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# Technical development within digital cell morphology

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**Nathan Debunne**  
**Mattias Hofmans**

Evolution



Why Digitize?



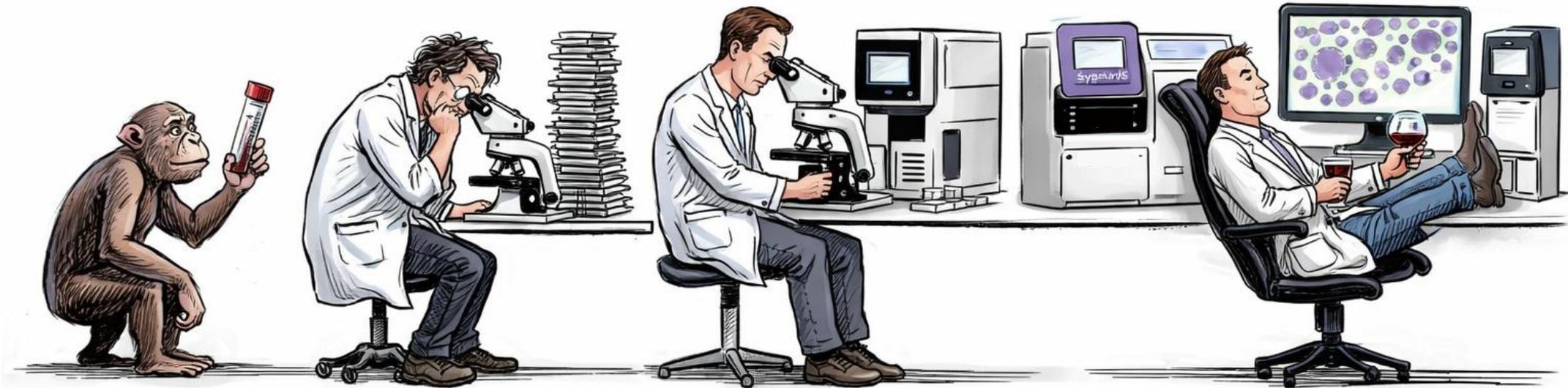
Challenges



Solutions of AI



Lessons Learned



Evolution      Why Digitize?      Challenges      Solutions of AI      Lessons Learned

1960      1970      1980      1990      2000      2010      2020



**1st Generation  
Original Stand-Alone Instruments**

|      |   |
|------|---|
| 1961 | CELLSCAN Leukocyte Pattern Analyzer     |
| 1966 | Cydac Scanning Microscope System        |
| 1976 | Hematrak Automated Differential Counter |
| 1979 | Abbott ADC-500                          |
| 1980 | Coulter diff3                           |

**2nd Generation  
Flow Cytometry-Based Instruments**

|      |                     |
|------|---------------------|
| 1977 | Technicon Hemalog D |
| 1979 | Coulter S-Plus      |
| 1984 | Ortho ELT-8/ds      |
| 1986 | Sysmex CC-800       |

**3rd Generation  
Modern ANN-Based Instruments**

|      |                                |
|------|--------------------------------|
| 2001 | CellaVision DiffMaster Octavia |
| 2004 | CellaVision DM96               |
| 2009 | CellaVision DM1200             |
| 2014 | CellaVision DM9600             |
| 2017 | Sysmex DI-60                   |
| 2020 | CellaVision DC-1               |
| 2020 | Scopio Labs X100/X100HT        |
| 2021 | Mindray MC-80                  |

**Peripheral blood**

Low accuracy  
Low speed

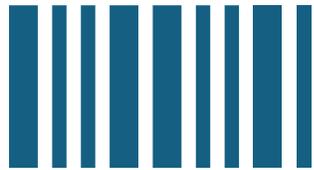
Accurate quantitation  
Faster TAT

Lack of differentiation

**Table 1.** General information of commercially available digital morphology analyzers for peripheral blood smear.

|                     | DM 1200   | DM 9600  | DI-60  | DC-1   | MC-80  | Scopio X100 (X100HT)  | VISION Hema *   |
|---------------------|---|--|--|--|--|---|---|
| Manufacturer        | Cellavision, Lund, Sweden   | Cellavision, Lund, Sweden                                  | Cellavision, Lund, Sweden                                  | Cellavision, Lund, Sweden  | Mindray, Shenzhen, China   | Scopio Labs, Tel Aviv-Yafo, Israel                              | West Medica, Wiener Neudorf, Austria                                  |
| Launched year       | July 2009   | April 2014   | 2013   | February 2019  | September 2021   | April 2020 (May 2022)   | NI  |
| US FDA approval     | Yes   | Yes  | Yes  | Yes  | No   | Yes   | No  |
| Intended use        | WBC differential, characterization of RBC morphology and PLT estimation | WBC differential, presenting overview image of RBC and PLT | WBC differential, presenting overview image of RBC and PLT | WBC differential, characterization of RBC morphology, and PLT estimation | WBC pre-classification, pre-characterization of RBC morphology, and PLT estimation | WBC differential, RBC morphology evaluation, and PLT estimation | WBC identification/pre-classification, RBC analysis, and PLT analysis |
| CE-marked           | Yes   | Yes  | Yes  | Yes  | Yes  | Yes   | Yes   |
| Throughput          | 20 slides/h for 100 WBC + RBC + PLT                                     | 30 slides/h for 100 WBC + RBC + PLT                        | 30 slides/h for 100 WBC + RBC + PLT                        | 10 slides/h for 100 WBC + RBC + PLT                                      | 60 slides/h for 100 WBC + RBC + PLT  | 15 slides/h for 200 WBC differential (40 slides/h)              | NI  |
| Supported stains ** | Romanowsky, RAL, MCDh   | Romanowsky, RAL, MCDh                                      | Romanowsky, RAL, MCDh                                      | Romanowsky, RAL, MCDh  | Romanowsky   | Romanowsky  | Romanowsky  |
| Installation type   | Stand-alone   | Stand-alone  | Integrated with Sysmex XN-series                           | Stand-alone or networked installation                                    | Integrated with Mindray's CAL 6000 and CAL 8000                                    | Stand-alone   | Stand-alone   |

\* VISION Hema is a clinical application module that is applied to the three analyzers (Vision Assist, Vision Pro, and Vision Ultimate). \*\* Romanowsky stains include May-Grünwald Giemsa, Wright-Giemsa, and Wright stains. Abbreviations: FDA, Food and Drug Administration; h, hour; MCDh, micro chromatic detection for hematology; NI, no information; PLT, platelet; RBC, red blood cell; WBC, white blood cell.



**Safety**

- 1) Barcodes
- 2) Electronic identification
- 3) No transportation
- 4) No loss of slides



**Quality**

- 1) More consistency
- 2) Review of same cells
- 3) Second opinion
- 4) Digital archiving



**Efficiency**

- 1) Faster review & TAT
- 2) Sharing with clinicians
- 3) Access to prior slides
- 4) Remote Review

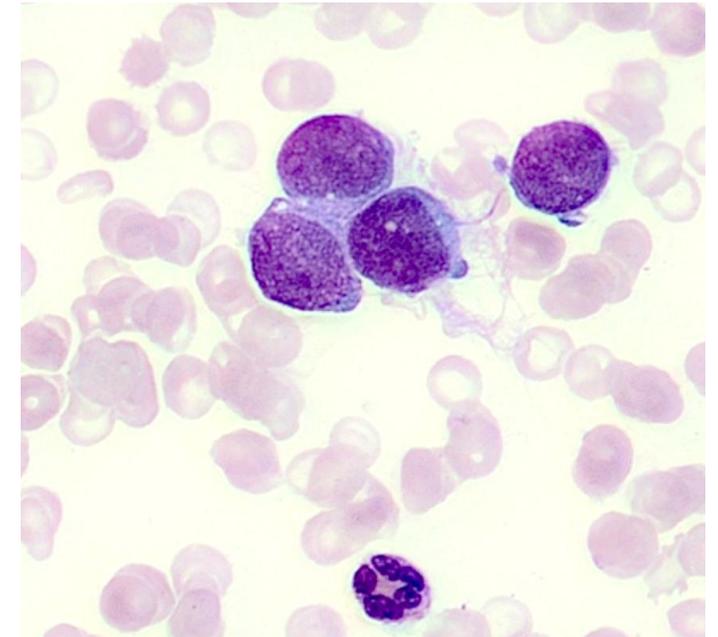


**Education**

- 1) Teaching databases
- 2) Presentations at multidisciplinary team meetings

### Imprecision: Blood vs Bone Marrow

- ✓ **Homogeneity** of the sample → Identification of ROI
- ✓ **Quality** of the sample and stain
- ✓ **Slide distribution error:** rare cells (< 10%)
- ✓ **Inconsistent** cell classification
- ✓ **Statistical error** (the statistical uncertainty ~ cells counted)





