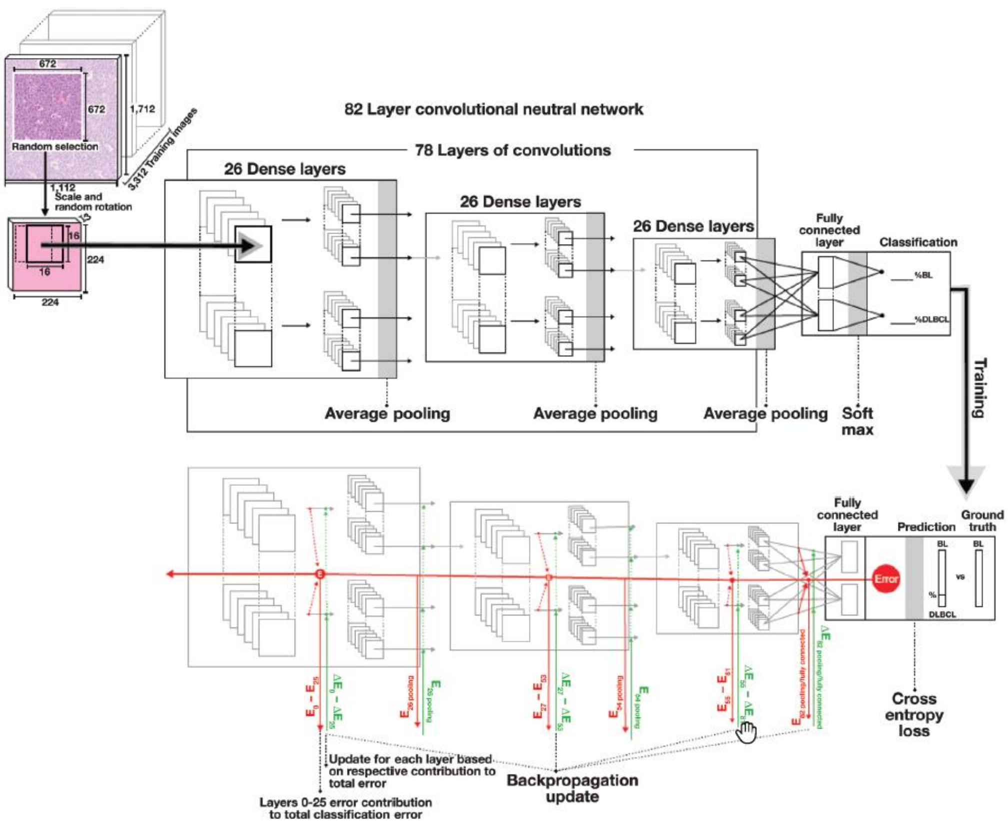
IHC selection



Am J Clin Pathol June 2020;153:743-759

Improving Augmented Human Intelligence to Distinguish Burkitt Lymphoma From Diffuse Large B-Cell Lymphoma Cases

Jeffrey S. Mohlman, MD, MPH,[1,2] *Samuel D. Leventhal,*[3] *Taft Hansen, MLS(ASCP),*[1,2] *Jessica Kohan,*[1,2] *Valerio Pascucci, PhD,*[3] *and Mohamed E. Salama, MD*[4]



DLBCL

CD20
CD3
CD5
CD10
CD45
BCL2
BCL6
MUM1
Ki-67
MYC

Burkitt Lymphoma

MYC
CD20
CD3
BCL2
EBER-ISH

Applications in the clinical hematology lab

Pre-analytical	Analytical	Post-analytical

☞ Pre-diagnosis
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- Screen slides
- Pre-order stain

☞ Automated classification of Hematopoietic cells

☞ Assist in the disease differential diagnosis

☞ As directed
- NLP for report generation

Ancillary testing (e.g. flow cytometry)

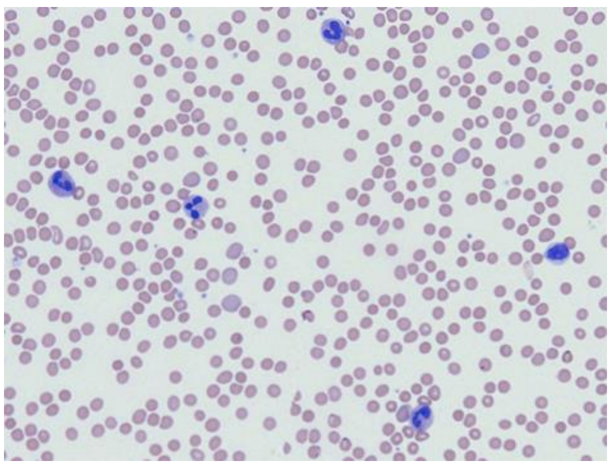
Why automate the manual differential?

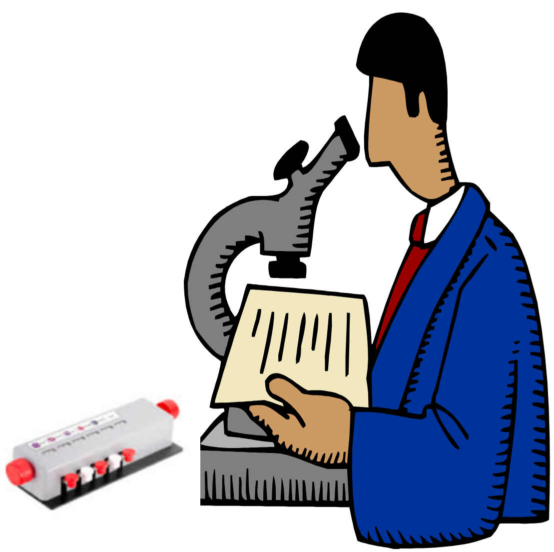
- *Declining availability of medical technologists, less graduates and accelerating retirements*

- *The need for a greater level of standardization and consistency for the manual differential*

- *Increasing demand for connectivity between healthcare providers*

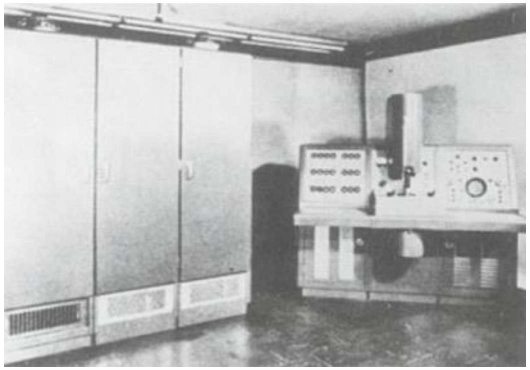
Computational Power in the Future of Hempath





