# Transforming Pathology Practice: Must-Know Technological Innovations in Hematopathology and Hematology

**Robert (Bob) Ohgami, MD, PhD, FCAP**

Professor, University of Utah and Vice-President of Research and Innovation, ARUP

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# Host

Madhu P. Menon, MD, PhD, FCAP

Associate Professor (Clinical)
*University of Utah School of Medicine*
Section Chief, Hematopathology
*ARUP Laboratories*

# Presenter

Robert S. Ohgami, MD, PhD, FCAP

Professor
*University of Utah School of Medicine*
Vice President
*ARUP Institute for Research and Innovation in Diagnostic and Precision Medicine™*
Medical Director, Hematopathology
*ARUP Laboratories*

# Panelists

Peng Li, MD, PhD

Associate Professor (Clinical)
*University of Utah School of Medicine*
Medical Director, Hematopathology
*ARUP Laboratories*

Jay L. Patel, MD, MBA

Professor (Clinical)
*University of Utah School of Medicine*
Vice President, PharmaDx and Clinical Trials
*ARUP Laboratories*

# Goals:

- Understand and learn about newer and emerging technologies in hematopathology and hematology

- Learn about the role of Applied Artificial Intelligence (AAI) and Generative AI (GenAI) in enhancing diagnostic precision and streamlining workflows

# Outline

- Introduction
  - » Brief history of hematopathology classifications
  - » Artificial intelligence
- Body
  - » Flow Cytometry
  - » Genetics and Genomics
  - » Digital Pathology
  - » Cytogenetics
  - » Generative Artificial Intelligence
- Conclusions
- The Future

# A brief history of hematopathology classification

- 1860s: Virchow and C
  - » Lymphosarcoma
- 1920s: Oberling, Brill
  - » "Reticulum cell sa
- 1950s and 1960s: Ra
  - » Architecture and c
- 1974-1978: Lukes an formulation
  - » Architecture, cell s
- 1994: Revised Europe
  - » Architecture, cell s
- 2001-2017: WHO clas
  - » Architecture, cell s
- 2022: WHO classifica
  - » Architecture, cell s

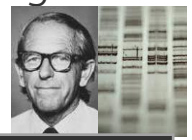
1950s: DNA discovered; Humans have 46 chromosomes

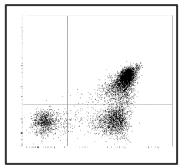
1960s: 1 color flow cytometry; simple IHC

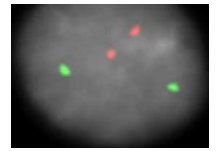


1970s: Sanger sequencing; Q&C and G banding

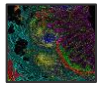
Improved IHC; Immuno-EM







**Technology Drives Medicine**



Roche 454

2010s: Imaging mass cytometry; 30+ color flow cytometry, Nanopore, Pacbio "single molecular real-time" sequencer; Metagenomics

*2020s: Artificial Intelligence and machine learning*

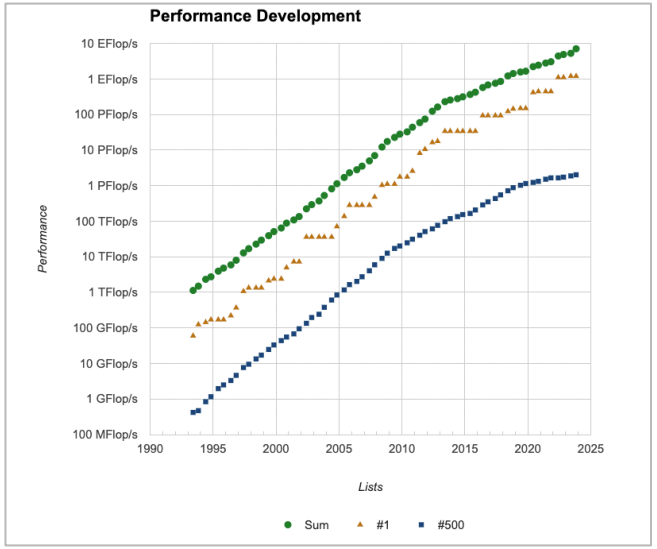
Norton AJ. Classification of non-Hodgkin's lymphomas. Ballieres Clin Haematol. 1996;9:641–52. doi: 10.1016/s0950-3536(96)80046-1. [PubMed] [CrossRef] [Google Scholar] 5. van Besien K, Schouten H. Follicular lymphoma: A historical review. Leuk Lymphoma. 2007;48:232–43. doi: 10.1080/10428190601059746. [PubMed] [CrossRef] [Google Scholar] Lukes RJ, Collins RD. A functional approach to the classification of malignant lymphoma. Recent Results Cancer Res. 1974;46:18–30. doi: 10.1007/978-3-642-80829-6_4. [CrossRef] [Google Scholar] 8. Lukes RJ, Collins RD. Immunologic characterization of human malignant lymphomas. Cancer. 1974;34.1488–503. doi: 10.1002/1097-0142(197410)34:8+<1488::AID-CNCR2820340822>3.0.CO;2-
Updated Kiel classification for lymphomas.Stansfeld AG, Diebold J, Noel H, Kapanci Y, Rilke F, Kelényi G, Sundstrom C, Lennert K, van Unnik JA, Mioduszewska O Lancet. 1988 Feb 6; 1(8580):292-3.
Bennett MH, Farrer-Brown G, Henry K, Jaliffe AM, Gerard-Marchant R, Hamlin I, et al. Classification of non-Hodgkin's lymphomas. Lancet. 1974:405–6. doi: 10.1016/S0140-6736(74)91786-3.
National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage - The Non-Hodgkin's Lymphoma Pathologic Classification Project. Cancer. 1982;49:2112–35.

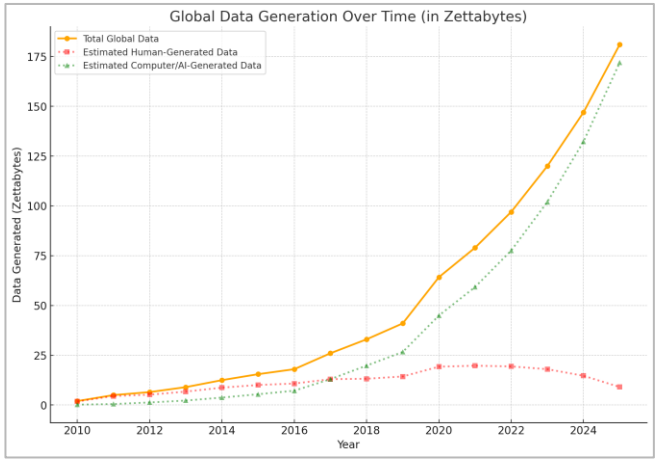
# History of Artificial Intelligence

- 1970's — Knowledge based approaches
- 1974-1980 — AI winter #1
- 1980-1988 — Expert systems and decision trees become popular
- 1986 — Neural Networks become popular
- 1988-1993 — AI winter #2
- 1990's — Support vector machines and random forest methods
- 1997 — IBM's deep blue defeats Kasparov
- 2000-2015 — Advancements in NLP (translators) and computer vision (image classifiers)
- 2015 — AlphaGo defeats a human Go player
- 2018 — BERT model revolutionizes NLP
- 2020's — Transformers - Generative Pretrained Transformers (GPTs) dominate, GPT3 from OpenAI
- 2021+ — Diffusion models for high quality images

Technology

Increasing
- Compute Power
- Data



# Safe bet… follow technology

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- Introduction
  - » Technology and Innovation in lymphoid and myeloid neoplasms
  - » Artificial intelligence
- Body
  - » Flow Cytometry
  - » Genetics and Genomics
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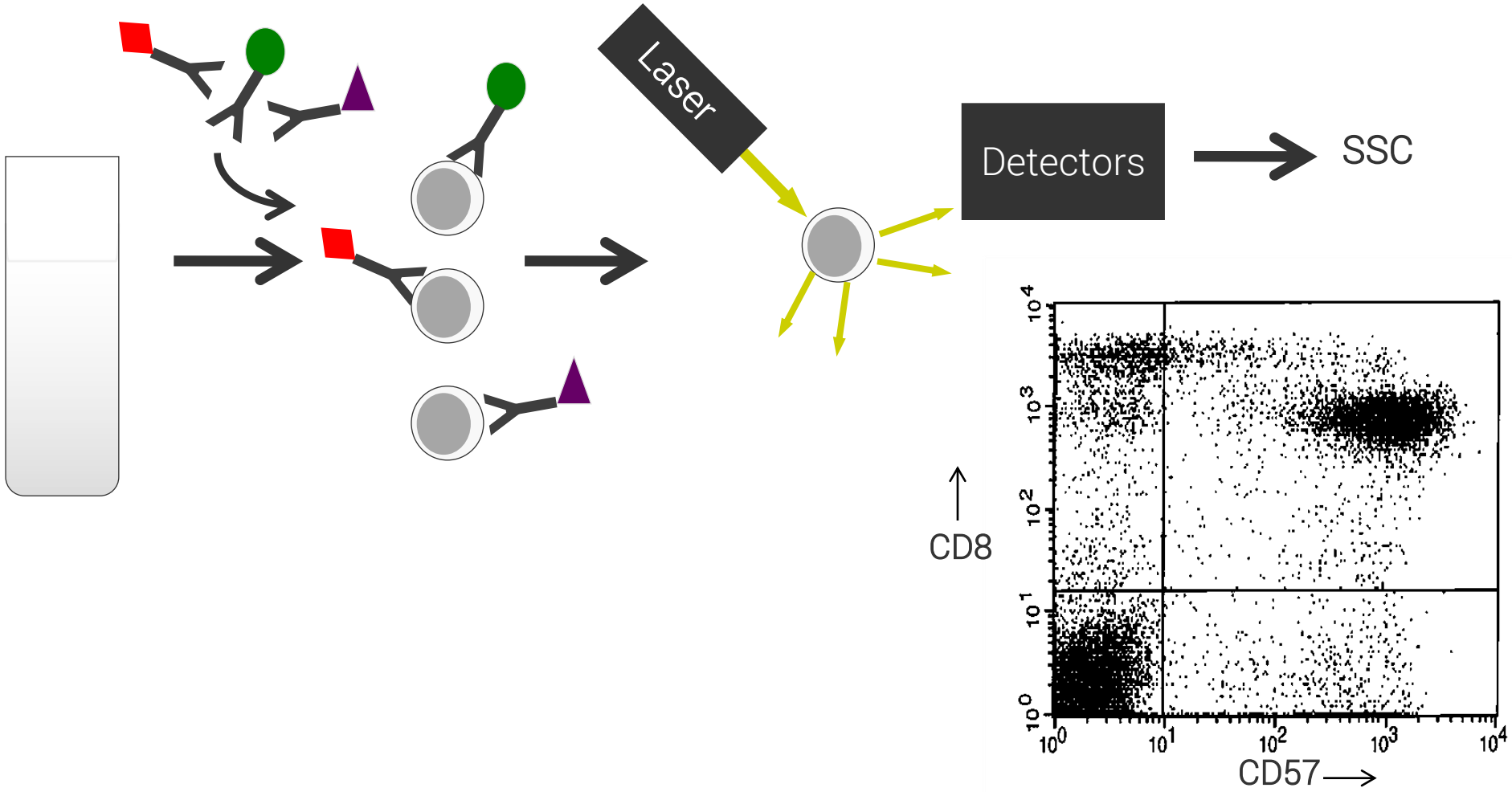
# Flow cytometry

