Vårmöte i Patologi
UMEÅ 2026 region västerbotten

Cytology: from morphology to AI and beyond

Arrigo Capitanio - Linköping

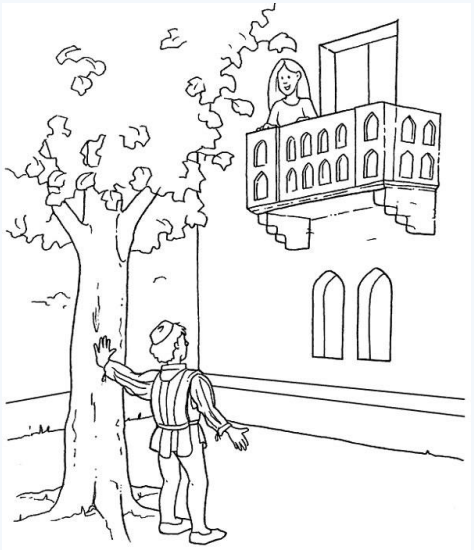
Introduction

Many advancements in medicine have arisen from research outside the field.

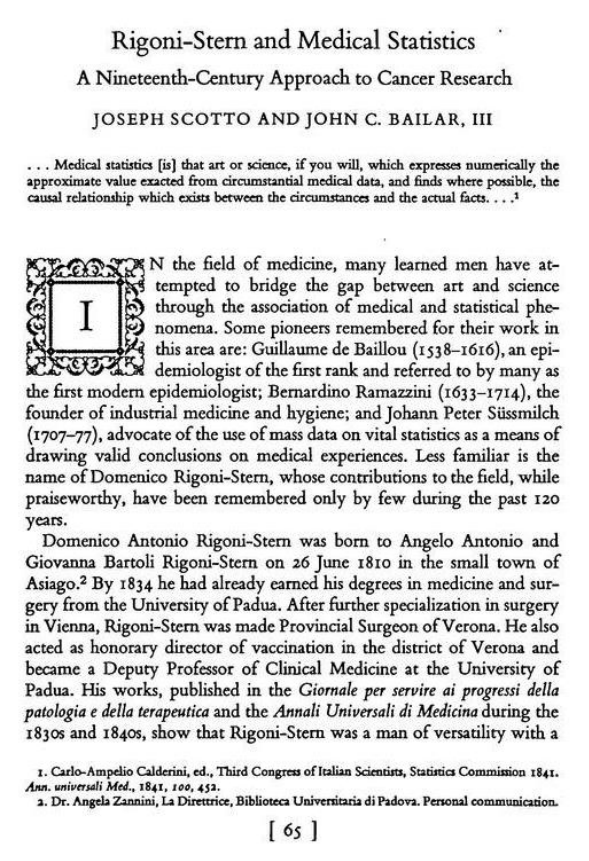
Even cytological investigations, or at least a substantial part of them, arose from studies that had nothing to do with them.

VERONA

- Romeo and Juliet
- The Two Gentlemen of Verona
- The Taming of the Shrew



1842 – Rigoni-Stern



Rigoni-Stern and Medical Statistics

A Nineteenth-Century Approach to Cancer Research

JOSEPH SCOTTO AND JOHN C. BAILAR, III

. . . Medical statistics [is] that art or science, if you will, which expresses numerically the approximate value exacted from circumstantial medical data, and finds where possible, the causal relationship which exists between the circumstances and the actual facts. . . .[1]

IN the field of medicine, many learned men have attempted to bridge the gap between art and science through the association of medical and statistical phenomena. Some pioneers remembered for their work in this area are: Guillaume de Baillou (1538–1616), an epidemiologist of the first rank and referred to by many as the first modern epidemiologist; Bernardino Ramazzini (1633–1714), the founder of industrial medicine and hygiene; and Johann Peter Süssmilch (1707–77), advocate of the use of mass data on vital statistics as a means of drawing valid conclusions on medical experiences. Less familiar is the name of Domenico Rigoni-Stern, whose contributions to the field, while praiseworthy, have been remembered only by few during the past 120 years.