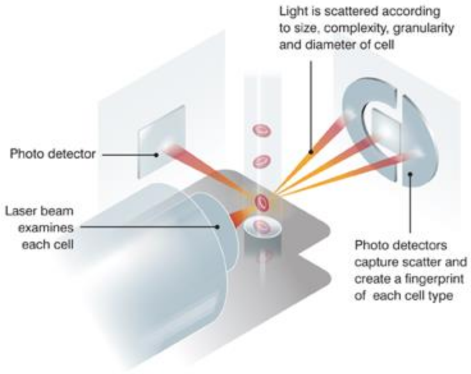
Automated classification of Hematopoietic cells

Cydac Scanning Microscope System

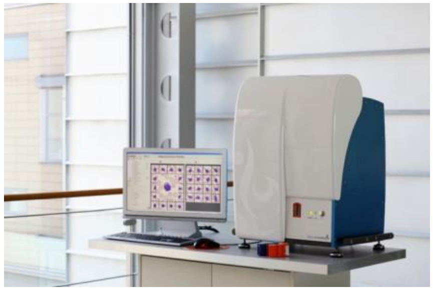


mid-1960s

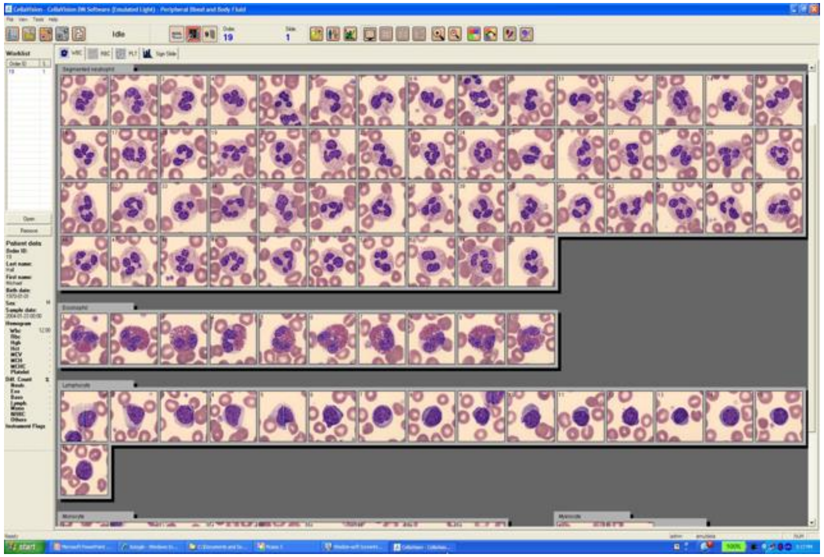
Automated flow cytometric based

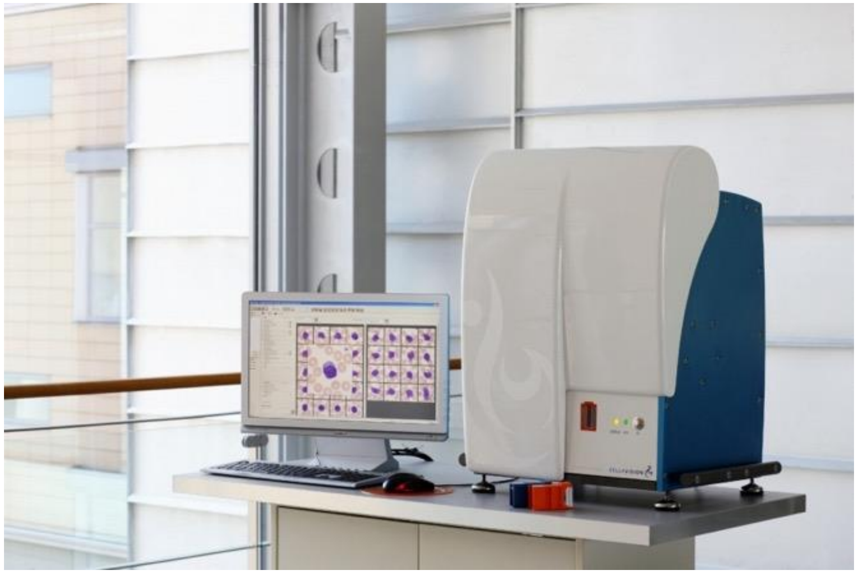


Modern digital cell morphology and remote viewing systems



Cellavision: Display cell counter results & flags





CellaVision® DM1200

Sysmex DI-60 Integrated System

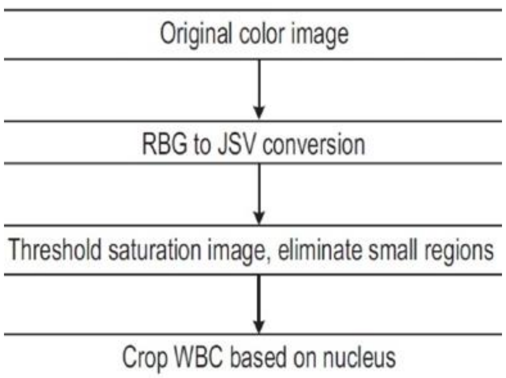
Ideal Digital Pathology Platform

- Agnostic Image Acquisition
- Deep Machine Learning
  - Accuracy
  - Handles stain and slide variability
  - Gets better over time
- Same platform for…
  - Blood WBC, RBC
  - Bone aspirate
  - Other cytology samples
- Enables remote pathology

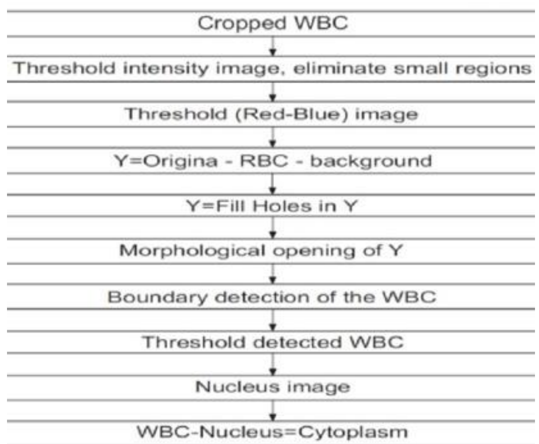
Modern digital cell morphology systems

- Knowledge-based “artificial neural network” algorithms
- Employ hierarchically-structured classification rules