Limitations to evaluate abundance (ML, ML, RL)

Limitations to screening for intracellular parasites (eg Leishmania)

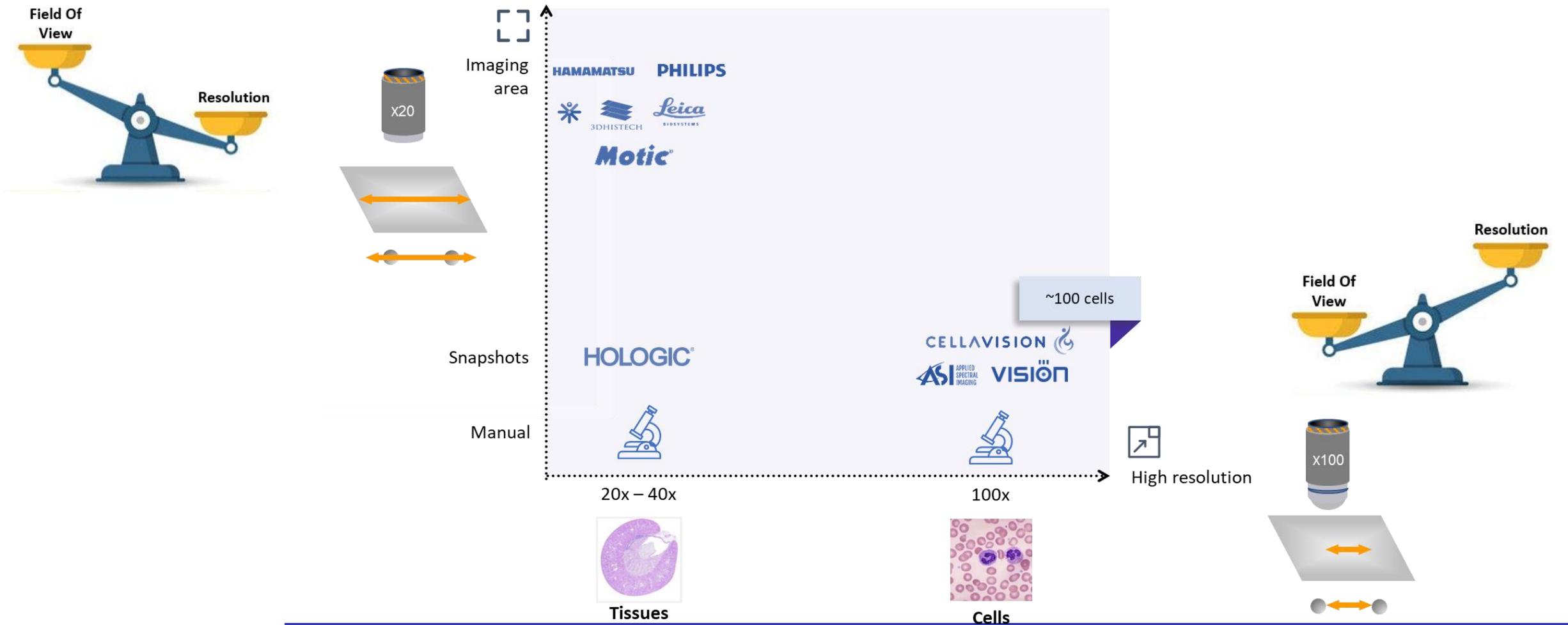
**Cells snapshots and not whole slide imaging**

Poorer performance for rare cell types (Mast cells)

Instrument pre-classification of cells could lead to inaccurate reporting of patient results (ROI)

Evolution      Why Digitize?      **Challenges**      Solutions of AI      Lessons Learned

Imprecision      Type of scanner      Data storage



Evolution

Why Digitize?

Challenges

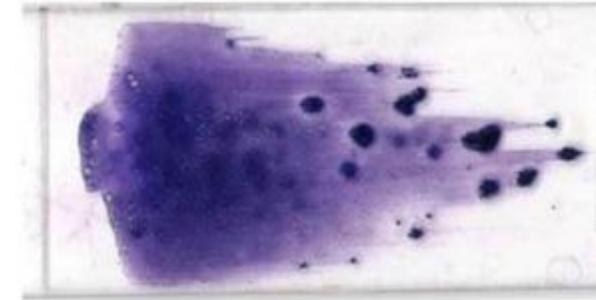
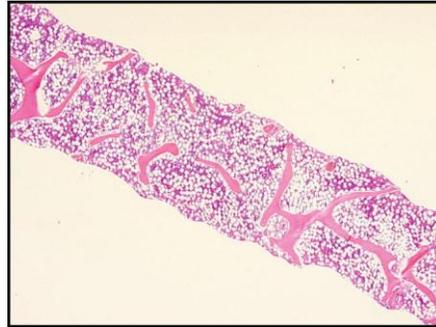
Solutions of AI

Lessons Learned

Imprecision

Type of scanner

Data storage



### H&E tissue section

- Relatively thin (4-5  $\mu\text{m}$  or less)
- Uniform thickness
- Less refraction
- Lower magnification

### Giemsa smear

- Relatively thick (5-10  $\mu\text{m}$ )
- Variable thickness
- More refraction
- Higher magnification

Evolution

Why Digitize?

Challenges

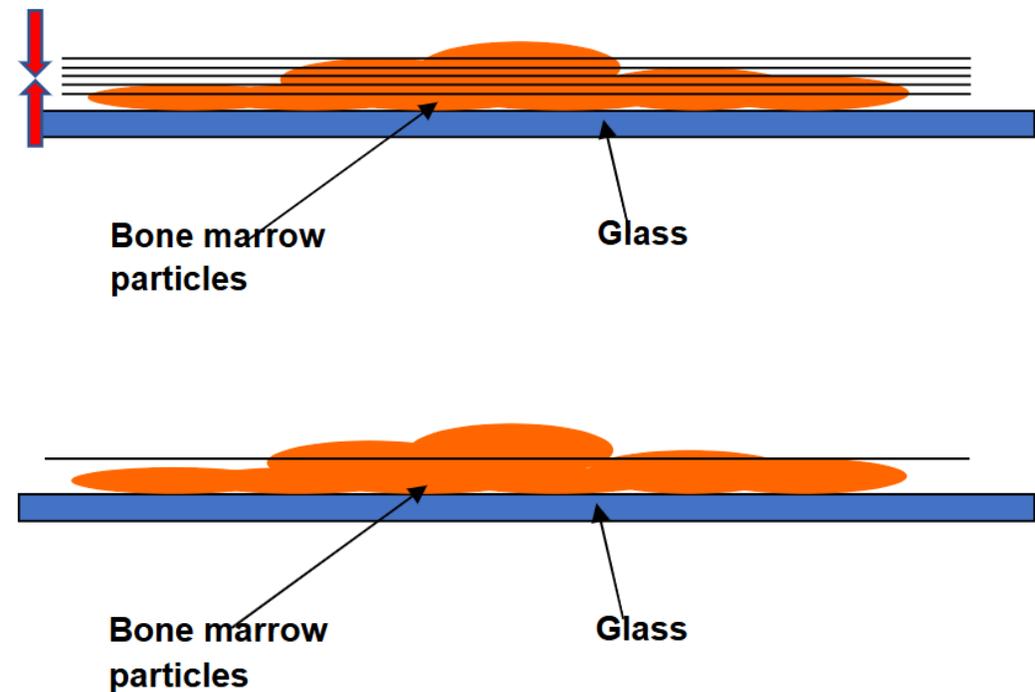
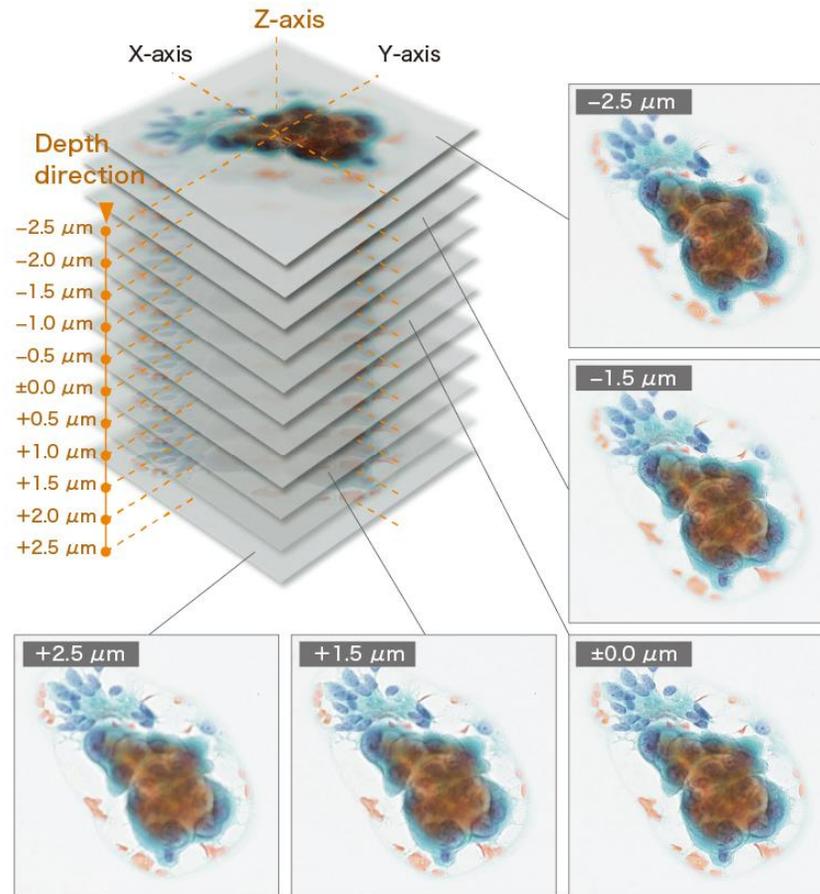
Solutions of AI