# "Classic" Fluorescence Flow Cytometry

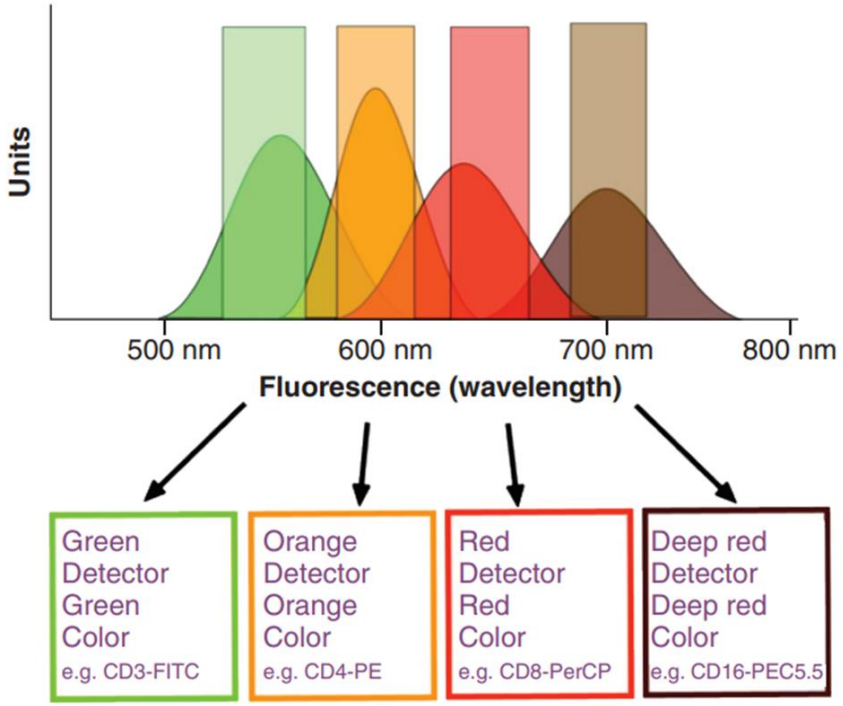


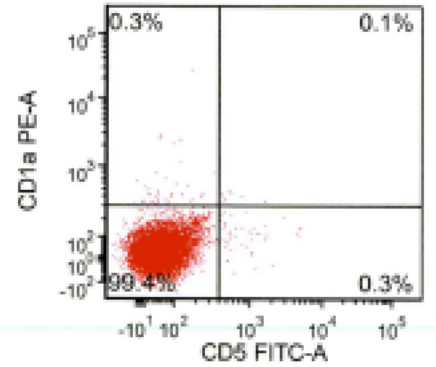
# "Classic" Flow Cytometry

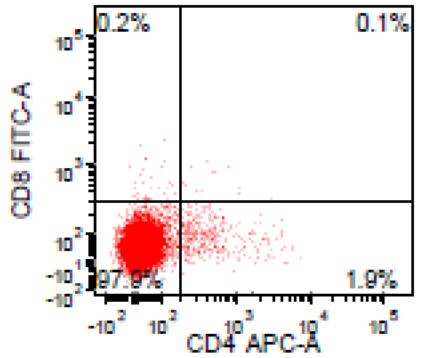
- Once there was one…
- Then two…
- Then four…
- Then ten…

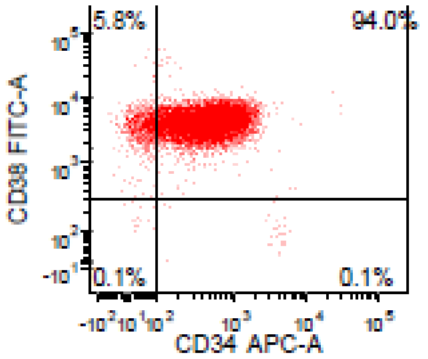
Compensation

- Correcting for fluorescence spillover
- Removing signal
- Requires solving a system of equations
- Creating a spillover matrix, apply it to the data



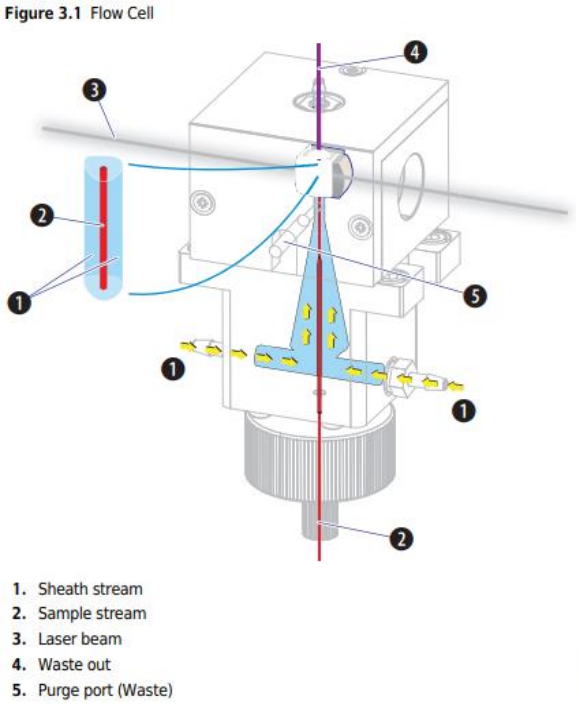



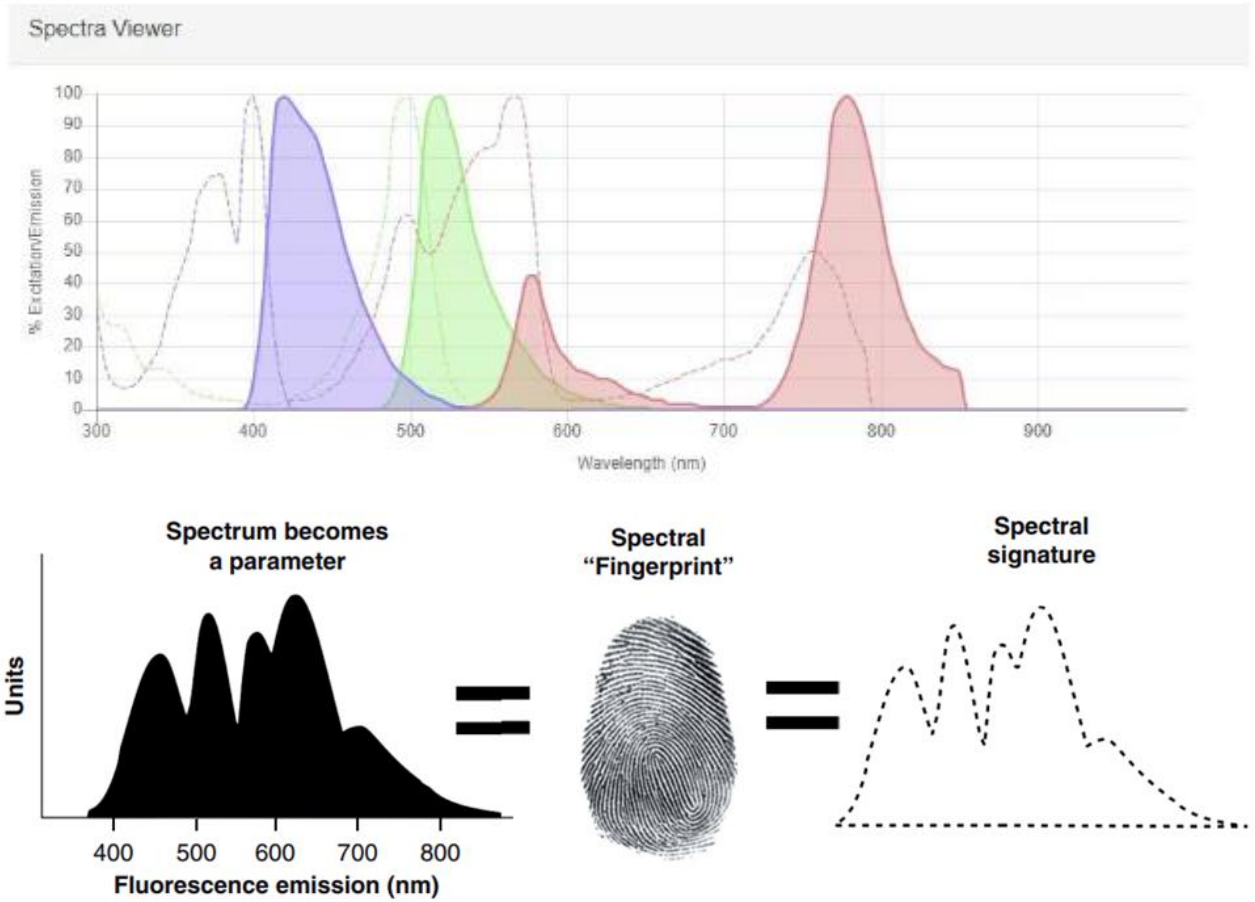

*https://www.labome.com/method/Flow-Cytometry-A-Survey-and-the-Basics.html*

*Robinson JP. Flow cytometry: past and future. Biotechniques. 2022 Apr;72(4):159-169. doi: 10.2144/btn-2022-0005. Epub 2022 Apr 4. PMID: 35369735.*