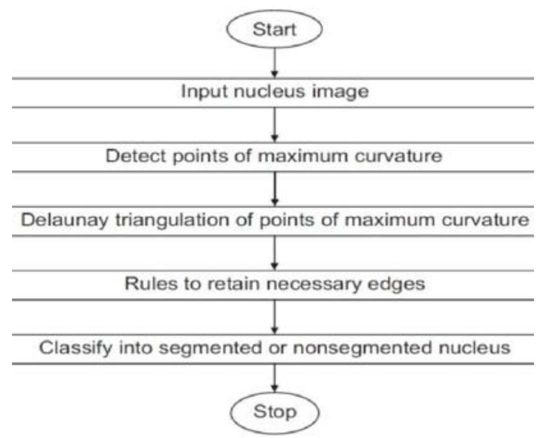
WBCs Detection



WBCs Segmentation



WBCs classification



- Neural learning techniques: mirror our manual teaching processes , are then used to refine the rules

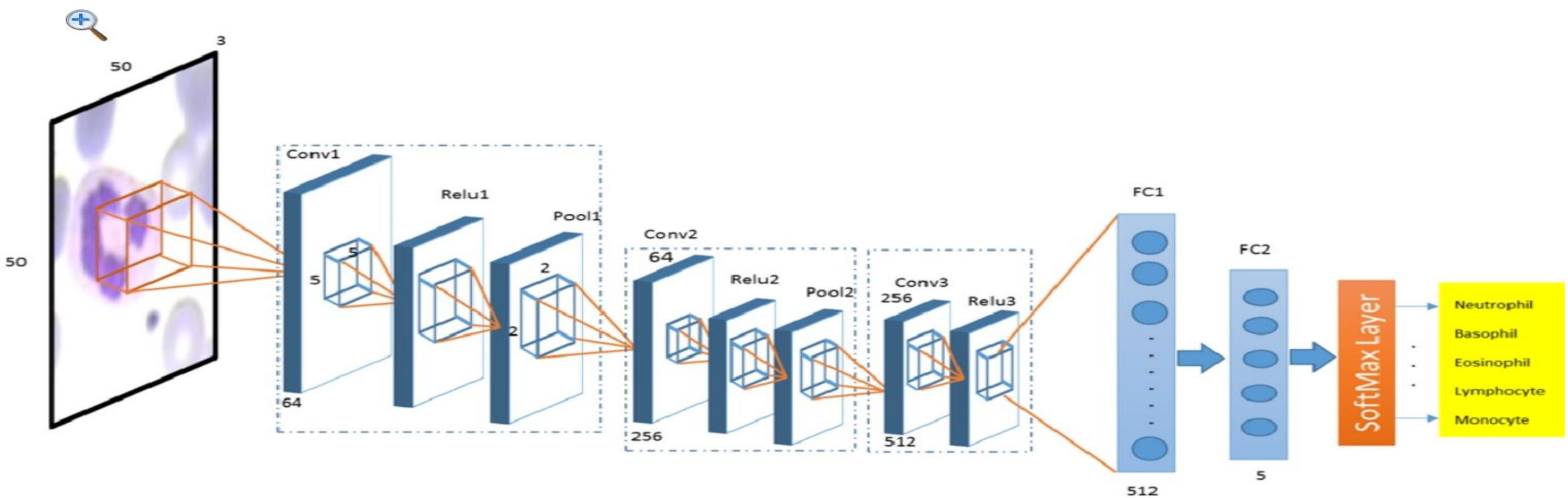
J Pathol Inform 2012; 3: 13

Recent Studies with traditional classification methods for WBC

Reference	Dataset (size/sources)	Used features/Total number	Classifier/1or 2 steps of classifier	Feature reduction	Classifier accuracy
Wang 2016	60/1	(Morph .+ Stat .+ Spect.)/(4 Morph. + Spect. oeff:ND.)	SVM/1	None	90%
Rezatofighi 2011	254/1	(Morph. + Text.)/(112)	(ANN + SVM)/2	SFS	96%
Prinyakupt 2015	1078/2	(Morph. + Stat.) /(15)	Linear and Naïve Bayes classifier/1	None	96%
Ramesh 2012	2172/1	(Morph. + Stat.) /(19)	LDA/2	None	93.90%
Putzu 2014	33/1	(Morph .+ Stat .+ Text.)/131	SVM/2	None	93%
Nazlibilek 2014	12 / 1	Cell sub-image /(14,400)	MLP/2	PCA	95%
Mathur 2013	267/1	(Morph. + Text.)/(7 Morph., Text.:ND.)	Naive Bayes classifier	None	92.70%
Ghosh 2016	487/1	(Morph .+ Stat .+ Text.)/(ND)	Fuzzy classifier/2	None	96%
Su 2014	450/2	(Morph .+ Stat .+ Text.)/(20)	MLP/1	None	99.10%

Comput Methods Programs Biomed. 2019 Jan;168:69-80. doi: 10.1016/j.cmpb.2017.11.015. Epub 2017 Nov 16.

White blood cells identification system based on convolutional deep neural learning networks.



balanced WBCs dataset classification is performed through the WBCsNet as a pre-trained network.

RESULTS: During our experiments, three different public WBCs datasets (2551 images) have been used which contain 5 healthy WBCs types. The overall system accuracy achieved by the proposed WBCsNet is (96.1%) which is more than different transfer learning approaches or even the previous traditional identification system. We also present features visualization for the WBCsNet activation which reflects higher response than the pre-trained activated one.

CONCLUSION: a novel WBCs identification system based on deep learning theory is proposed and a high performance WBCsNet can be

A Deep Learning Approach To Automatically Classify Pathological Cell Images In Peripheral Blood

True \ Predicted	APL	BL	CLL	FL	HCL	MCL	N	PC	RL	SMZL	SS
APL	90.1	6.8	0.0	0.0	0.0	1.5	0.0	0.0	0.0	0.0	1.5
BL	3.5	88.1	0.1	1.0	0.0	4.2	0.2	1.8	0.7	0.1	0.3
CLL	0.0	0.8	84.1	3.0	1.1	2.0	4.7	0.0	0.2	3.0	1.2
FL	0.3	1.7	3.2	64.4	0.0	11.8	12.5	0.2	0.0	0.3	5.5
HCL	0.0	0.0	0.0	0.0	97.6	0.0	0.5	0.0	0.0	1.9	0.0
MCL	0.0	5.6	6.7	5.4	0.2	70.5	3.5	0.1	0.8	4.7	2.4
N	0.1	0.8	5.0	1.1	1.2	0.5	82.7	0.2	3.3	2.7	2.4
PC	0.0	3.0	0.0	0.3	0.0	2.4	0.3	90.9	1.8	0.0	1.2
RL	0.0	1.8	0.1	0.0	0.1	0.3	5.3	0.4	89.2	2.4	0.3
SMZL	0.0	0.6	2.6	0.0	1.5	2.7	5.0	0.0	1.8	85.0	0.8
SS	0.0	0.0	2.7	2.8	0.0	4.8	5.7	0.0	0.6	0.1	83.3

Figure 1. Confusion matrix of the classification performance of the deep neural model for the test set of cell images.