Domenico Antonio Rigoni-Stern was born to Angelo Antonio and Giovanna Bartoli Rigoni-Stern on 26 June 1810 in the small town of Asiago.[2] By 1834 he had already earned his degrees in medicine and surgery from the University of Padua. After further specialization in surgery in Vienna, Rigoni-Stern was made Provincial Surgeon of Verona. He also acted as honorary director of vaccination in the district of Verona and became a Deputy Professor of Clinical Medicine at the University of Padua. His works, published in the *Giornale per servire ai progressi della patologia e della terapeutica* and the *Annali Universali di Medicina* during the 1830s and 1840s, show that Rigoni-Stern was a man of versatility with a

1. Carlo-Ampelio Calderini, ed., Third Congress of Italian Scientists, Statistics Commission 1841. *Ann. universali Med.*, 1841, *100*, 452.
2. Dr. Angela Zannini, La Direttrice, Biblioteca Universitaria di Padova. Personal communication.

[65]

In 1842

Domenico Antonio

Rigoni-Stern

A gynecologist from Verona

Published:

”Fatti statistici relativi alle malattie cancerose”

(Statistical facts related to cancer diseases)

The world's first published cancer epidemiological study**.**

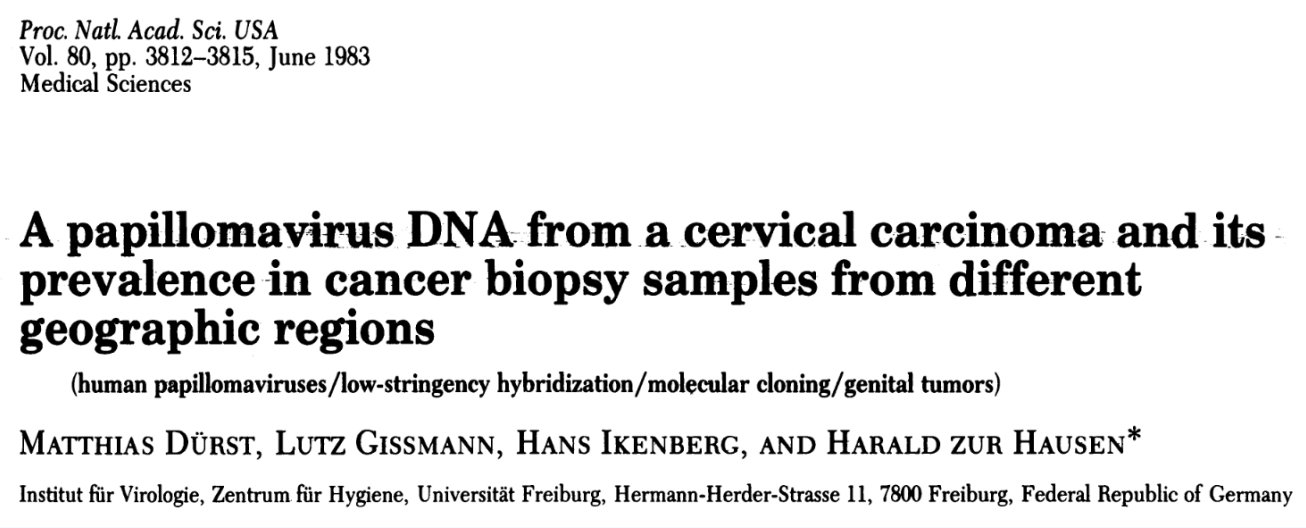
He studied approximately 2,500 women's cancer deaths and their marital status between 1760 and 1839.

1842 – Rigoni-Stern

He noticed that nuns in Verona (generally nulliparous) were more susceptible to breast cancer than other women who had children.

He also observed that uterine cancer was much more frequent in Married Women, Widows, and Prostitutes than in Nuns.

Introducing the idea of a link between sexual activity and uterine cancer.



Proc. Natl. Acad. Sci. USA
Vol. 80, pp. 3812–3815, June 1983
Medical Sciences

A papillomavirus DNA from a cervical carcinoma and its prevalence in cancer biopsy samples from different geographic regions

(human papillomaviruses/low-stringency hybridization/molecular cloning/genital tumors)