# What about newer flow cytometry technologies?

# Spectral Flow Cytometry

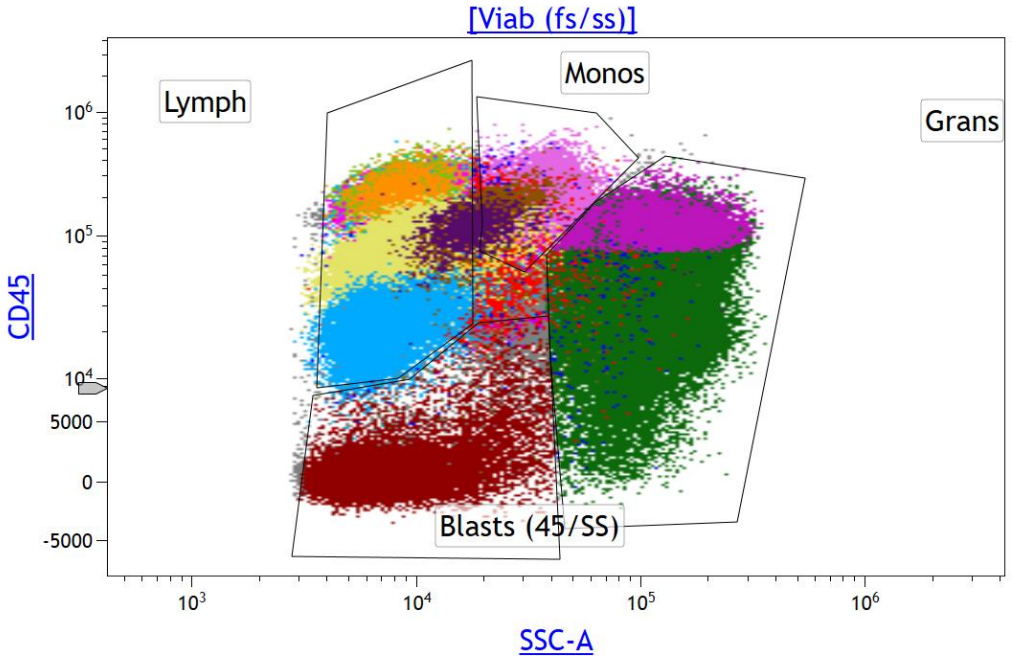


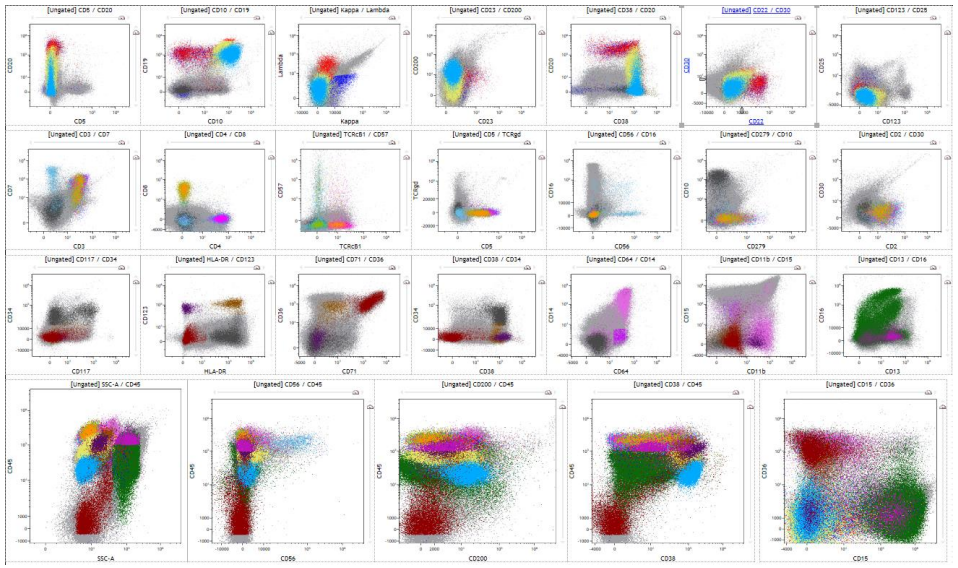




*40 colors in one tube*

*https://www.novusbio.com/antibody-news/conventional-flow-cytometry-vs-spectral-flow-cytometry*

# Spectral Flow Cytometry



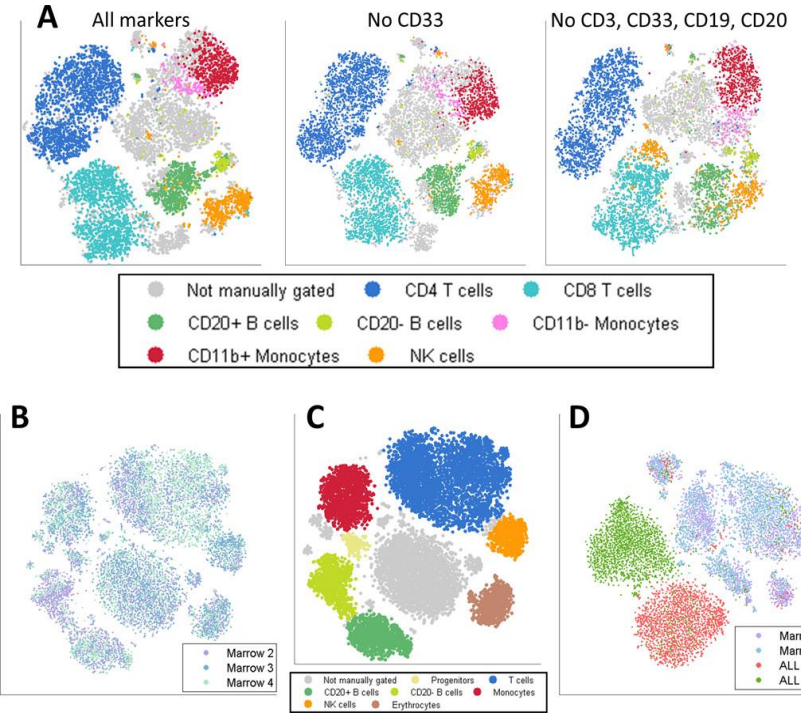
*40 colors in one tube*

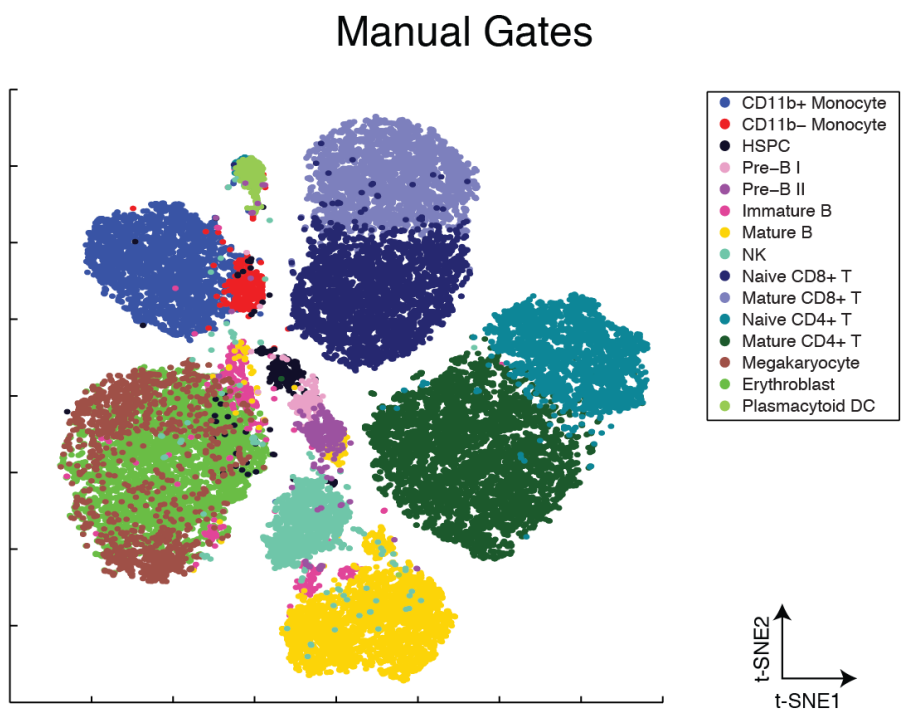
- K
- Mast Cells
- Eos?
- Erythroids
- Basophils
- PDCs
- Stage 1 HG
- Stage 2 HG
- TRBC1+/8+
- TRBC1/8-
- TRBC1+/4+
- TRBC1-/4+
- g/d T cells
- NK cell 2
- NK cells 7
- Plasma Cells
- CD34+ Blasts
- Lambda 20/22
- Kappa 20/22
- Lambda 19
- Kappa 19
- Lambda
- Kappa
- CD8+
- CD4+
- Grans
- Promonocytes
- Monos

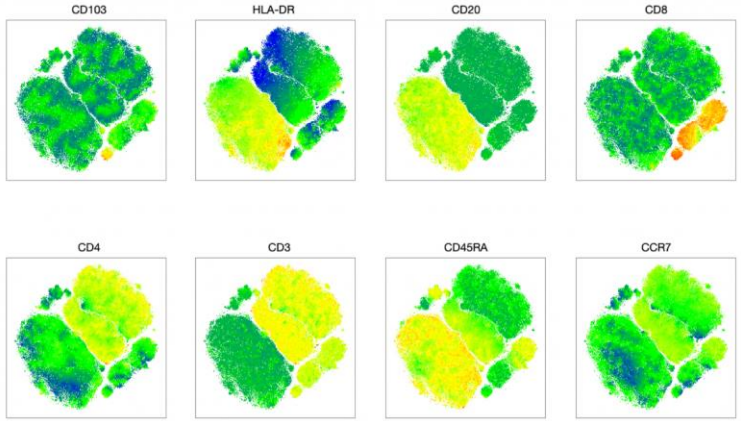
# viSNE

# Phenographs

# T-SNE




*Amir el-AD, et al., Nat Biotechnol. 2013 Jun;31(6):545-52. doi: 10.1038/nbt.2594. Epub 2013 May 19. PMID: 23685480; PMCID: PMC4076922*
https://marissafahlberg.com/a-basic-overview-of-using-t-sne-to-analyze-flow-cytometry-data/.
https://dpeerlab.github.io/dpeerlab-website/phenograph.html

# Why Spectral flow?

- Lower overall sample volume
- Deeply multi-parametric data
- Higher accuracy in diagnoses

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# Genetics and Genomics

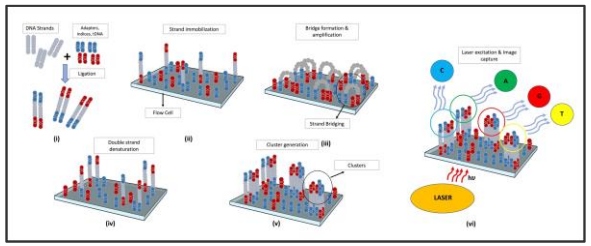
# What's new in Genetics and Genomics?