- *46469 digital cell images from PB*
- *12 normal or pathological condition*
- *a practical diagnosis support tool*

Abstract 185, ISLH 2019

International Journal of Laboratory Hematology
The Official journal of the International Society for Laboratory Hematology

ORIGINAL ARTICLE INTERNATIONAL JOURNAL OF LABORATORY HEMATOLOGY

ICSH recommendations for the standardization of nomenclature and grading of peripheral blood cell morphological features

L. PALMER*, C. BRIGGS†, S. MCFADDEN‡, G. ZINI§, J. BURTHEM¶, G. ROZENBERG**, M. PROYTCHEVA††, S. J. MACHIN†

*Haematology Laboratory, Middlemore Hospital, Auckland, New Zealand
†University College London Hospitals, London, UK
‡McFadden Consulting, Columbus, OH, USA
§Università Cattolica del Sacro Cuore, Rome, Italy
¶Institute of Cancer Sciences, University of Manchester,

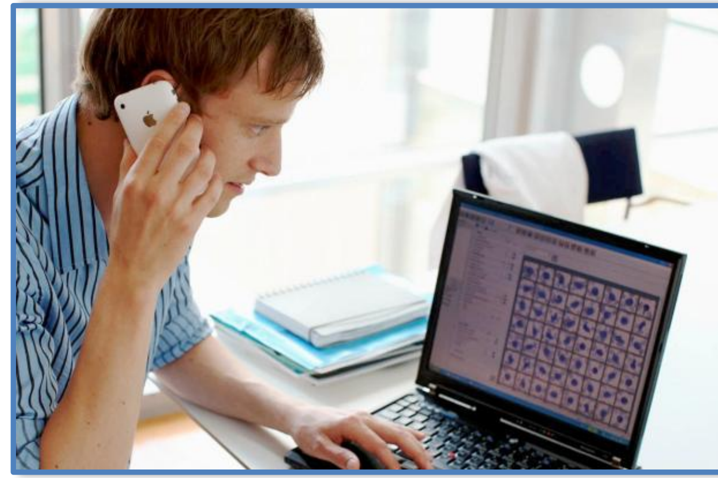
SUMMARY

These guidelines provide information on how to reliably and consistently report abnormal red blood cells, white blood cells and platelets using manual microscopy. Grading of abnormal cells, nomenclature and a brief description of the cells are provided. It is important that all countries in the world use consistent reporting of blood cells. An international group of morphology experts have decided on these guidelines using consensus opinion. For some red

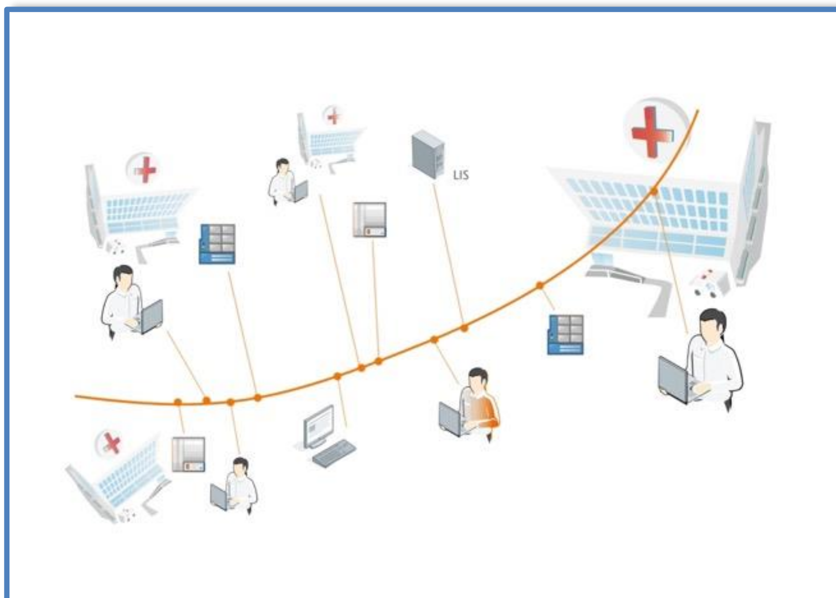
Table 1. Morphology Grading Table

Cell Name	Grading System Few/1+	Mod/2+, %	Many/3+, %
RBC			
Anisocytosis	N/A	11–20	>20
Macrocytes	N/A	11–20	>20
Oval macrocytes	N/A	2–5	>5
Microcytes	N/A	11–20	>20
Hypochromic cells	N/A	11–20	>20
Polychromasia	N/A	5–20	>20
Acanthocytes	N/A	5–20	>20
Bite cells	N/A	1–2	>2
Blister cells	N/A	1–2	>2
Echinocytes	N/A	5–20	>20
Elliptocytes	N/A	5–20	>20
Irregularly contracted cells	N/A	1–2	>2
Ovalocytes	N/A	5–20	>20
Schistocytes	<1%	1–2	>2
Sickle cells	N/A	1–2	>2
Spherocytes	N/A	5–20	>20
Stomatocytes	N/A	5–20	>20
Target cells	N/A	5–20	>20
Teardrop cells	N/A	5–20	>20
Basophilic stippling	N/A	5–20	>20
Howell-Jolly bodies	N/A	2–3	>3
Pappenheimer bodies	N/A	2–3	>3
WBC			
Döhle bodies	N/A	2–4	>4
Vacuolation (neutrophil)	N/A	4–8	>8
Hypogranulation (neutrophil)	N/A	4–8	>8
Hypergranulation (neutrophil)	N/A	4–8	>8
Platelets			
Giant Platelets	N/A	11–20	>20