Lessons Learned

Imprecision

Type of scanner

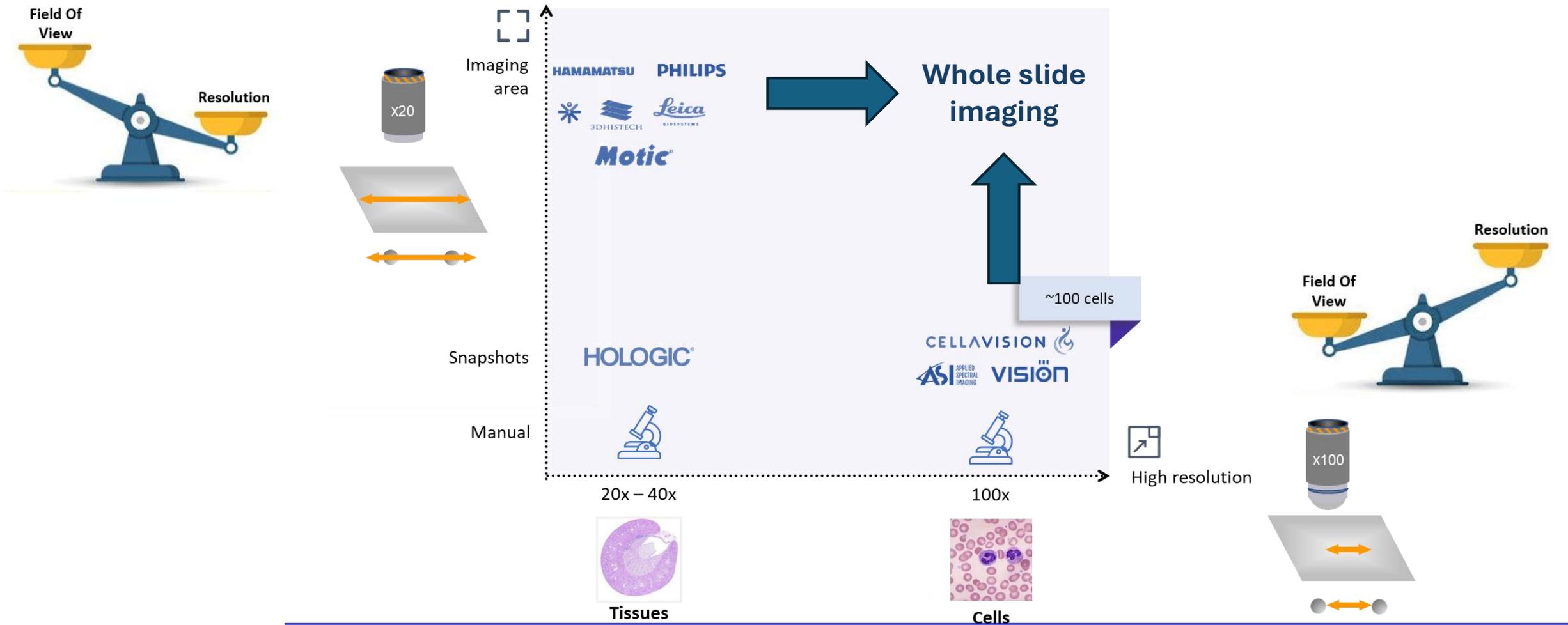
Data storage



Different levels of scanning are shown as 1 image

Evolution      Why Digitize?      **Challenges**      Solutions of AI      Lessons Learned

Imprecision      Type of scanner      Data storage



Evolution

Why Digitize?

Challenges

Solutions of AI

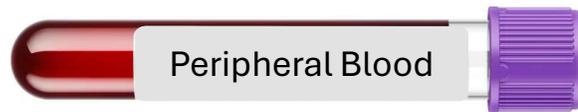
Lessons Learned

Imprecision

Type of scanner

Data storage

|                             | Scopio X100 or X100HT   | Morphogo  |
|-----------------------------|---|---|
| Manufacturer                | Scopio Labs, Tel Aviv-Yafo, Israel  | ZhiWei Information & Technology Co., Ltd Hangzhou, China                    |
| Launched year               | September 2022  | May 2022  |
| US FDA approval             | Yes   | No  |
| Intended use                | Automatically locates and presents images of hematopoietic cells, quality assessment, blast cell, plasma cell, and M:E ratio estimation | No  |
| CE-marked                   | Yes   | Yes   |
| Technology                  | Full-field cell morphology<br>AI-powered DSS <b>Decision support systems</b>  | Whole slide image<br>CNN-based AI system <b>Convolution neural networks</b> |
| Throughput                  | X100: up to 3 slides/h<br>X100HT: up to <b>9 slides/h</b>   | Up to <b>8 slides/h</b> (500 nucleated cells + all megakaryocytes)          |
| Magnification               | Up to 100× (full field)   | Up to 100× (100×: ROI only)   |
| Oiling Method               | X100: manual dispensing<br>X100HT: automatic dispensing   | Automatic dispensing  |
| Discovering ROI             | No need to setup ROI for review,<br>100× Full-field review  | Whole slide review by 40×,<br>ROI review by 100×                            |
| Slide preparation technique | Wedge spread, squash, touch print   | Wedge spread  |