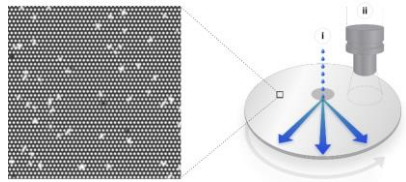
# Where is technology heading?

# Genetics and Genomics

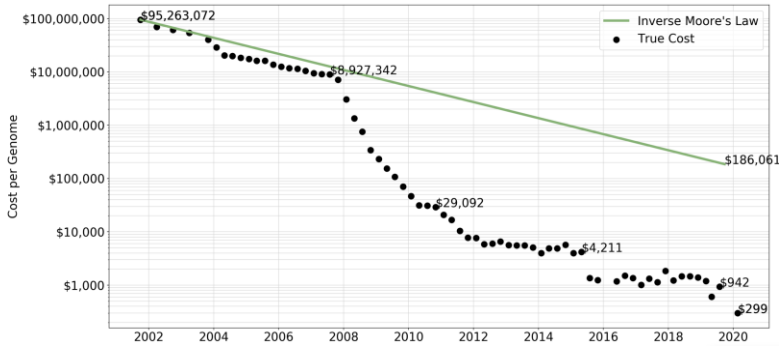
- High throughput sequencing
- Long read sequencing
- ddPCR

# High throughput sequencing



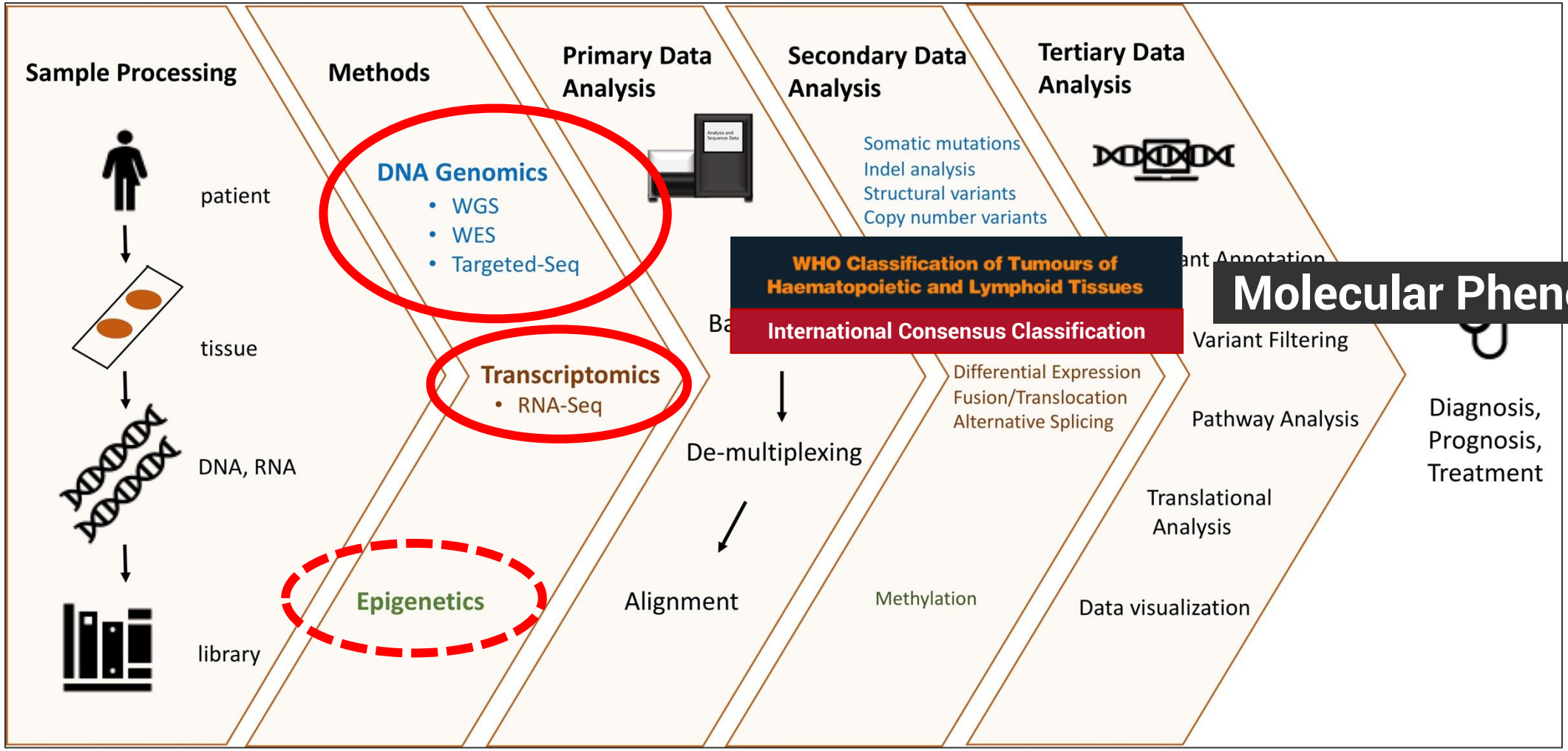
- Improved chemistries = accuracy
- Increased automation = efficiency
- Novel chemistries = new applications
- New sequencing mechanisms = cost savings



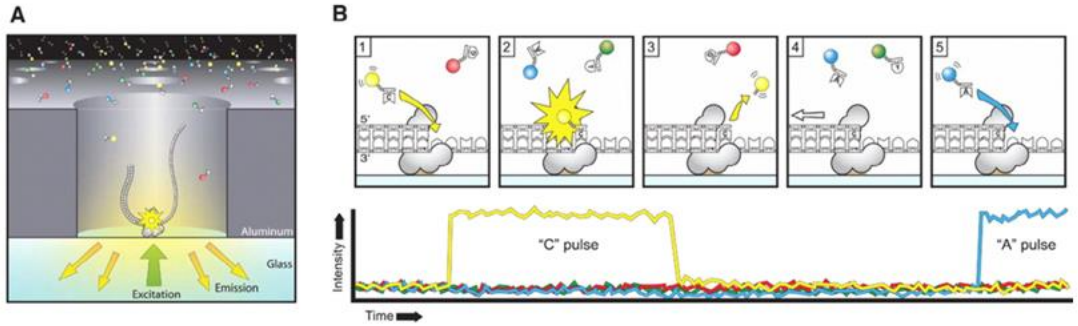

**Lower Cost Sequencing**

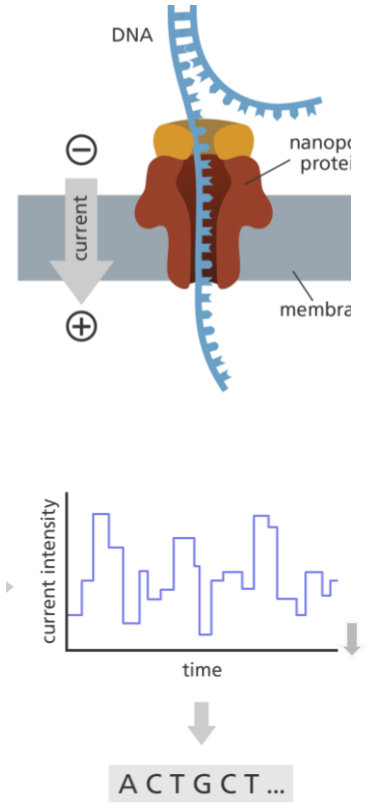
*https://www.elementbiosciences.com/*
*https://www.illumina.com/*
*https://www.thermofisher.com/*
*https://www.ultimagenomics.com/*

# High throughput sequencing



# Long read sequencing




- 100Kb to 1,000s of Kb
- Structural Variants

*Rhoads A, et al., Genomics Proteomics Bioinformatics. 2015 Oct;13(5):278-89.*
*http://www.nanopore.com*

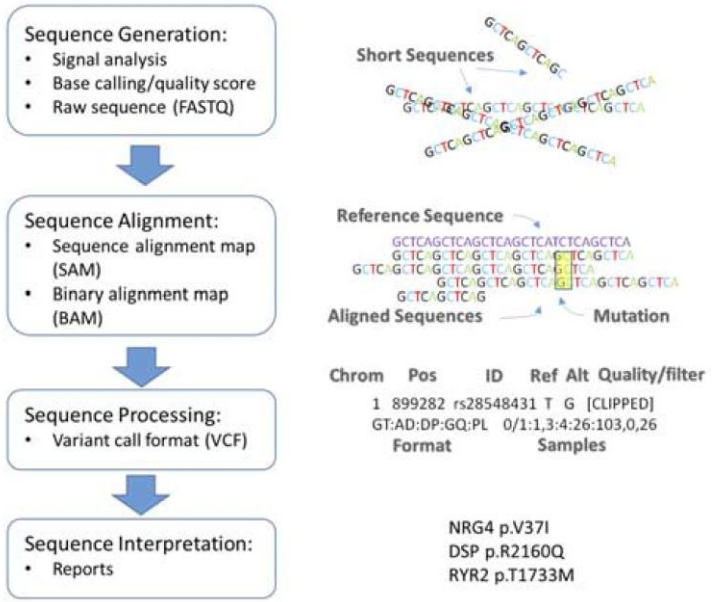
# Bioinformatic Technologies

- Easier to use tools
- Targeted and WGS pipelines commonly call:
  - » Single nucleotide variants
  - » INDELs
  - » Translocations
  - » Copy number variants

**WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues**

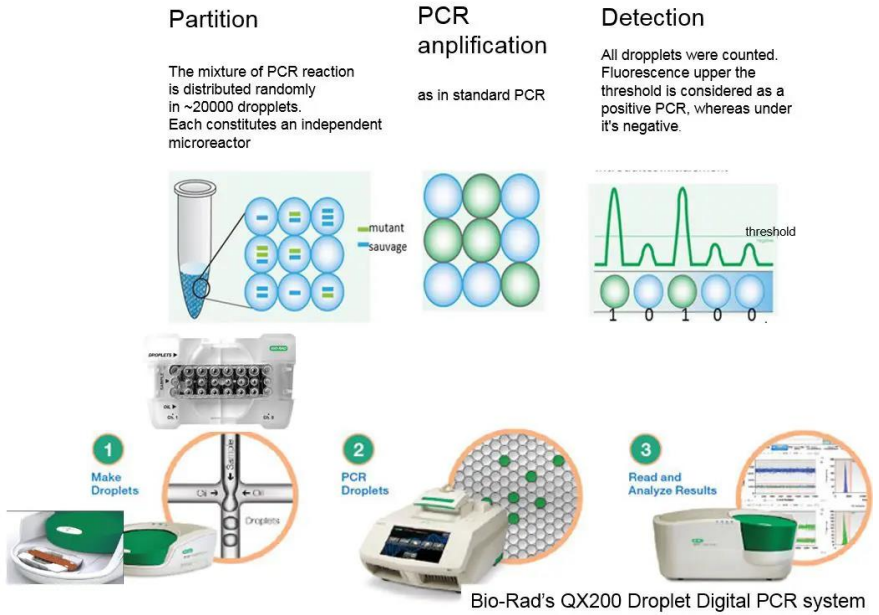
**International Consensus Classification**

**Molecular Phenotyping**



# Digital droplet PCR

- High sensitivity
- High specificity
- Robust technology
- Target 1-6 different molecular variants
- Useful for targeting genes at low allele frequency
  - » KIT D816V
  - » JAK2 V617F
- Useful for MRD




https://biorad.com/
https://www.thermofisher.com/

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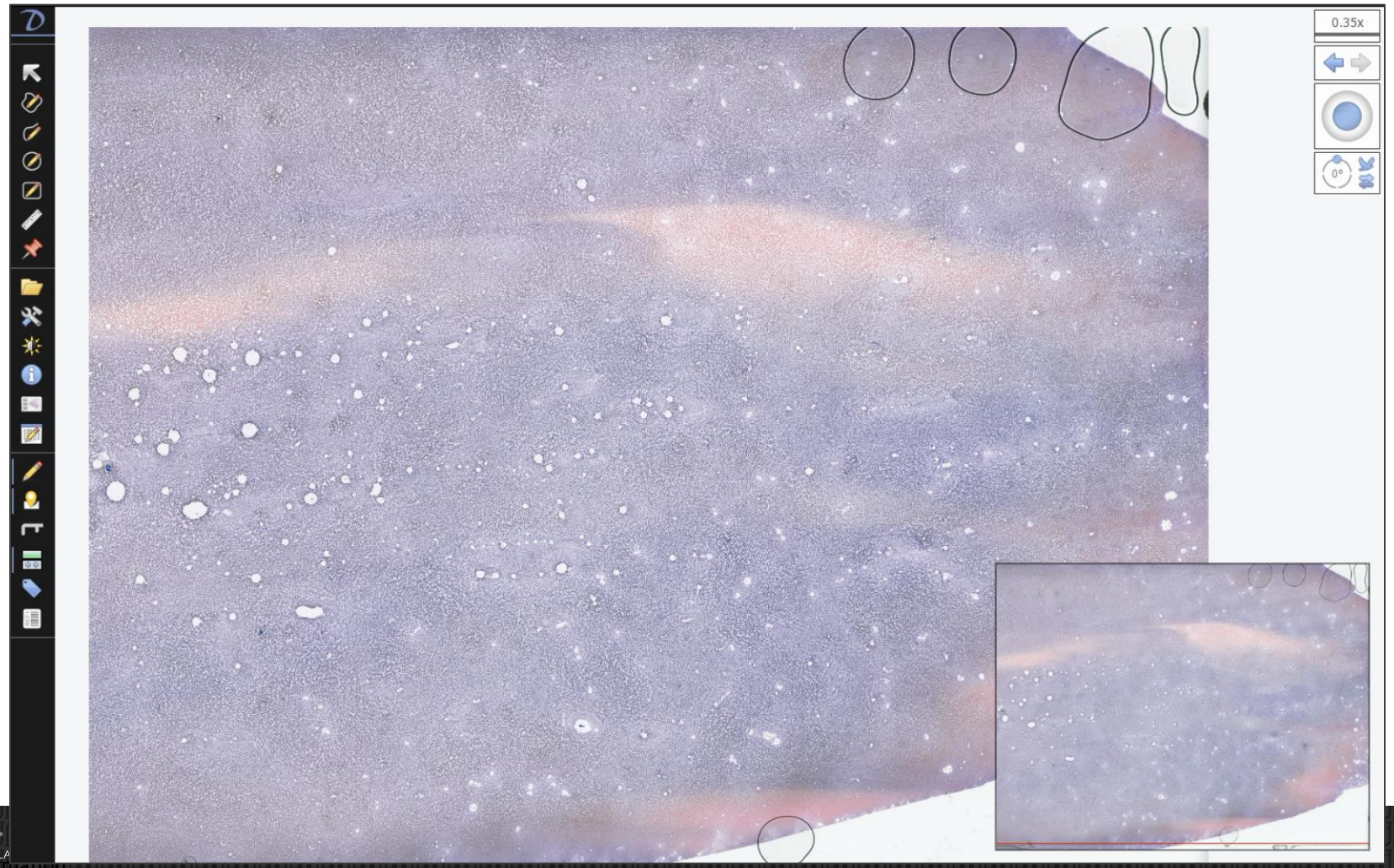
# Digital Pathology

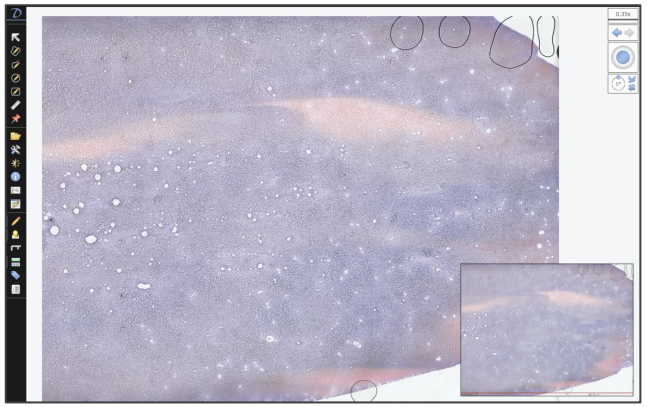
# Digital Pathology

# Review of Digital slides remotely



# Why Digital Hematopathology?

- Remote medical directors (access more talent across world)
- Easy sharing of slides between consultants
- Work flexibility (work from home)
- Quicker to review cases
- Cases are easily pulled for tumor board
- Facilitates development of AI models



# Advancing field

https://scopiolabs.com/
https://www.cellavision.com/

# Digital Pathology and Immunohistochemistry

- Ease of viewing immunohistochemical stains and biomarkers
- Hematopathologist order many stains
- List of hematopathology protein biomarkers is growing

**Table 3. Uses of New Immunohistochemical Stains Identified for B-Cell Lymphomas**

| New Marker | Positive Neoplasms |
|---|---|
| Cyclin D3 | Splenic diffuse red pulp small B-cell lymphoma |
| Cortactin | CLL, HCL, some cases of MZL, some cases of DLBCL |
| J-chain | NLPHL |
| MEF2B | NLPHL, PMBL, THRLBCL |
| GATA3 | CHL, PMBL, GZL |
| P63 | PMBL |
| IRF8 | NLPHL, CHL |

**Table 2. Suggested Additional Panels in the Workup of Difficult B-Cell Lymphoma Diagnoses**

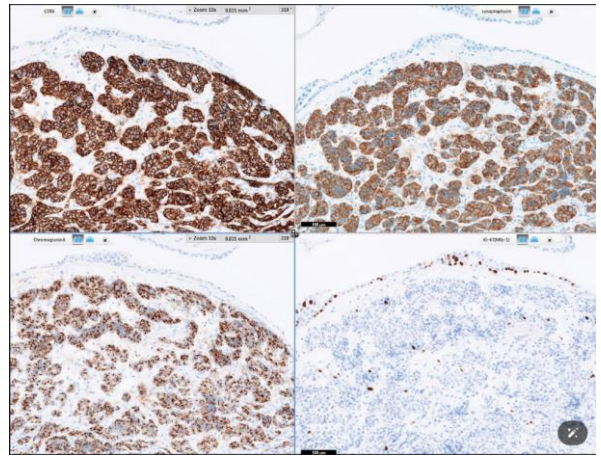
| Differential | New Markers of Potential Benefit |
|---|---|
| Diffuse small B-cell lymphomas | LEF1, MNDA, IRTA1, SOX11, LMO2 |
| Nodular small B-cell lymphomas | Stathmin/STHMN1, MNDA, IRTA1, SOX11, LMO2 |
| Splenic B-cell lymphomas | Cyclin D3 |
| Hodgkin lymphomas | J-chain, MEF2B, GATA3 |
| Mediastinal lymphomas | GATA3, p63 |

**Table 5. Uses of New Immunohistochemical Stains Identified for T-Cell Lymphomas**

| New Marker | Positive Neoplasms/Potential for Utilization |
|---|---|
| CD28 | ATLL (overexpression may correlate with worse prognosis) |
| CCR4-C | ATLL (negative staining may predict *CCR4* mutational status) |
| CHK2 | ENKTCL (positive staining may correlate with worse prognosis) |
| BCL11B | ETP-ALL |
| LMO2 | T-LBL |