Remote Review: Connectivity Benefits



- Clinicians access to images reduces TAT
- Real-time collaboration
- Email images anywhere
- Access from anywhere
- Image storage
- Maintain competency across multiple sites
- Centralize expertise
- Share staff



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Post-analytical

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- NLP for report generation

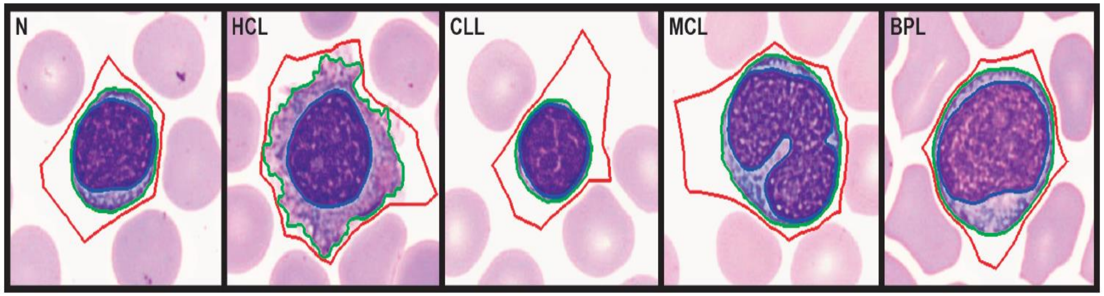
Ancillary testing (e.g. flow cytometry)

Automatic Recognition of Atypical Lymphoid Cells From Peripheral Blood by Digital Image Analysis

Santiago Alférez,[1] Anna Merino, MD, PhD,[2] Laura Bigorra,[1,2] Luis Mujica, PhD,[1] Magda Ruiz, PhD,[1] and Jose Rodellar, PhD[1]

From the [1]Universitat Politècnica de Catalunya, Barcelona, Spain, and [2]Department of Hemotherapy-Hemostasis, Hospital Clinic, Barcelona, Spain.

- Collected samples from normal, CLL, HCL, and MCL
- Segmentation (Based on color clustering)
  - Cell region
  - Cytoplasm region
  - Region surrounding cell
- Feature Extraction (113)
  - Geometric features
  - Color/Texture
  - Cytoplasm profile features



Am J Clin Pathol 2015;143:168-176

Confusion Matrix of the LDA Classification and 10-Fold Cross-Validation for the Training Set

True	Predicted, %[a]				
	N	HCL	CLL	MCL	BPL
N	99.45	0.00	0.00	0.00	0.55
HCL	1.66	97.67	0.00	0.00	0.67
CLL	0.92	0.00	98.71	0.19	0.18
MCL	1.25	0.00	0.00	97.50	1.25
BPL	4.00	1.33	0.00	0.00	94.67

BPL, B-prolymphocytes; CLL, chronic lymphocytic leukemia; HCL, hairy cell leukemia; LDA, linear discriminant analysis; MCL, mantle cell lymphoma; N, normal lymphocytes.

[a] The rows represent the true diagnosis and the columns the predicted diagnosis given by the classification algorithm for each type of lymphoid cell. Accuracy = 98.07% and SD = 0.80.

Am J Clin Pathol 2015;143:168-176

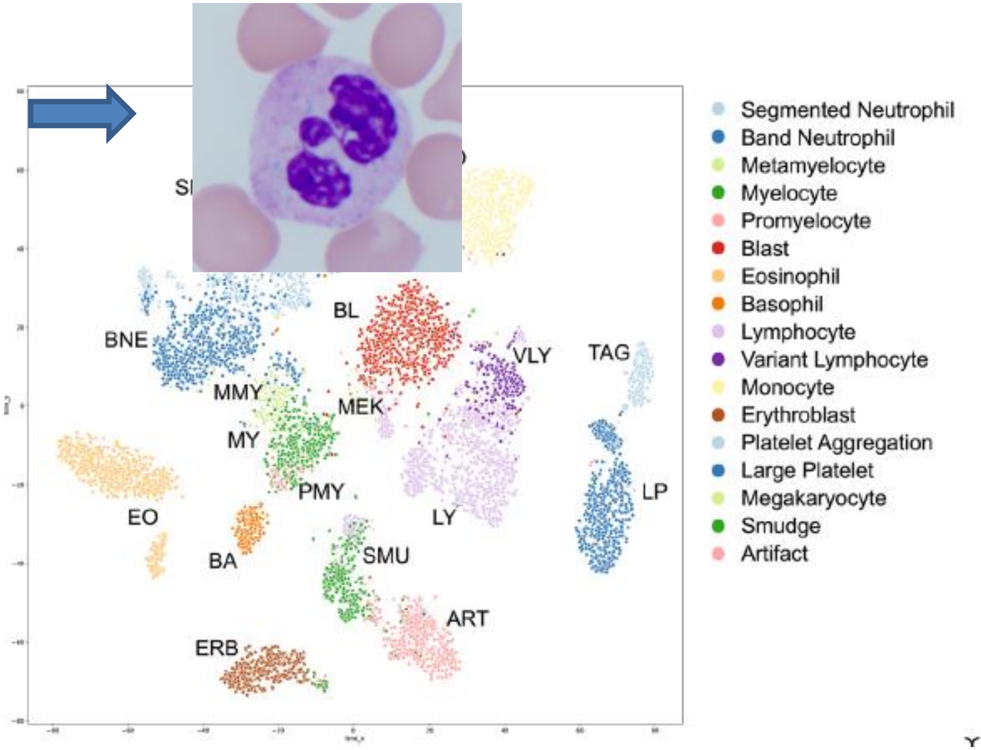
Nature research

A novel automated image analysis system using deep convolutional neural networks can assist to differentiate MDS and AA

Konobu Kimura,[1,2] Yoko Tabe,[1,3] Tomohiko Ai,[3] Ikki Takehara,[2] Hiroshi Fukuda,[4] Hiromizu Takahashi,[4] Toshio Naito,[4] Norio Komatsu,[5] Kinya Uchihashi,[2] and Akimichi Ohsaka[1,6]

Sci Rep. 2019; 9: 13385.