165.000 differentiations



83%  
No review

27.900 smears



10 MB/  
smear

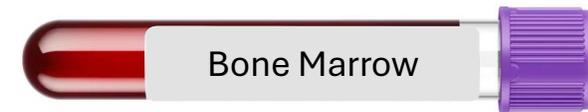
280 GB  
/year



**100/1**

**10/1**

**1/50**



1.500 differentiations



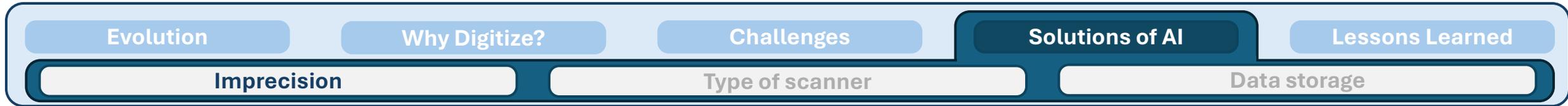
3.000 smears



5 GB/  
smear

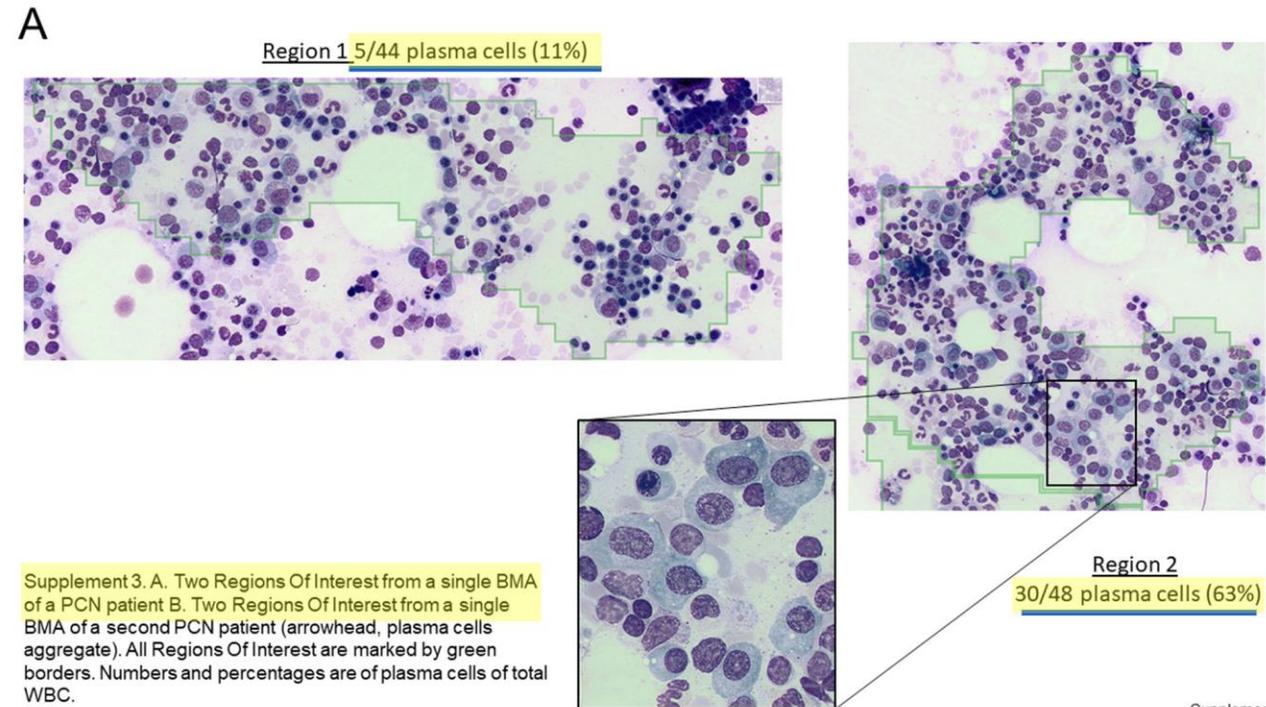
15.000 GB  
/year





**Detection and classification**

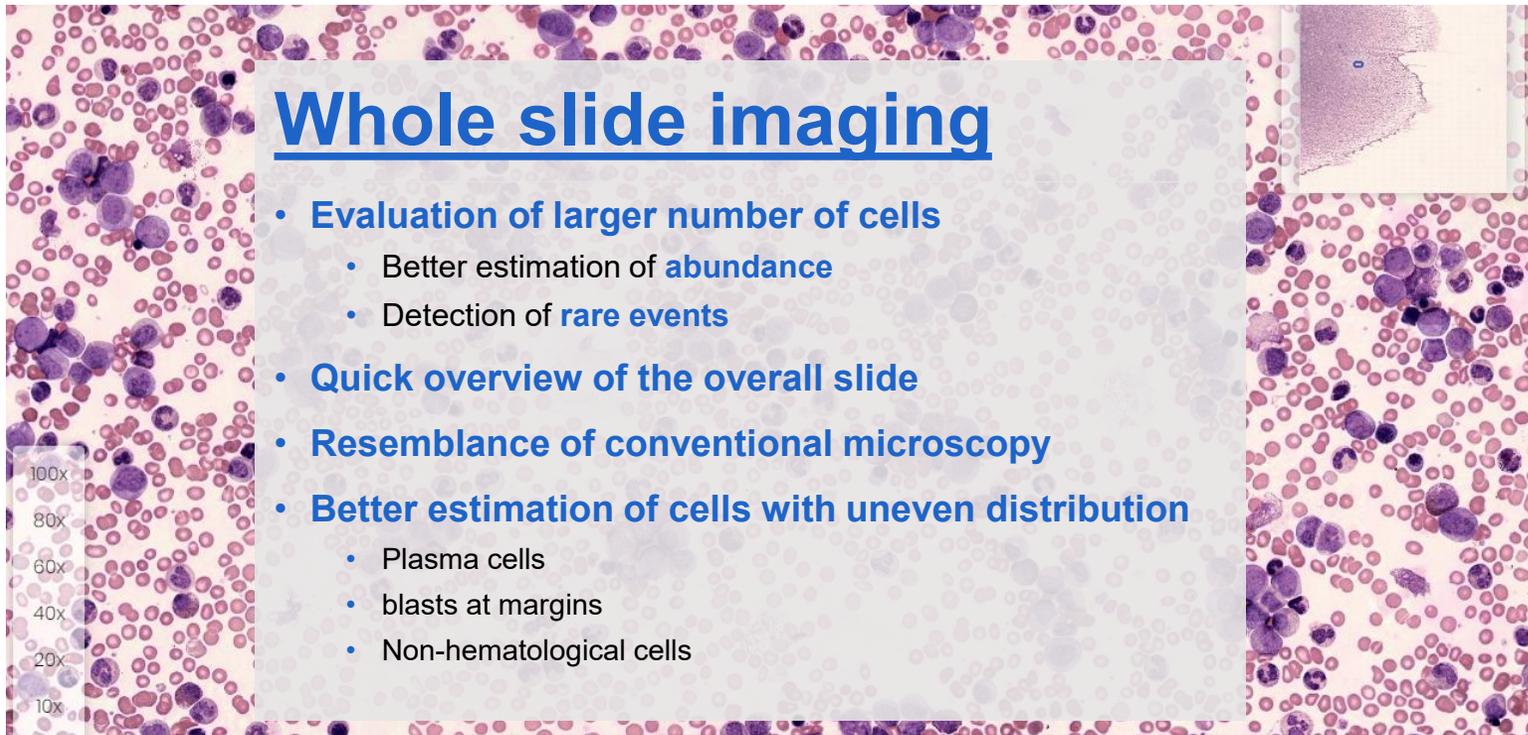
- Identification of thousands of cells
- 
- Pattern recognition
- 
- Identifying regions of interest