MATTHIAS DÜRST, LUTZ GISSMANN, HANS IKENBERG, AND HARALD ZUR HAUSEN*

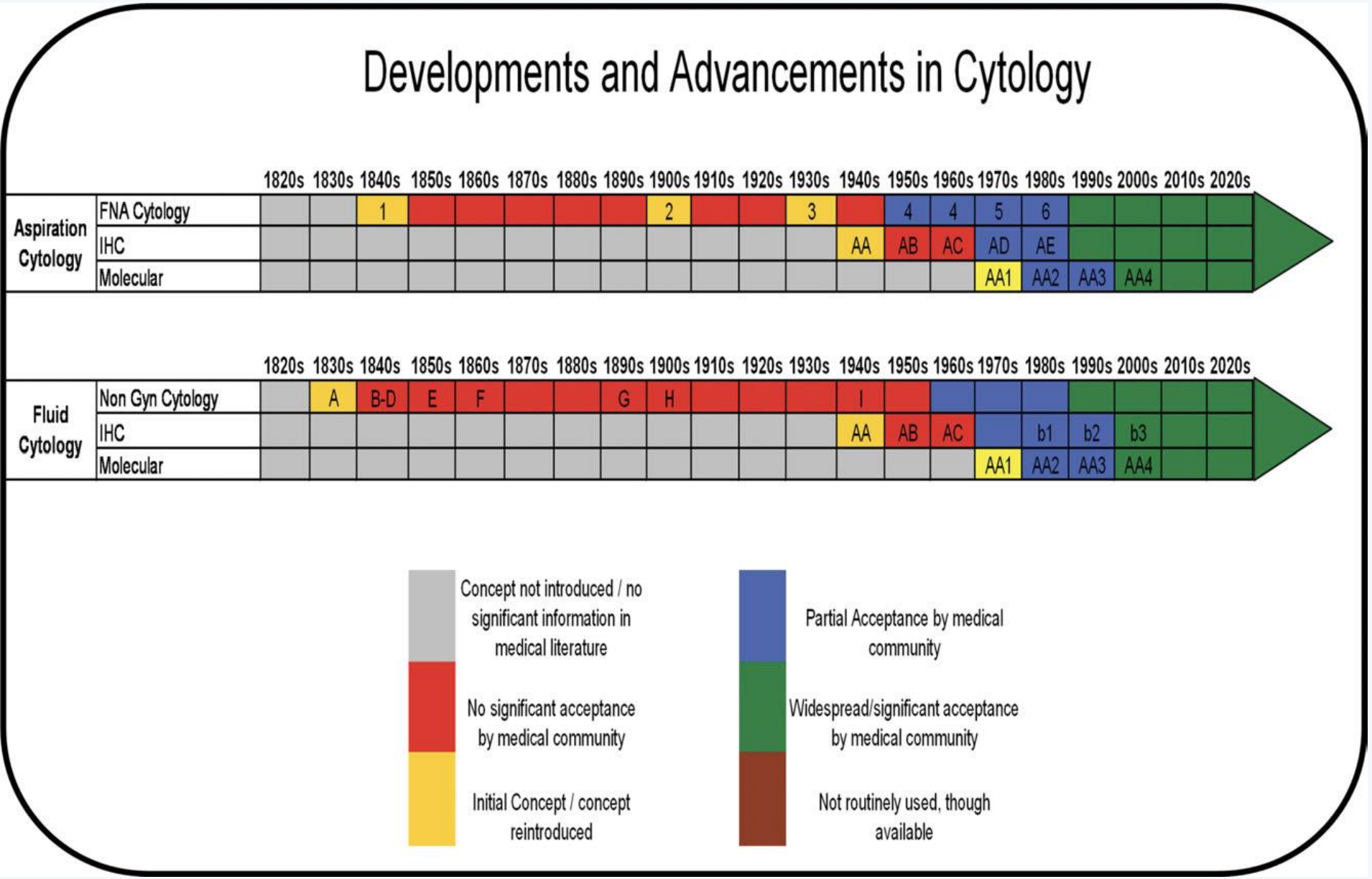
Institut für Virologie, Zentrum für Hygiene, Universität Freiburg, Hermann-Herder-Strasse 11, 7800 Freiburg, Federal Republic of Germany

1842 – Rigoni-Stern

He certainly could not imagine that his findings would contribute to the development of the most widespread method of investigation to prevent cervical cancer:

The cervical cytology.