Cell type	Sensitivity (%)	Specificity (%)
Segmented Neutrophil	98.0	97.7
Band Neutrophil	98.0	97.0
Metamyelocyte	93.9	96.0
Myelocyte	98.1	96.9
Promyelocyte	98.6	97.6
Blast	97.2	98.7
Lymphocyte	99.3	96.5
Variant Lymphocyte	95.0	98.2
Monocyte	99.5	99.1
Eosinophil	99.6	100.0
Basophil	98.5	99.5
Large Platelet	99.7	99.4
Megakaryocyte	93.5	99.6
Platelet Aggregation	95.7	99.3
Erythroblast	99.8	99.4
Smudge	95.4	98.0
Artifact	99.0	98.7



t-distributed Stochastic Neighbor Embedding (t-SNE)

Nature research

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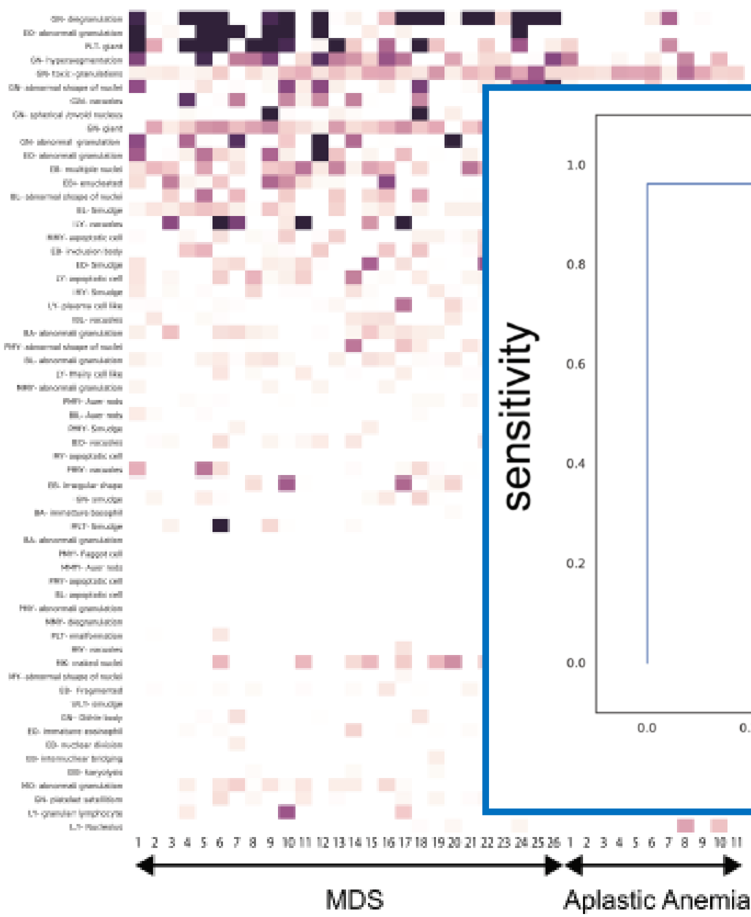
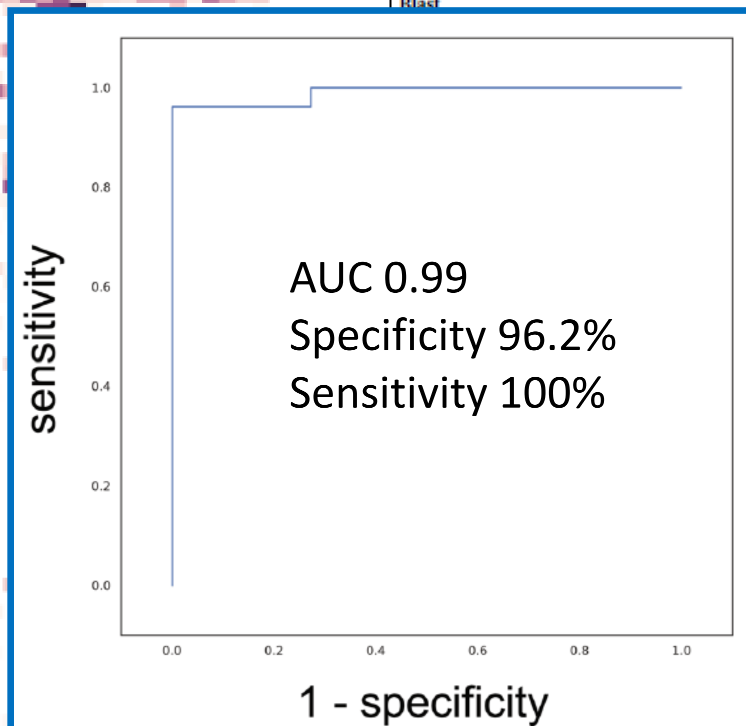


Cell type	Sensitivity (%)	Specificity (%)	AUC	images for validation*
Blast				
		94.4	0.975	107
		95.4	0.926	62
		94.5	0.950	112
		95.9	0.960	61
		97.4	0.978	53
		97.5	0.904	64
		92.6	0.955	130
		92.2	0.986	173
		93.9	0.977	233
		93.8	0.931	105
		97.3	0.992	244
		86.6	0.947	84
		95.2	0.969	139
		95	0.966	75
		94.7	0.958	90
		92.8	0.953	113
		94.5	0.903	154
		92.5	0.893	110
		59.9	0.878	55
Large platelet				
giant platelet	61.5	97.5	0.801	174



AUTOMATIC DETECTION OF DYSPLASTIC CELLS USING DEEP LEARNING

Andrea Acevedo[1], Anna Merino[2], Santiago Alférez[1], Laura Boldú[2], Angel Molina[2], Jose Rodellar[1]

[1] Technical University of Catalonia, Barcelona, Spain/[2] Hospital Clinic of Barcelona, Barcelona, Spain