Supplement 3

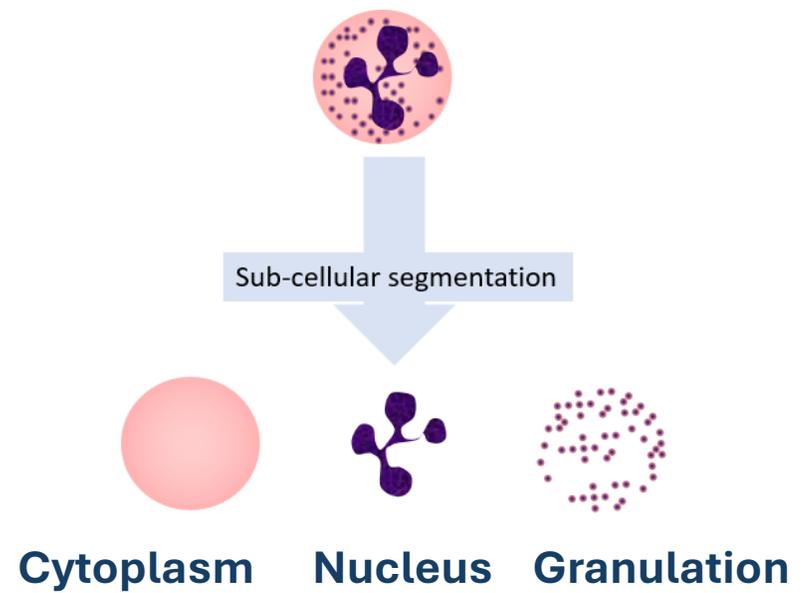


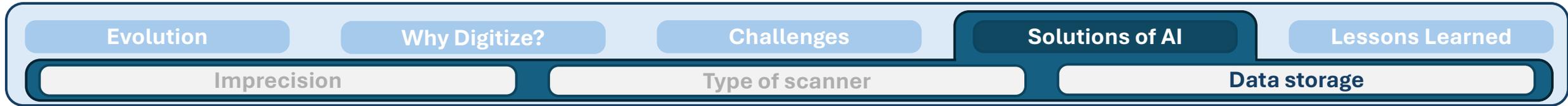
**WSI & Morphometry**



## Whole slide imaging

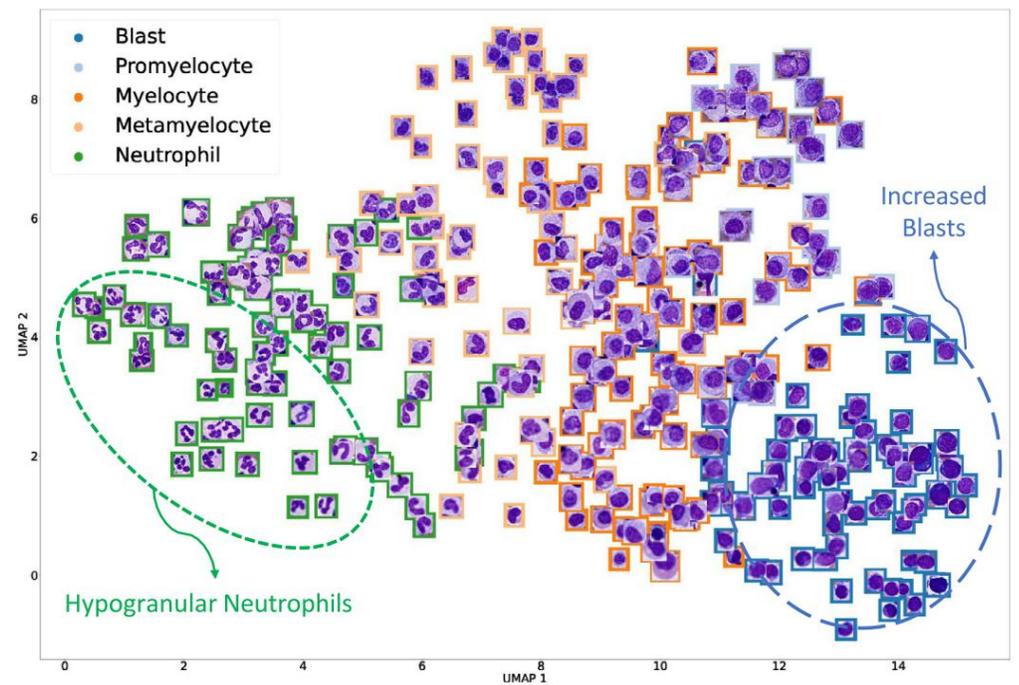
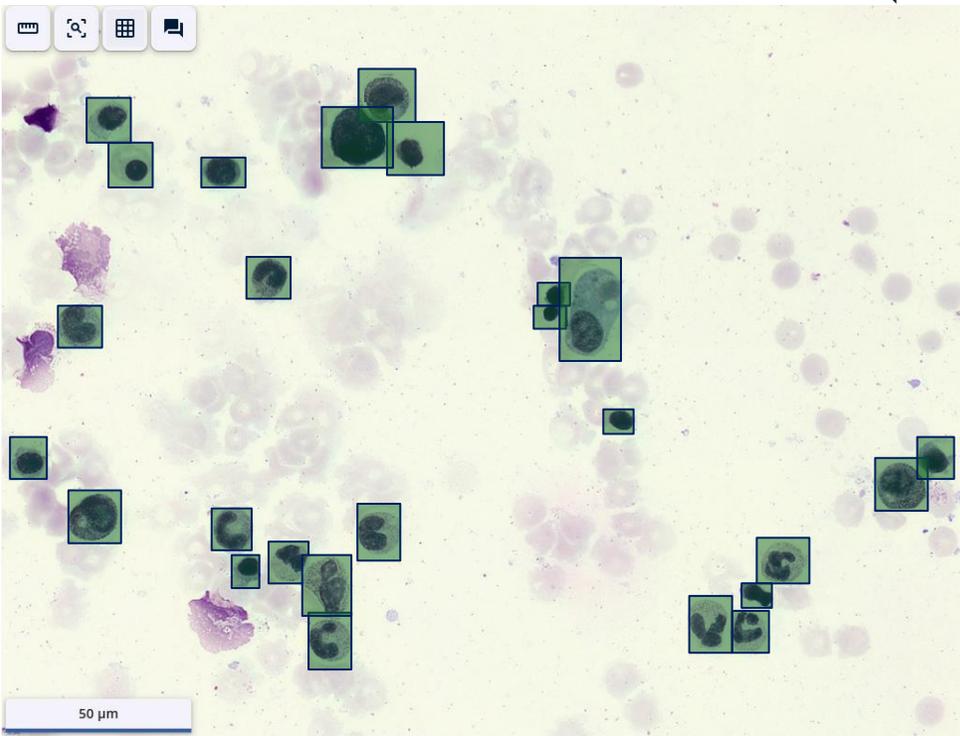
- **Evaluation of larger number of cells**
  - Better estimation of **abundance**
  - Detection of **rare events**
- **Quick overview of the overall slide**
- **Resemblance of conventional microscopy**
- **Better estimation of cells with uneven distribution**
  - Plasma cells
  - blasts at margins
  - Non-hematological cells



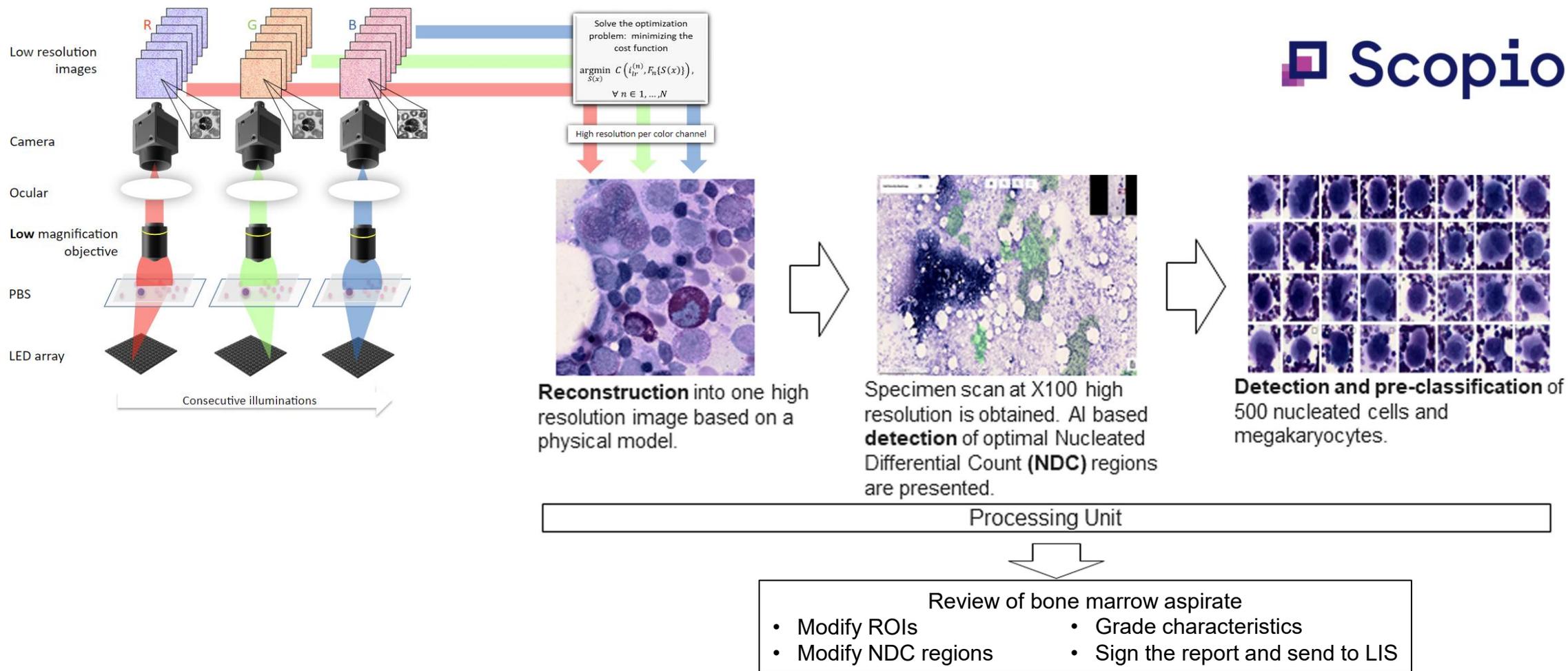


Cell projection plots

Work flow optimization



Evolution      Why Digitize?      Challenges      Solutions of AI      **Lessons Learned**



Evolution

Why Digitize?