Cytology timeline



Cancer Cytopathology
A Journal of the American Cancer Society

Review Article | Free Access

Targeting tyrosine kinases in cancer

The converging roles of cytopathology and molecular pathology in the era of genomic medicine

Catherine I. Dumur PhD, Michael O. Idowu MD, Celeste N. Powers MD, PhD

First published: 07 August 2012 | https://doi.org/10.1002/cncy.21225 | VIEW METRICS

1 – The beginning

From Müller (1838) to Lopes Cardozo & Papanicolaou (40's of XX century)

ON THE

NATURE

AND

STRUCTURAL CHARACTERISTICS

OF

CANCER,

AND OF THOSE

MORBID GROWTHS

WHICH MAY BE CONFOUNDED WITH IT.

BY J. MÜLLER, M.D.

PROFESSOR OF ANATOMY AND PHYSIOLOGY IN THE UNIVERSITY OF BERLIN,

&c. &c. &c.

TRANSLATED FROM THE GERMAN,

WITH NOTES,

BY CHARLES WEST, M.D.

GRADUATE IN MEDICINE OF THE UNIVERSITY OF BERLIN.

ILLUSTRATED WITH NUMEROUS STEEL PLATES AND WOOD ENGRAVINGS.

LONDON:

PRINTED FOR SHERWOOD, GILBERT, AND PIPER,

PATERNOSTER ROW.

1840.

COURS

DE

MICROSCOPIE

COMPLÉMENTAIRE DES ÉTUDES MÉDICALES

ANATOMIE MICROSCOPIQUE ET PHYSIOLOGIE

DES

FLUIDES DE L'ÉCONOMIE

ATLAS

AU MICROSCOPE-DAGUERRÉOTYPE

PAR

AL. DONNÉ

ET LÉON FOUCAULT

A PARIS

CHEZ J.-B. BAILLIÈRE

LIBRAIRE DE L'ACADÉMIE ROYALE DE MÉDECINE

1845

ATLAS

OF

URINARY SEDIMENTS;

WITH SPECIAL REFERENCE

TO THEIR CLINICAL SIGNIFICANCE.

BY DR. HERMANN RIEDER,

OF THE UNIVERSITY OF MUNICH.

TRANSLATED

BY FREDERICK CRAVEN MOORE, M.Sc., M.D. (VICT.),

ASSISTANT LECTURER AND DEMONSTRATOR OF PATHOLOGY, OWENS COLLEGE.

Edited and Annotated

BY A. SHERIDAN DELÉPINE, M.B., C.M. (EDIN.), B.Sc.,

PROFESSOR OF PATHOLOGY IN OWENS COLLEGE AND VICTORIA UNIVERSITY, MANCHESTER.

WITH THIRTY-SIX PLATES, COMPRISING 167 FIGURES (MANY IN COLOURS) AND SEVERAL FIGURES IN THE TEXT.

LONDON:

CHARLES GRIFFIN AND COMPANY, LIMITED;

EXETER STREET, STRAND.

1899.

The way to diagnostic cytology was actually a “Long and winding road”.

In the first thirty years of the twentieth century,
Cytology was partly opposed and partly simply ignored.

1919: Gloyne (the first pathologist at the London Chest Hospital)
talking about cancer cells in pleural fluids:

"*Most pathologists are now agreed that it is practically impossible to identify these cells in film preparations*"

1922: Bland-Sutton, one of the most authoritative English pathologists of the early 20th century:

"In *the appearance of a cell from cancer, there is nothing characteristic of the disease, nothing that would lead a pathologist to identify it as a malignant cell*"

James Ewing, a great contributor to the classification of human tumours

was absolutely and definitely contrary to the use of diagnostic tissue biopsies because of the fear of cancer spreading.

Martin Hayes

Martin Hayes (1913-1977) refused to threat patients without a sure preoperative diagnosis.
He started performing big needle aspirations of the tumour masses.

FNA Cytology

Only in the thirties did **Martin and Ellis** at the Memorial Hospital (now Memorial Sloan-Kettering Cancer Centre) start performing true FNA cytology.