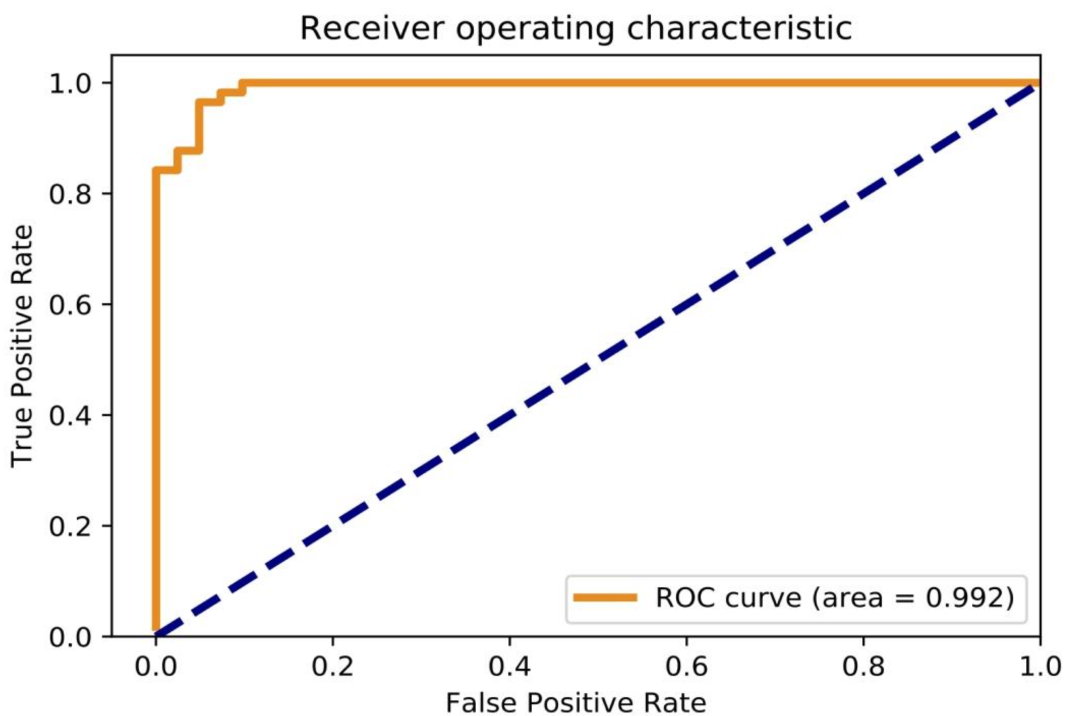


Figure 2: ROC curve of the test by smear. The area under the curve is 0.992.

Integration with other clinical data

Neoplastic Blasts or Non-neoplastic Immature Mononuclear Cells? Towards Rule Based Identification Using Electronic Health Records Data Mining

Nicholas J. Bevins, H. Elizabeth Broome *UCSD, La Jolla, CA, United States*

Patient Data within Month	**P Value**
Received stem cell mobilizing drug	2.7E-4**
Received corticosteroids	9.8E-4*
Received anti-neoplastic therapy	8.3E-6**
RBC flagged abnormal	1.7E-6**
PLT flagged abnormal	1.4E-6**
Myelocytes, promyelocytes, or metamyelocytes resulted	1.3E-4**
LDH resulted	3.2E-10**
If resulted -> LDH flagged abnormal	2.0E-3*
Blood culture resulted	1.5E-3*
If resulted -> Organism identified	0.7
Diagnosis of CML/AML/MDS	3.1E-9**
Bone marrow biopsy performed	1.5E-3*

Conclusions: *the development of a multi-variate rules-based mechanism to aid the distinction of blasts from IMC in proper clinical context.*

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Applications in the clinical hematology lab

Pre-analytical

☞ Pre-diagnosis
- Case assignment
- Screen slides
- Pre-order stain

Analytical

☞ Automated classification of Hematopoietic cells

☞ Assist in the disease differential diagnosis

Post-analytical

☞ As directed
- NLP for report generation

Ancillary testing (e.g. flow cytometry)

AJCP / Original Article

Augmented Human Intelligence and Automated Diagnosis in Flow Cytometry for Hematologic Malignancies

Am J Clin Pathol 2020;XX:1–9

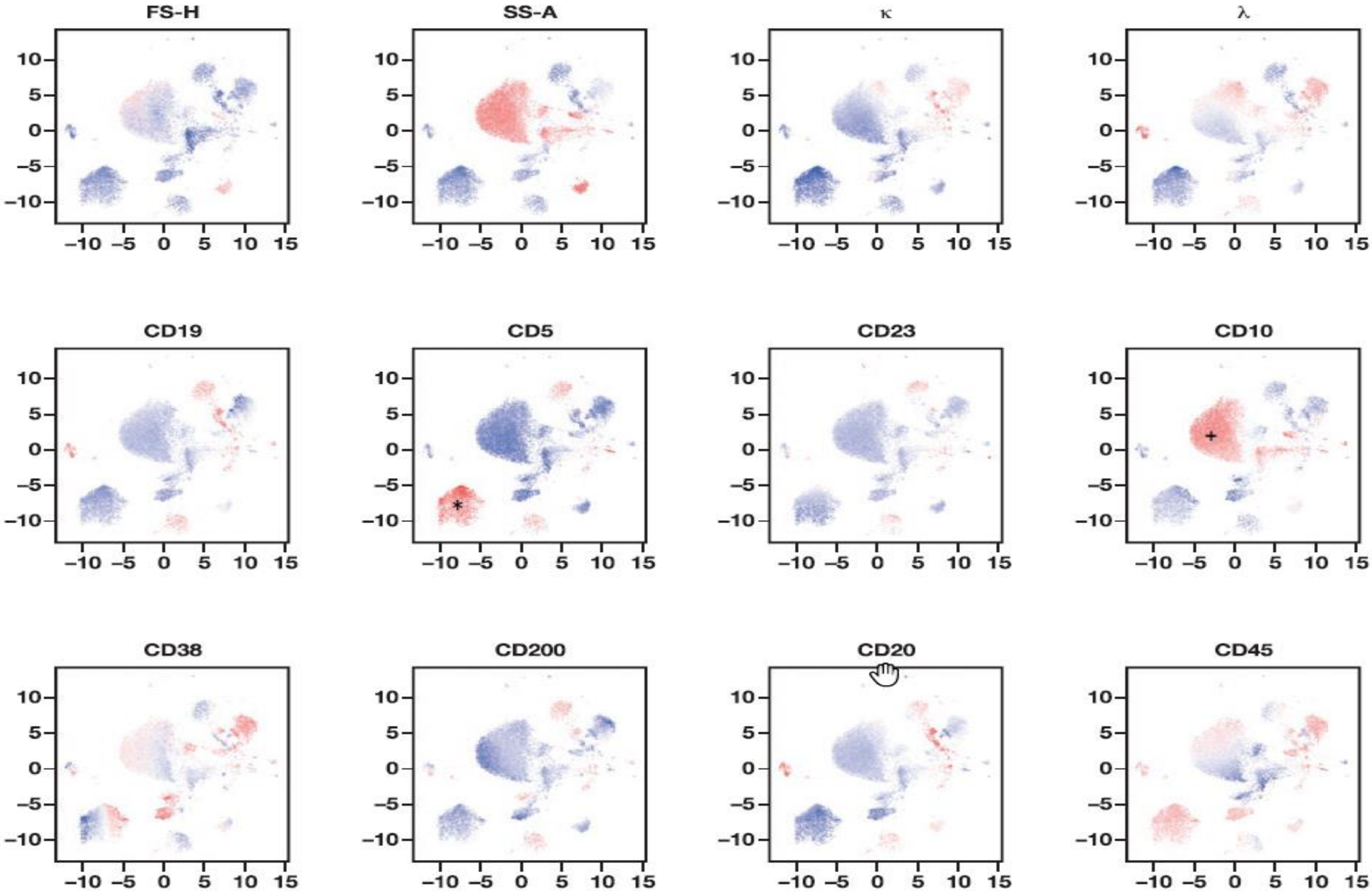
David P. Ng, MD,[1,2] and Lauren M. Zuromski, MS[3]