Challenges

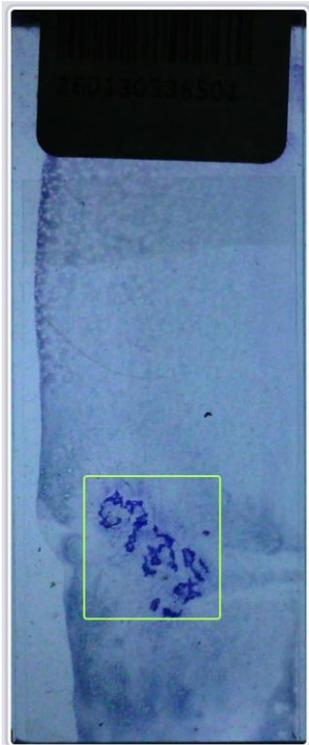
Solutions of AI

Lessons Learned

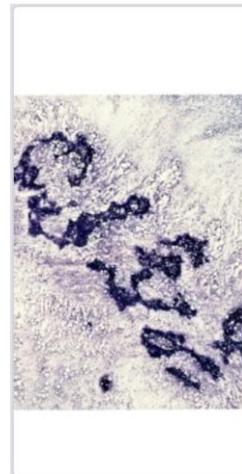
Workflow

Validation

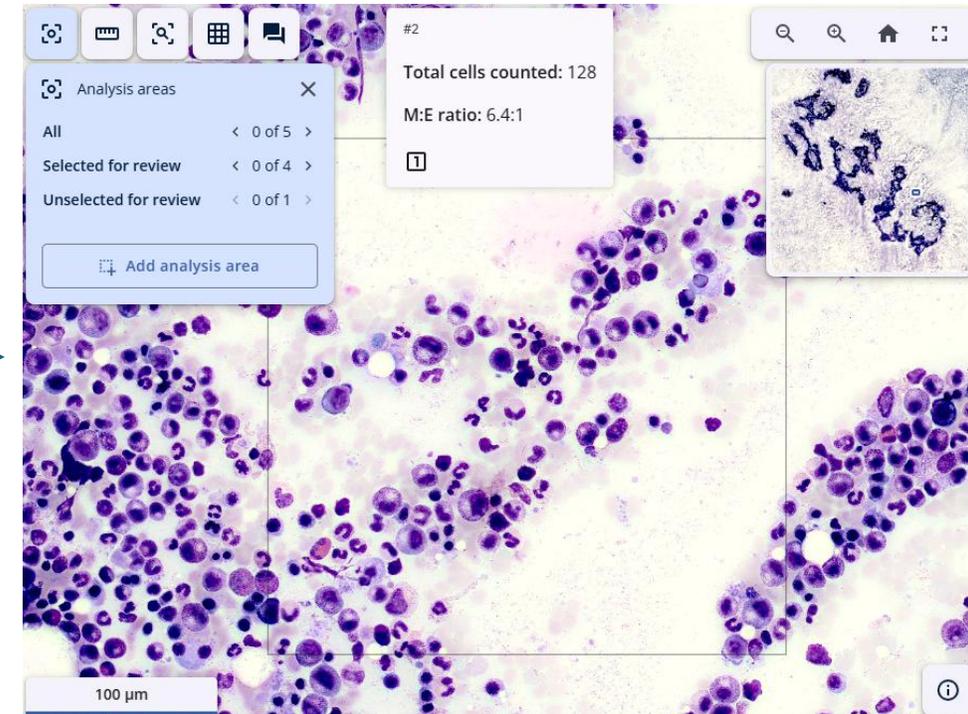
Color complexity



Full-field scanning:  
AI vs MANUEEL?



Analysis area:  
AI vs MANUEEL?



Evolution

Why Digitize?

Challenges

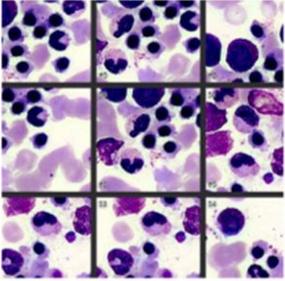
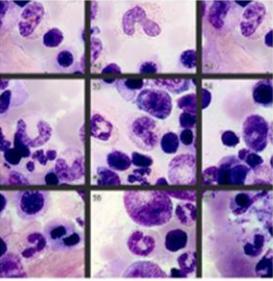
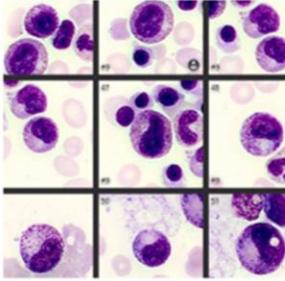
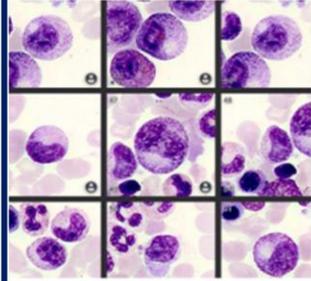
Solutions of AI

Lessons Learned

Workflow

Validation

Color complexity

|                     | Full Field AI<br>Scan Area AI   | Full Field MAN<br>Scan Area AI   | Full Field AI<br>Scan Area MAN   | Full Field MAN<br>Scan Area MAN  |
|---------------------|---|--|--|--|
| <b>FIGURE</b>       | <br>★ ☆ ☆ ☆ ☆ | <br>★ ★ ☆ ☆ ☆ | <br>★ ★ ★ ★ ☆ | <br>★ ★ ★ ★ ★ |
| <b>UNCLASSIFIED</b> | 21%   | 20%  | 0.9%   | 0.7%   |
| <b>TIME</b>         | 21 min  | 10 min   | 20 min   | 11 min   |

Evolution

Why Digitize?