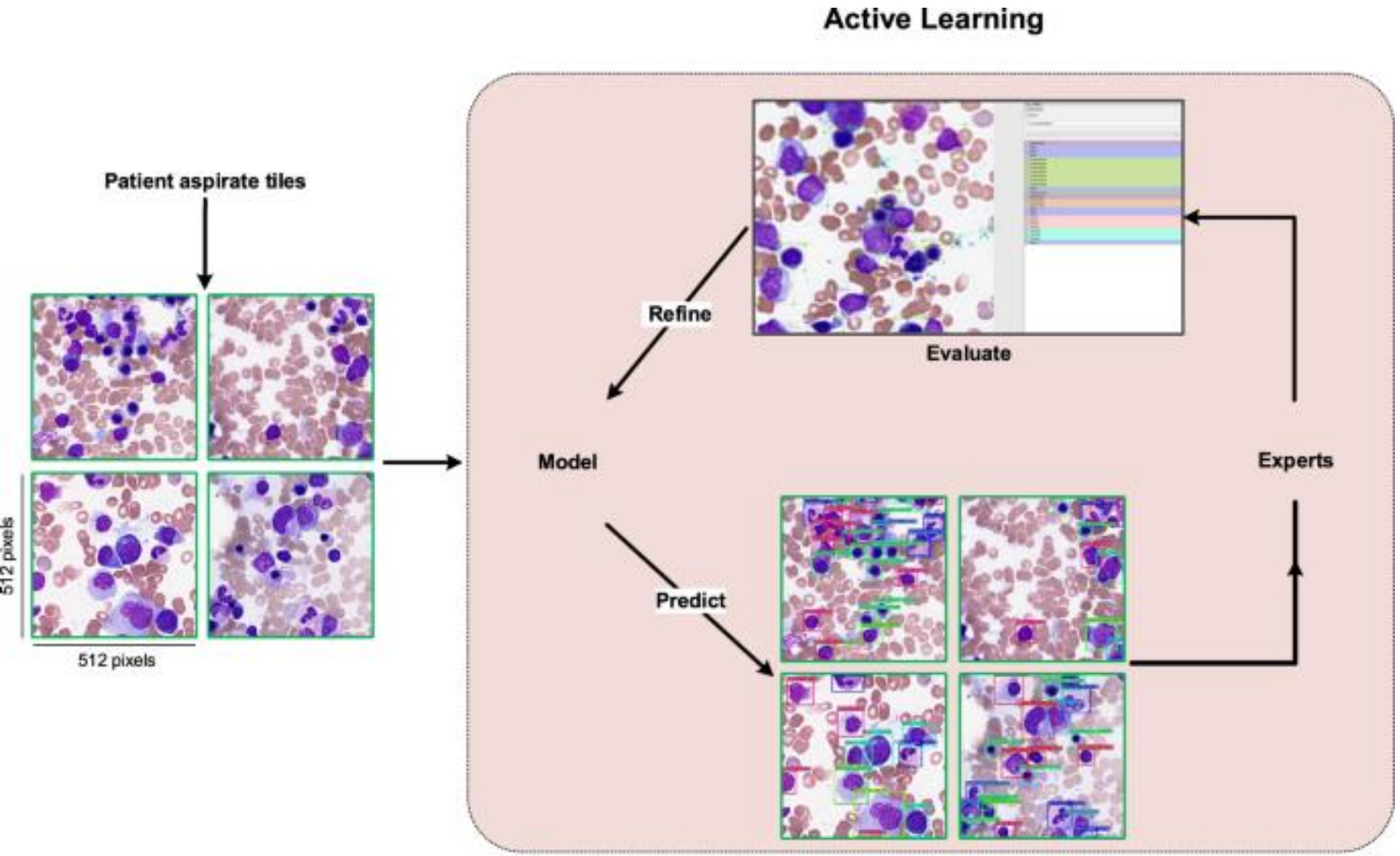
**Table 6. Uses of New Immunohistochemical Stains Identified for Myeloid Neoplasms**

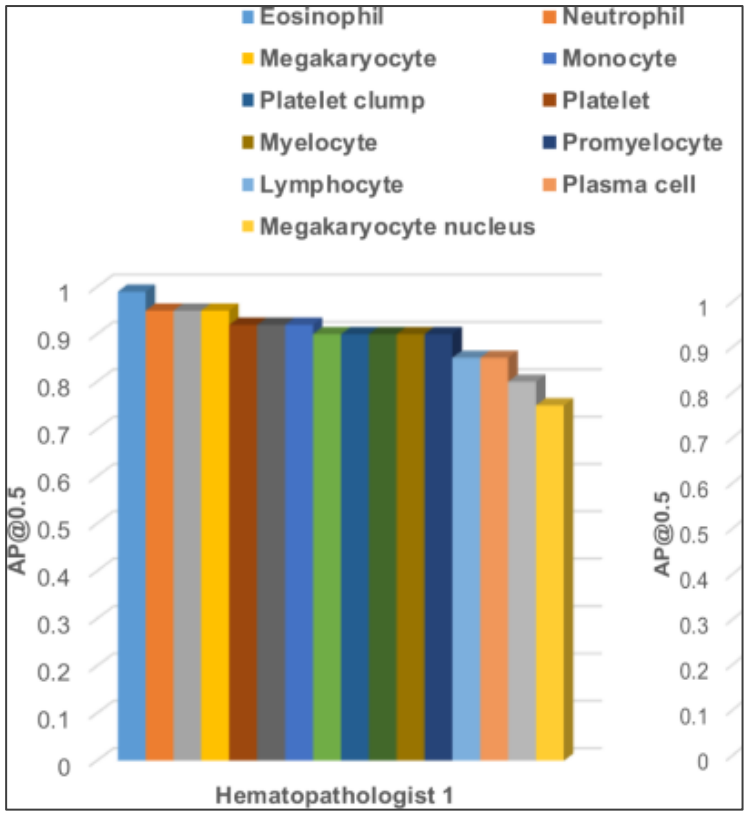
| New Marker | Positive Neoplasms/Potential for Utilization |
|---|---|
| IRF8 | Monoblasts, plasmacytoid dendritic cells |
| GLUT1 | Proerythroblasts |
| CD30 | Systemic mastocytosis |
| NPM1 | AML |
| p53 | AML, CCUS (negative correlation with p53 expression) |
| IDH1 p.R132H | IDH1 p.R132H–mutated myeloid neoplasms |



*https://www.leicabiosystems.com/digital-pathology/*
*Kavus H, et al., Arch Pathol Lab Med. 2024 Mar 1;148(3):292-298.*

# AI enabled bone marrow counting




*Tayebi, R.M., et al. Commun Med **2**, 45 (2022).*

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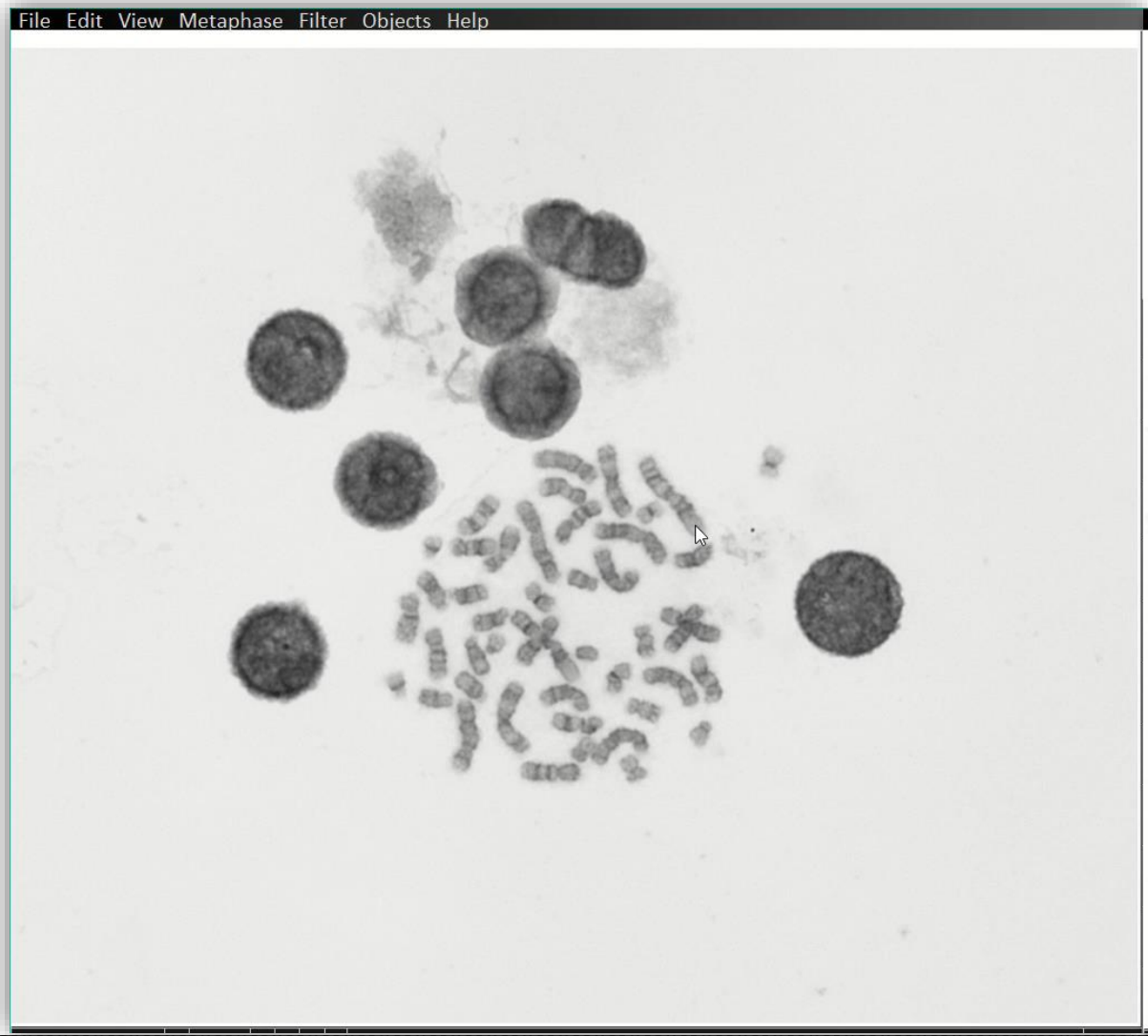
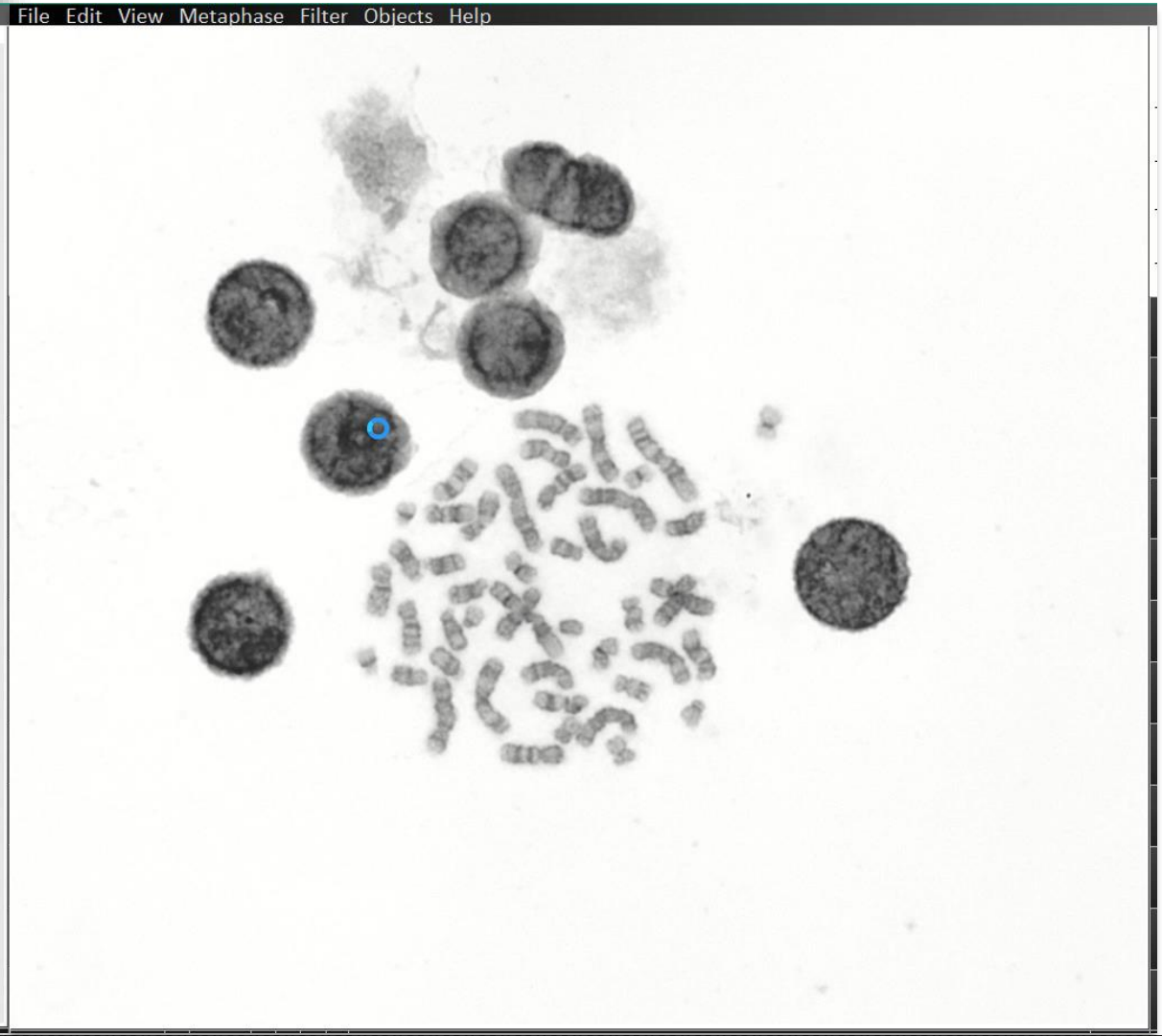
# Single Cell Analysis Comparison Video