And in the forties, **Paul Lopes-Cardozo** in the Netherlands

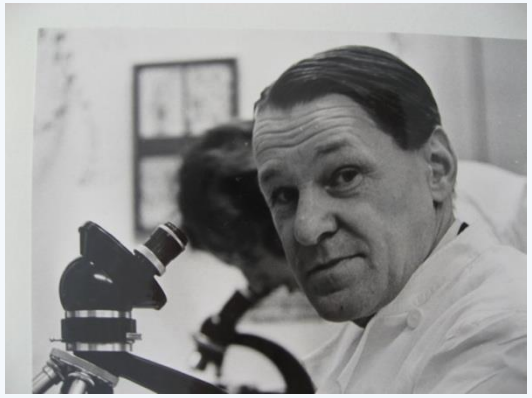


TABLE 11 (Martin and Ellis, 1934)

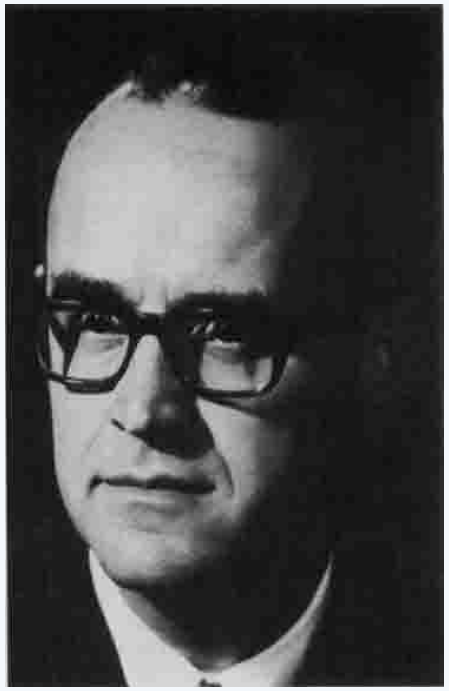
POSITIVE DIAGNOSES OF CANCER MADE BY ASPIRATION BIOPSY AT MEMORIAL HOSPITAL

	Cases
Cervical nodes or tumours, including the parotid and submaxillary salivary glands	662
Breast	280
Bones	140
Prostate	55
Lung	41
Upper and lower jaws	27
Thyroid	17
Tonsil	15
Antrum	15
Base of tongue	11
Miscellaneous (axillary and inguinal nodes, intra-oral tumours, orbit, various soft part tumours, etc.)	142
Total	1405

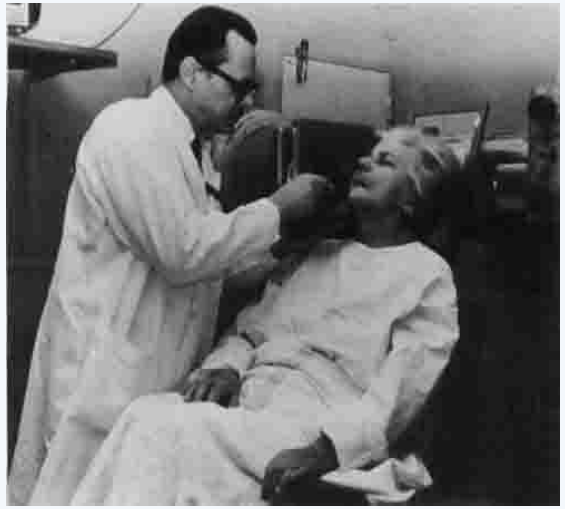
FNA cytology in Europe – The Karolinska Group