Challenges

Solutions of AI

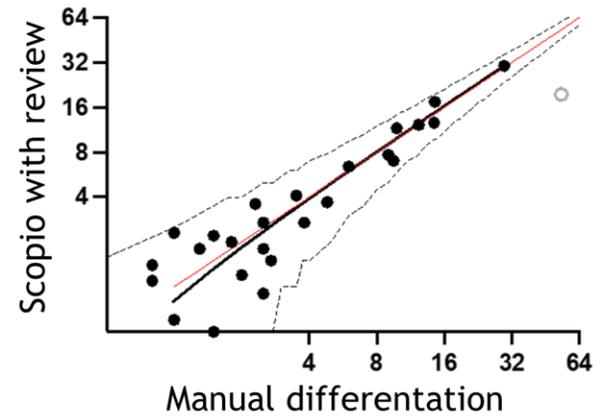
Lessons Learned

Workflow

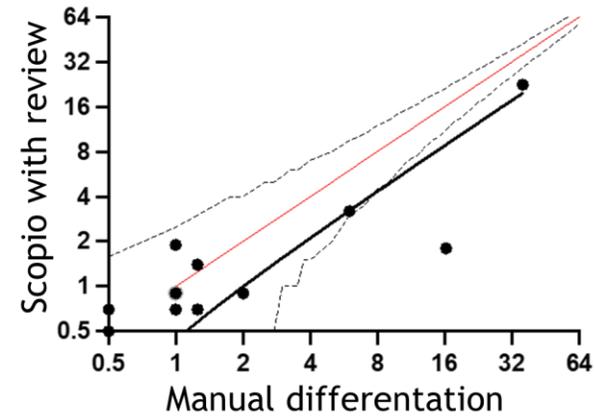
Validation

Color complexity

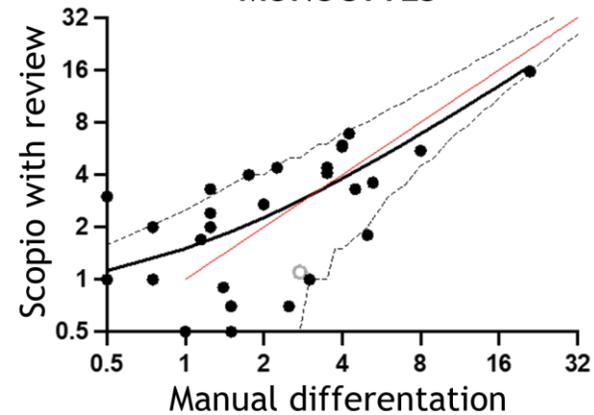
**BLASTS**



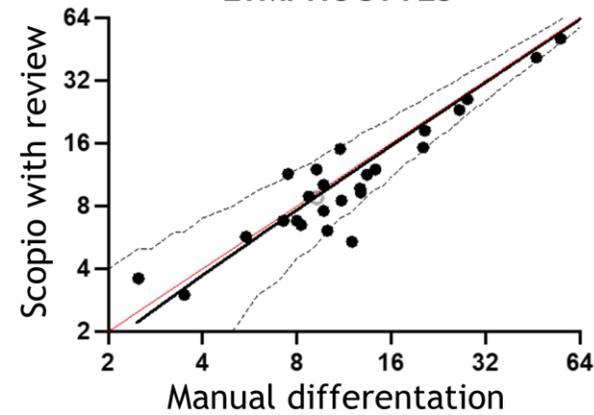
**PLASMACELLS**

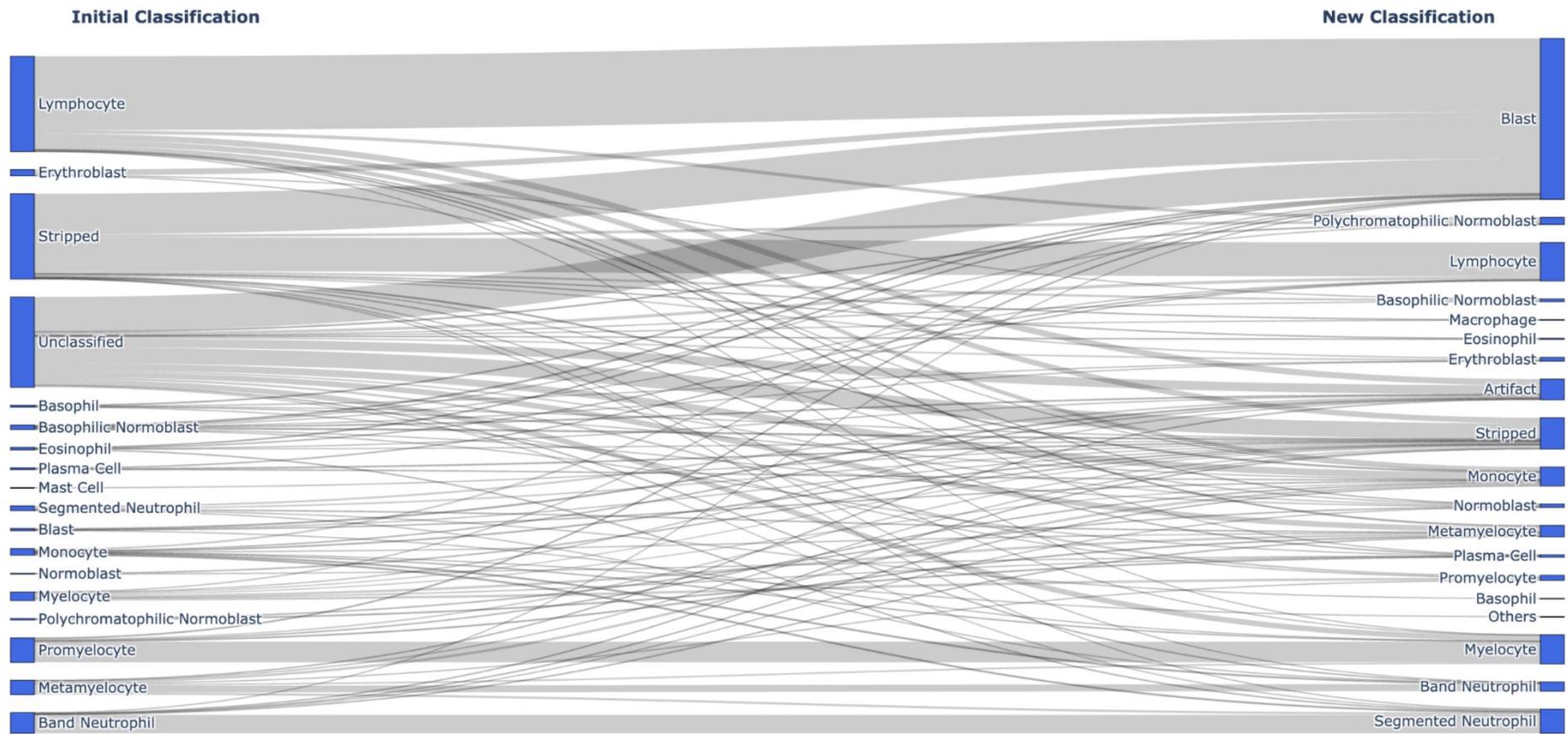


**MONOCYTES**



**LYMPHOCYTES**





Evolution

Why Digitize?

Challenges

Solutions of AI

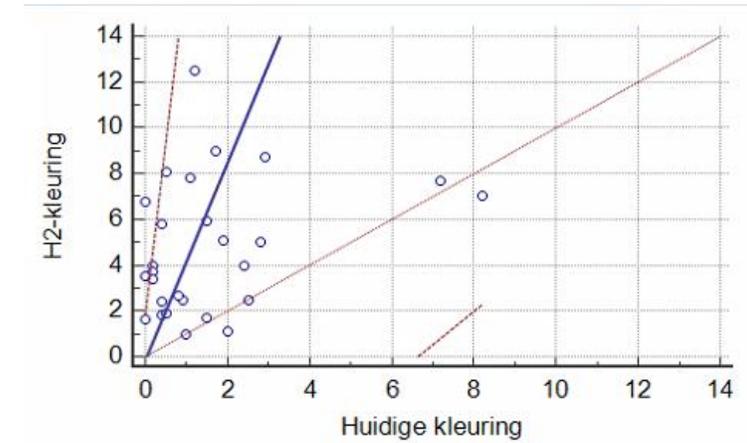
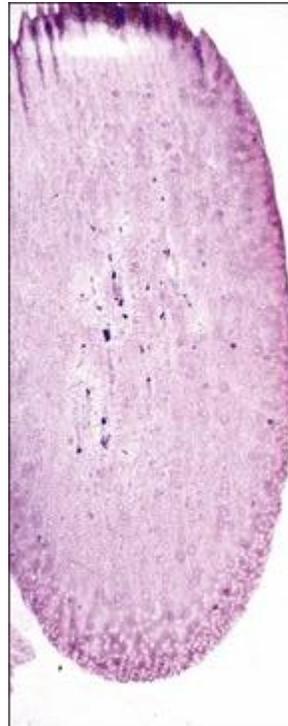
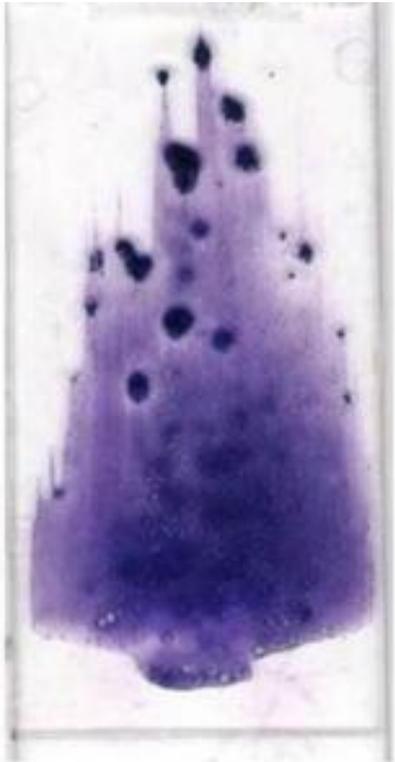
Lessons Learned

Workflow

Validation

Color complexity

## May-Grünwald Giemsa stain



Evolution

Why Digitize?

Challenges

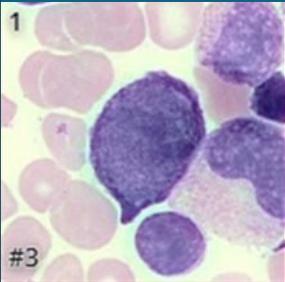
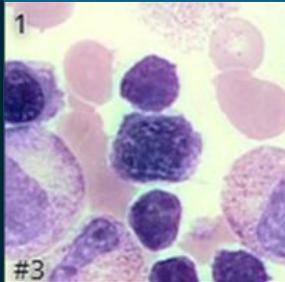
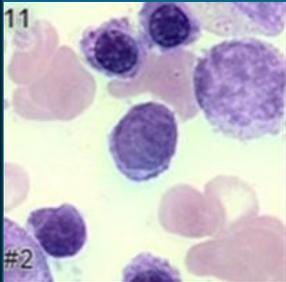
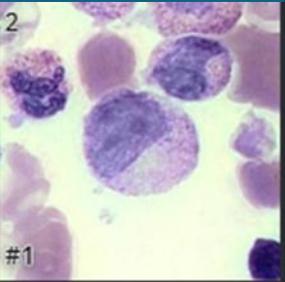
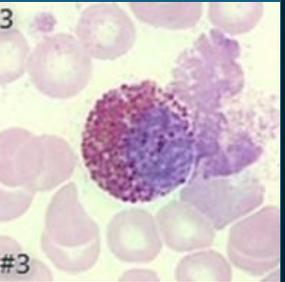
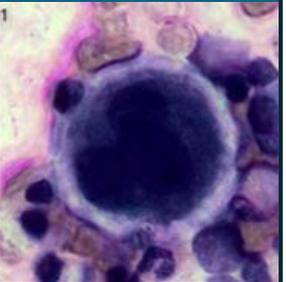
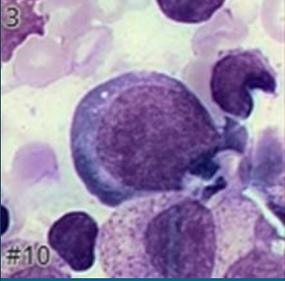
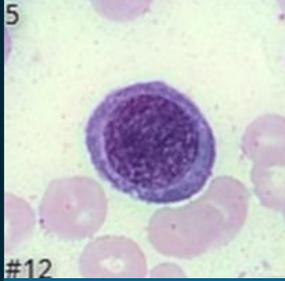
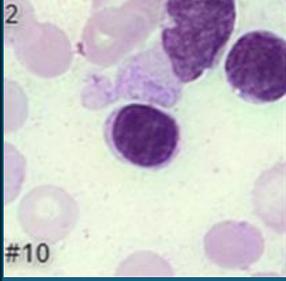
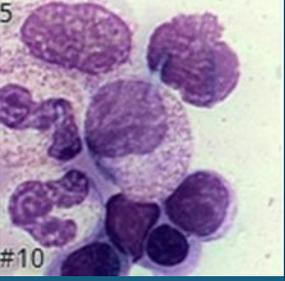
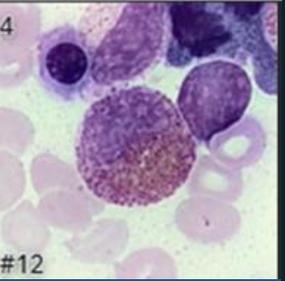
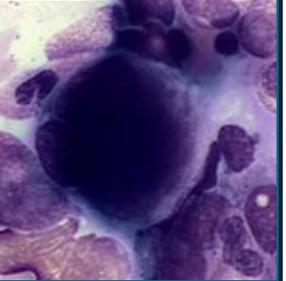
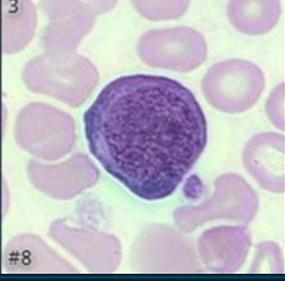
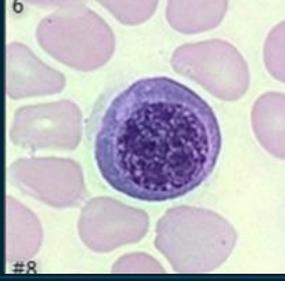
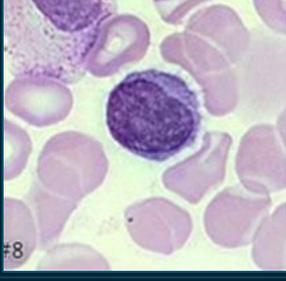
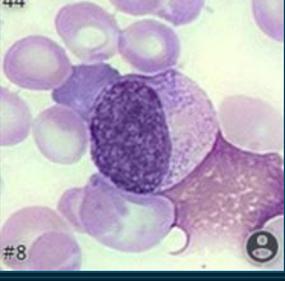
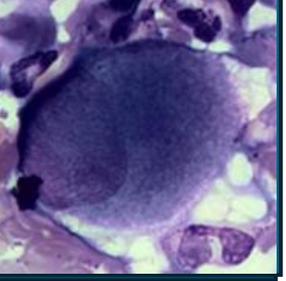
Solutions of AI