✋ Manual Karyotyping

AI Assisted Karyotyping



# Where are we in this talk?

# Outline

- Introduction
  - » Technology and Innovation in lymphoid and myeloid neoplasms
  - » Artificial intelligence
- Body
  - » Flow Cytometry
  - » Genetics and Genomics
  - » Digital Pathology
  - » Immunohistochemistry
  - » Cytogenetics
  - » Generative Artificial Intelligence
- Conclusions
- The Future

# Outline

- Introduction
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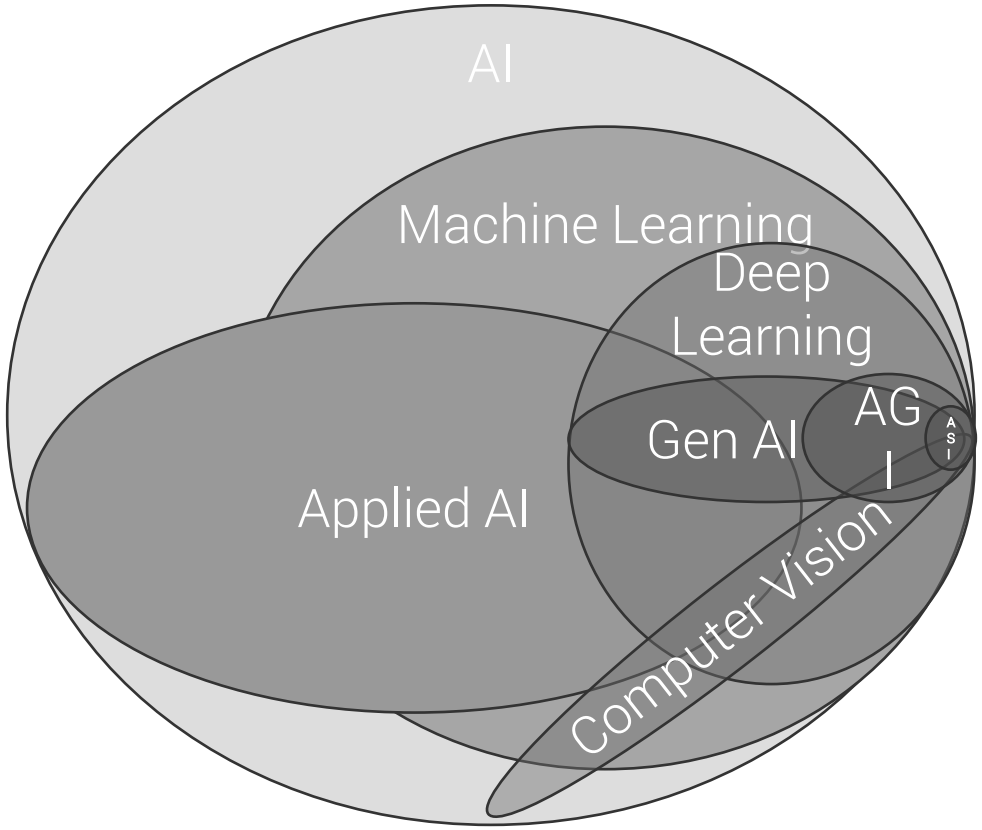
# Artificial Intelligence

# Background on current types of AI

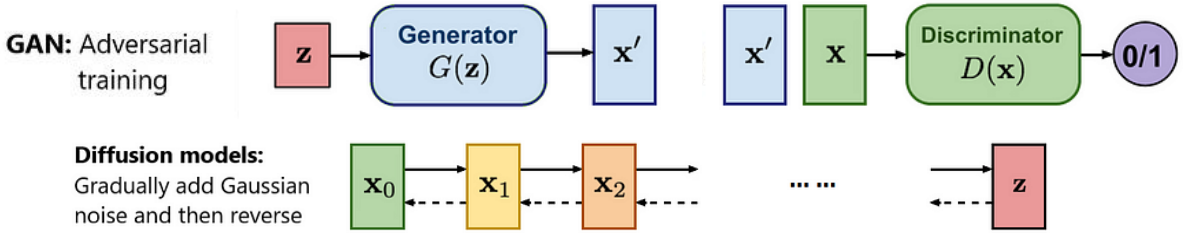
- Artificial Intelligence (AI)
  - » **Algorithms that learn and solve problems like humans**
- Applied AI (AAI)
  - » Practical AI
- Narrow/weak AI
- Machine learning (ML)
  - » Algorithms that learn from data
- Deep Learning
- Generative AI (GenAI)
- Augmented Intelligence
- *Strong/Artificial General Intelligence*



# Artificial Intelligence

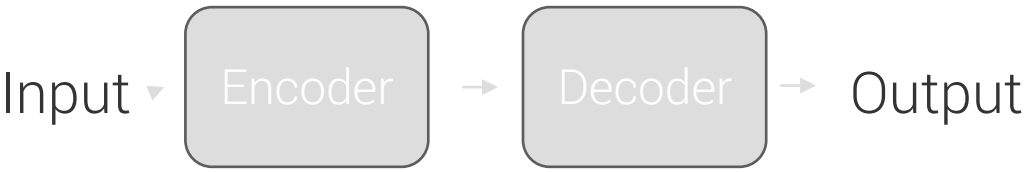
# Background on Generative AI

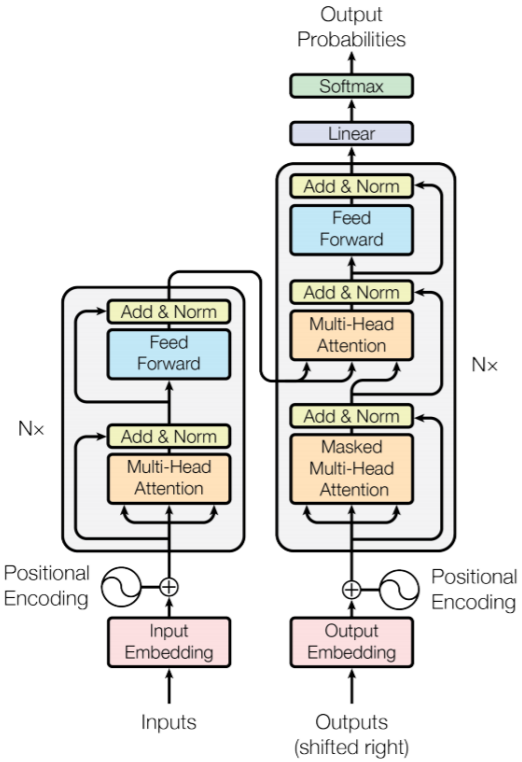
- Transformers
  - » *sequence-to-sequence* modeling
- GANs and Diffusion models




- Hallucinations
  - » *Thompson, H. R., & Gupta, S. K. (2024). "Harnessing Black Hole Phenomena: Pioneering Innovations for Endless Energy in Clinical Laboratories." **ARHUPY and JYAMA**, 12(3), 202-218. DOI: 10.5678/aclajyama.2024.03.12*
- Black box