DOI: 10.1093/AJCP/AQAA166

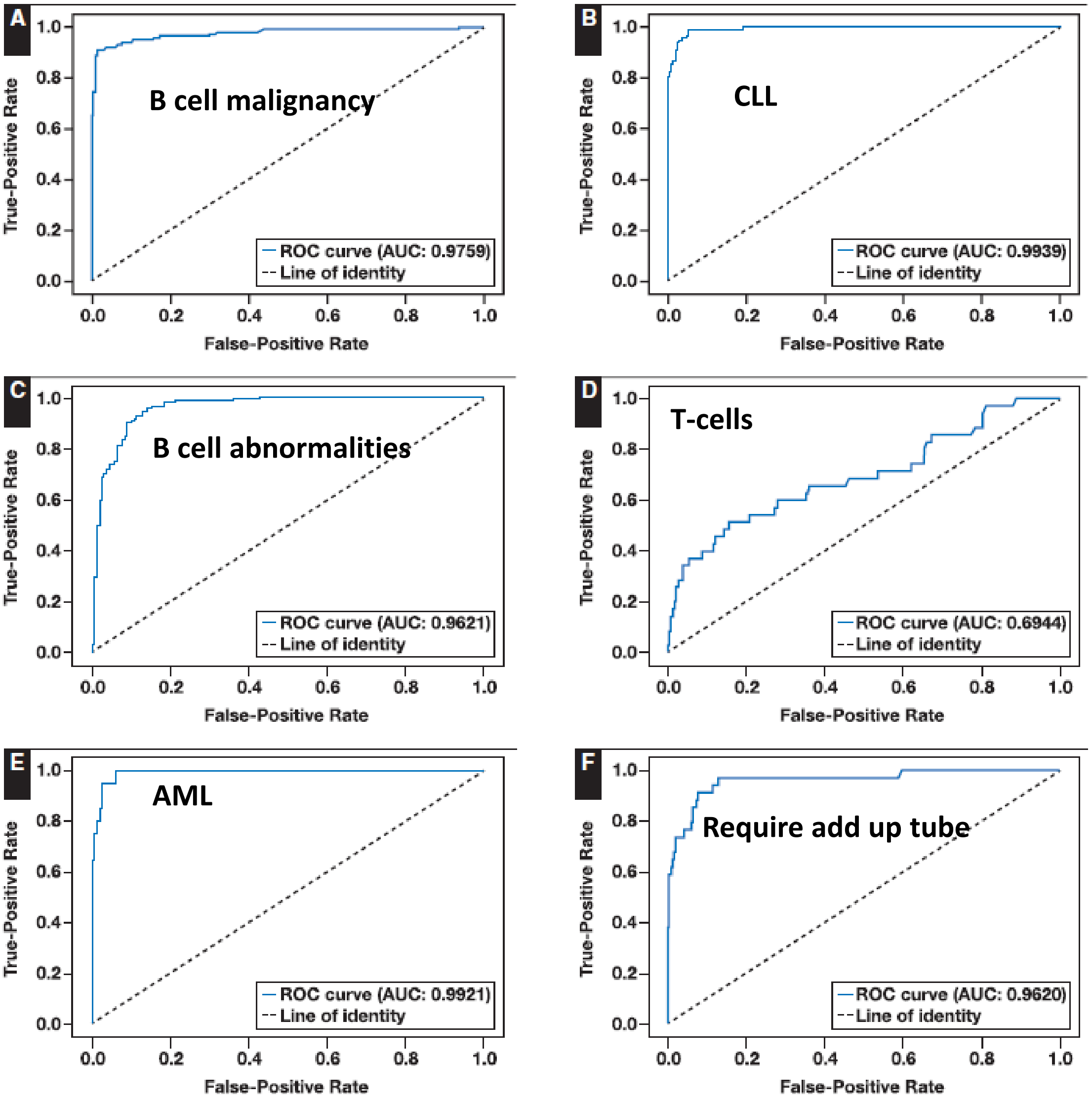
- 3,417 PB cases from 10 color tube
- *feature extraction and dimensionality reduction UMAP on the raw flow cytometry data*
- *followed by random forest classification to classify cases without gating on specific population*

B-Cell Diagnostic Characteristics of Training and Testing Cases

Finding	No. (%) of Training Cases[a] Training%	No. (%) of Testing Cases[a] Testing%
Normal[b]	2,026 (74.13)	516 (76.11)
CD10+ BNHL	9 (0.33)	4 (0.59)
CD5+ BNHL	29 (1.06)	5 (0.74)
CD5–CD10– BNHL	96 (3.51)	31 (4.57)
BNHL (generic)	2 (0.07)	0 (0.00)
B-ALL/LBL	19 (0.70)	2 (0.29)
CLL	491 (17.97)	99 (14.60)
DLBCL	1 (0.04)	0 (0.00)
HCL	16 (0.59)	2 (0.29)
Plasma cell leukemia	22 (0.80)	6 (0.88)
Absence of CD20	38 (1.39)	17 (2.51)
N_BNHL[c]	674 (24.66)	145 (21.39)


FS-H
SS-A
κ
λ
CD19
CD5
CD23
CD10
CD38
CD200
CD20
CD45

Results



Conclusion

- *> 95% accuracy in diagnosing all B-cell malignancies*
- *Higher for specific malignancies for which the panel was designed, e.g. CLL*
- *By adjusting classifier cutoffs, 100% sensitivity could be achieved with an albeit low 14% specificity.*
- *Hypothetically, this allow 11% of the cases to be autoverified without human intervention.*
- *Clinical implementation*
  - *↑ quality control,*
  - *↓ TAT*
  - *↓ staff workloads*

Thank You

Questions