Lessons Learned

Workflow

Validation

Color complexity

|            | Erythroblast  | Polychromatic normoblast   | Lymphocyte  | Myelocyte  | Eosinophil  | Megakaryocyt   |
|------------|---|--|---|--|---|--|
| Protocol 1 |  <p>1<br/>#3</p>   |  <p>1<br/>#3</p>   |  <p>11<br/>#2</p>  |  <p>2<br/>#1</p>    |  <p>3<br/>#3</p>   |  <p>1</p> |
| Protocol 2 |  <p>3<br/>#10</p> |  <p>5<br/>#12</p> |  <p>2<br/>#10</p> |  <p>5<br/>#10</p>  |  <p>4<br/>#12</p> |          |
| Protocol 3 |  <p>3<br/>#8</p> |  <p>6<br/>#8</p> |  <p>#8</p>       |  <p>44<br/>#8</p> |  <p>1<br/>#8</p> |         |

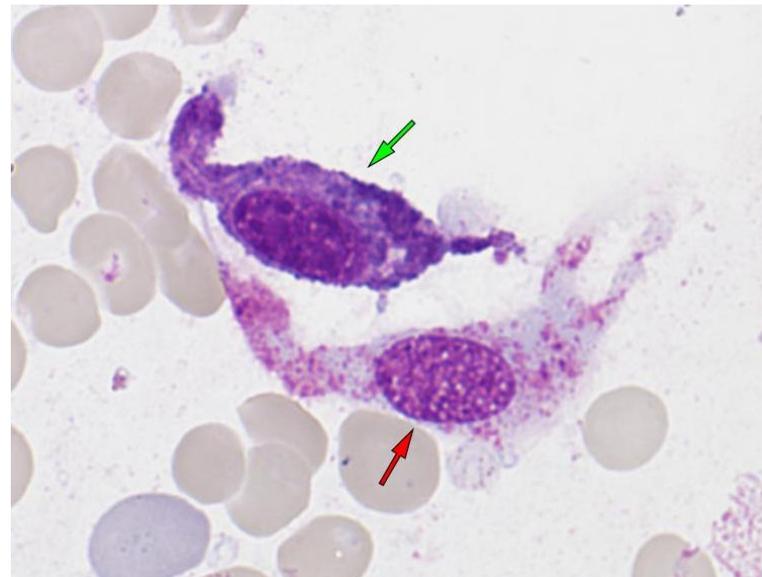
Future perspectives

## Rare cell types

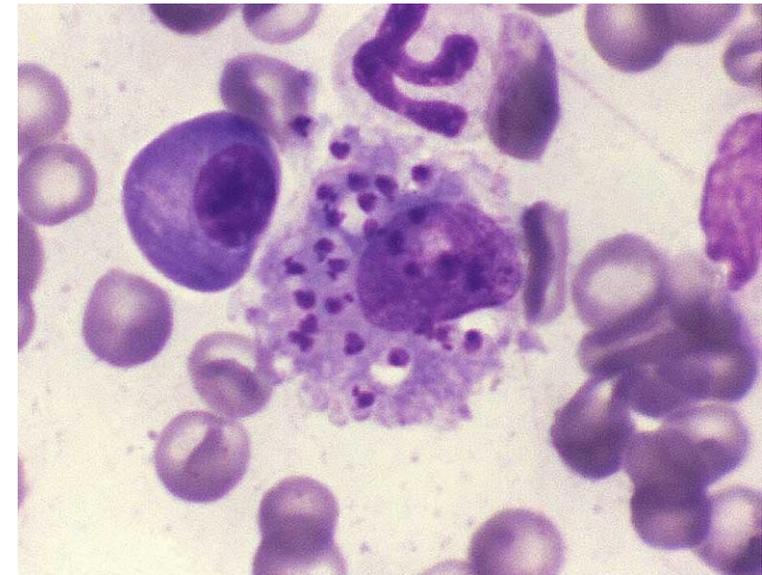
APL



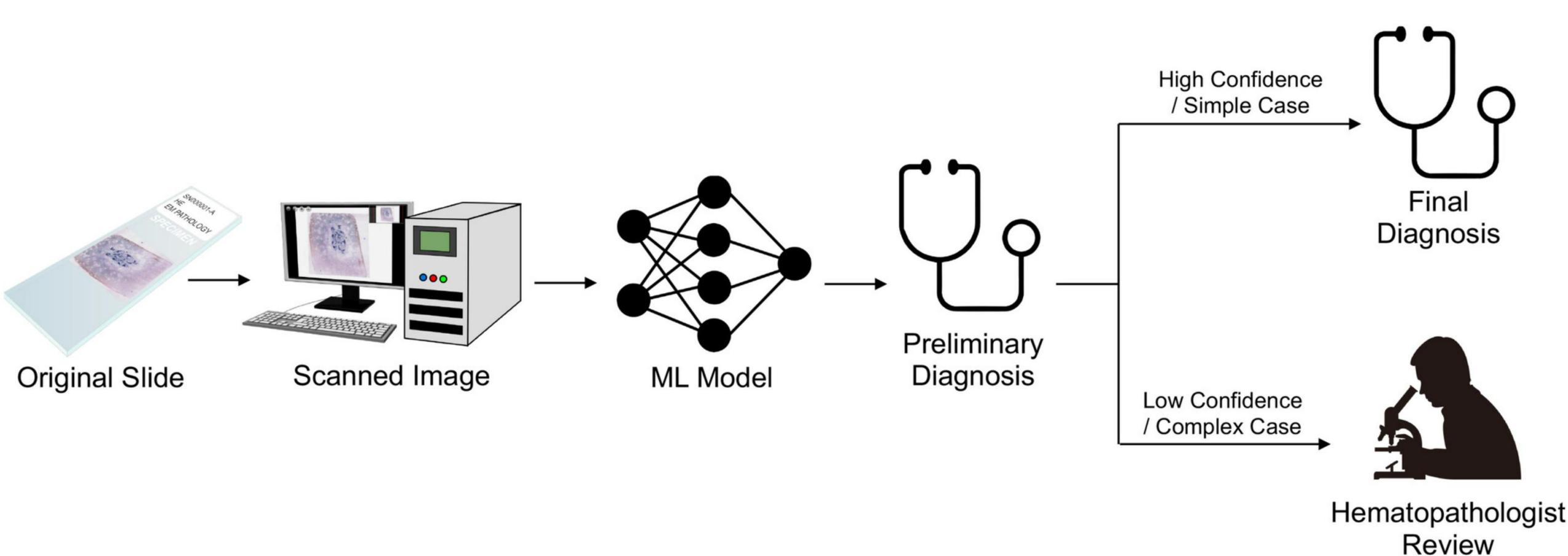
Mast cells



Leishmania



## Future perspectives



# Thank you!



MATTIAS HOFMANS, PhD

Klinisch bioloog

Laboratorium voor klinische chemie en hematologie UZ Gent



ANNEMIE DE CRAEMER

Medisch laboratoriumtechnoloog

Laboratorium voor klinische chemie en hematologie UZ Gent

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Universitair Ziekenhuis Gent  
C. Heymanslaan 10 | B 9000 Gent  
T +32 (0)9 332 21 11  
E [info@uzgent.be](mailto:info@uzgent.be)

[www.uzgent.be](http://www.uzgent.be)

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