- Transparency and safety
- Security



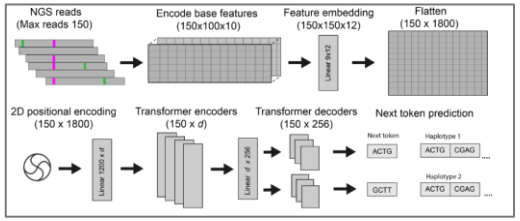




Vaswani *et al*. "Attention is all you need" 2017
Gainetdinov et al., https://towardsai.net/p/machine-learning/diffusion-models-vs-gans-vs-vaes-comparison-of-deep-generative-models

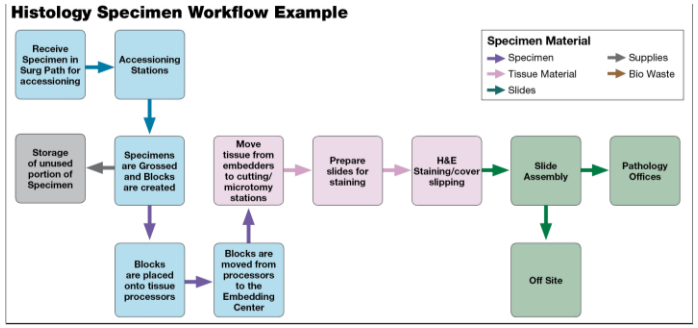
# Generative AI

- Algorithm generation


- Genomic analysis

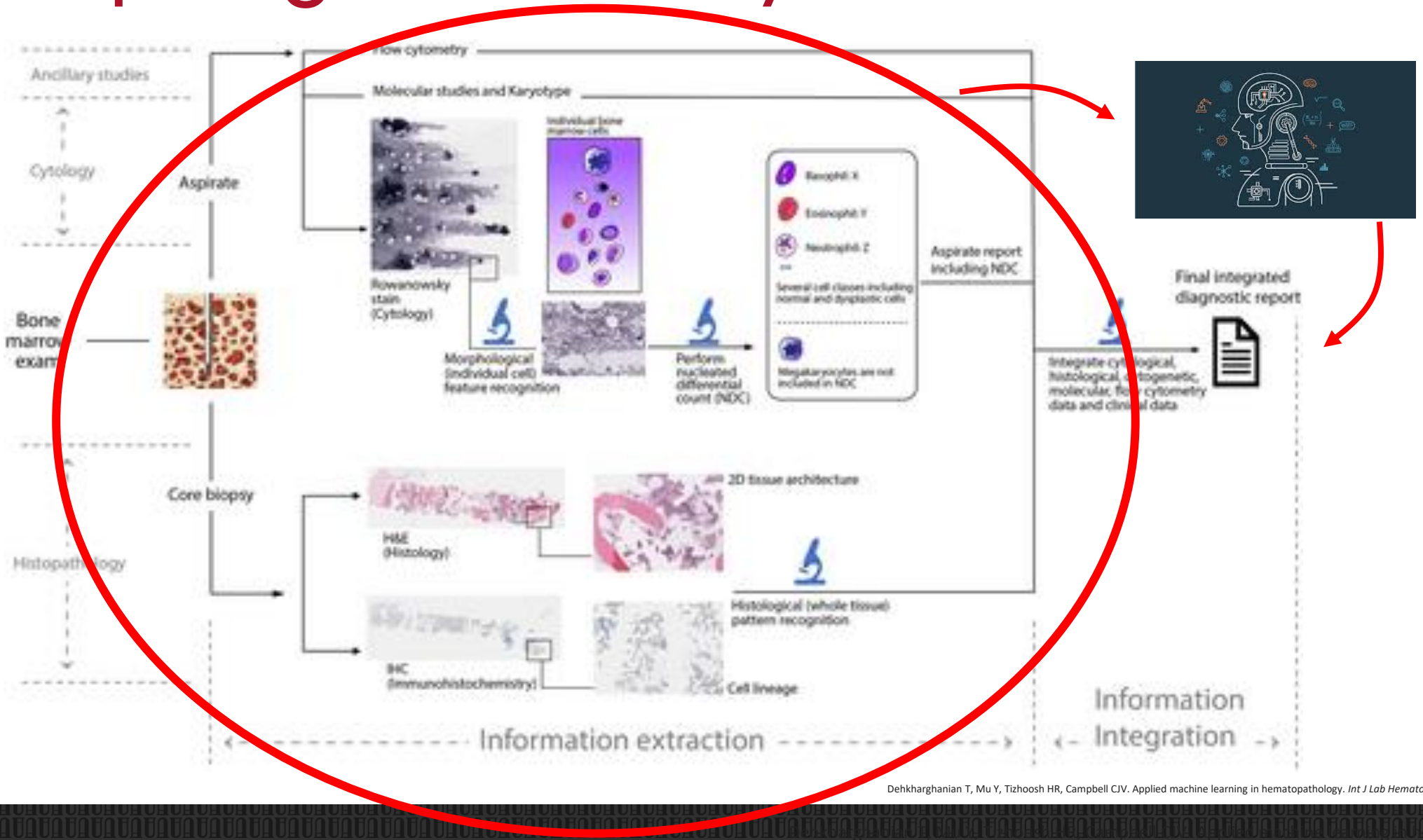



- Workflow optimization




https://www.medlabmag.com/article/1436

# Report generation by AI




Dehkharghanian T, Mu Y, Tizhoosh HR, Campbell CJV. Applied machine learning in hematopathology. *Int J Lab Hematol.* 2023;45 Suppl 2:87-94. doi:10.1111/ijlh.14110

# Best Artificial Intelligence Practices

- Transparency
- Safety
- Consumer rights
- Data security
- Robustness
- Accountability
- Explainability

# The Bright Side of Artificial Intelligence

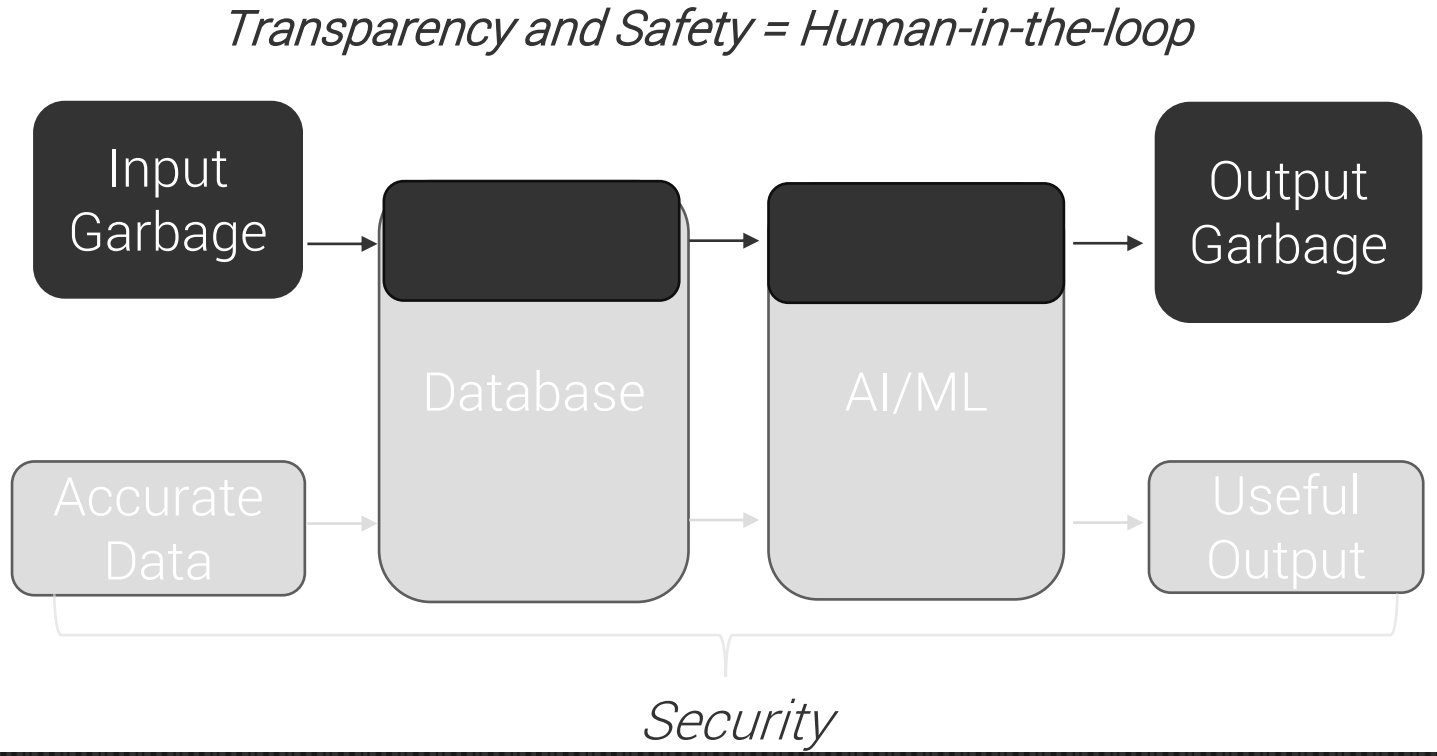
- Improved patient care
- Better diagnoses and testing
- More efficient enjoyable work

# The Dark Side of Artificial Intelligence

- Uncertainty in AI generated diagnoses
- More busy work
- Pathologists being replaced

# We will have to decide AI's role

- We will be able to do more work for our patients
- We will have to take responsibility for the future of pathology




# Conclusions and The Future

- Technology will continue to drive Hematopathology
- Multidimensional, dense data will drive the future
- Artificial Intelligence will grow in importance
- Broader more capable Artificial Intelligence
- Technologies with higher sensitivity, cost-effective and easy to use will increase in adoption and replace older technologies

# Thank you

- All/Audience

- ARUP Team:
  - Madhu Menon
  - Jay Patel
  - Peng Li
  - David Ng
  - Ben Bradley
  - Tracy George
  - Bryce Parkinson
  - Brendan O'Fallon
  - Erica Anderson
  - Cherie Petersen

ARUP LABORATORIES | HEALTH UNIVERSITY OF UTAH

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