His works boosted further studies all over Europe

but mainly in Stockholm at Radiumhemmet, where



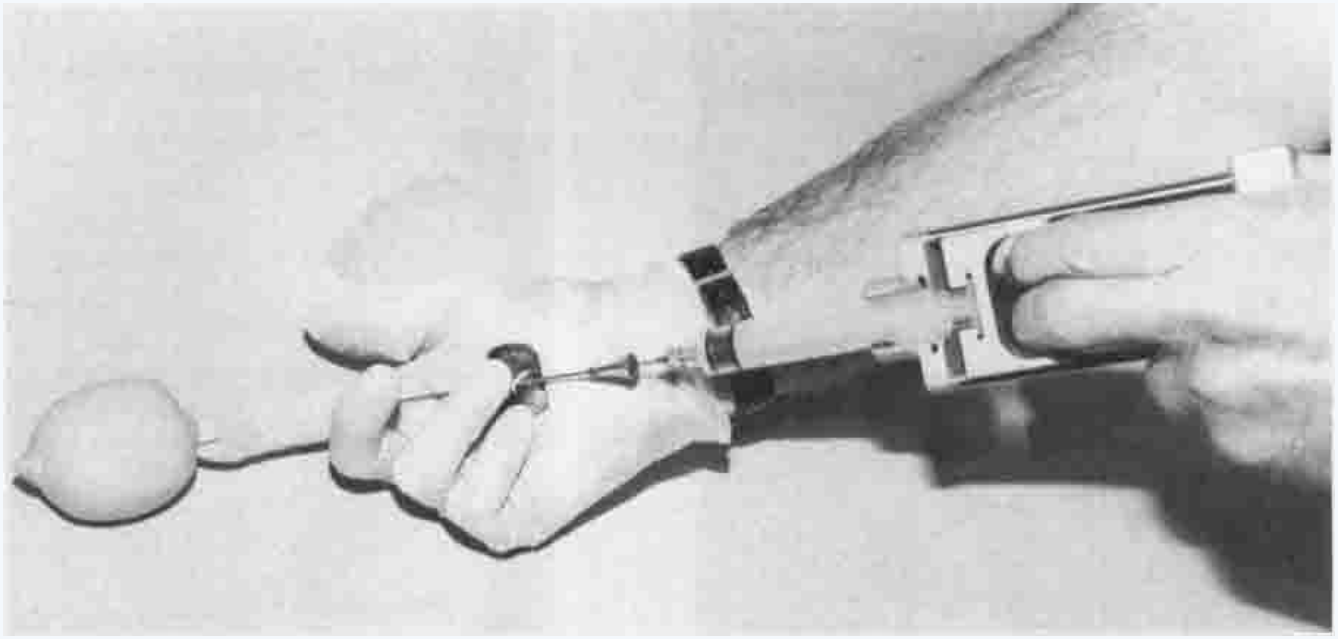
Joseph Zajicek



Sixten Franzen

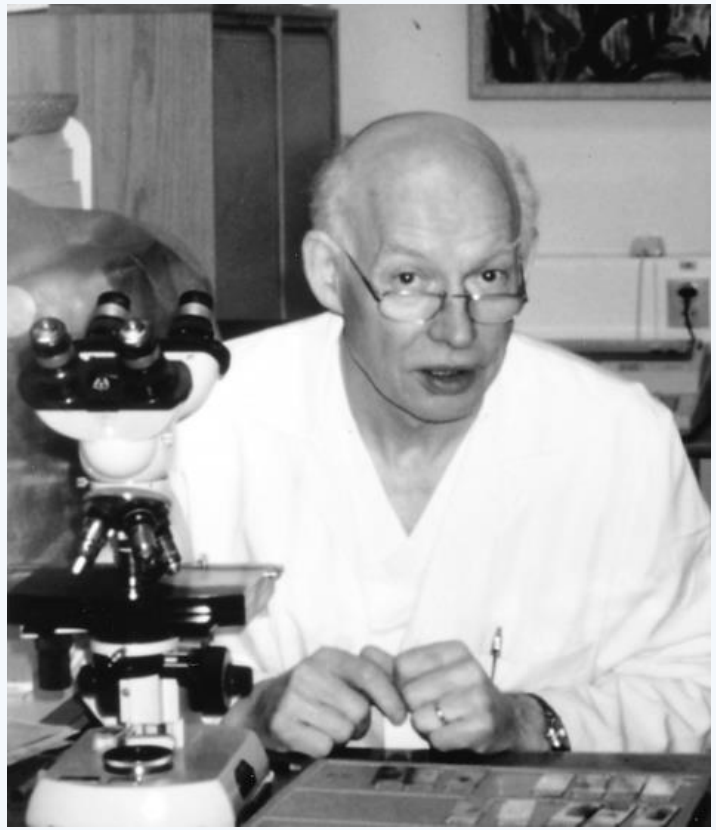
Pier Luigi Esposti

The Karolinska group



One-hand syringe holder and needle guide

The Karolinska group

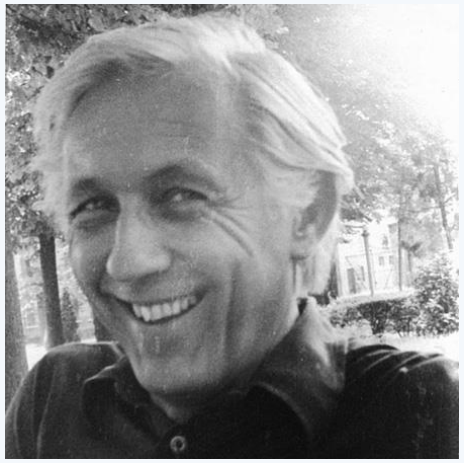


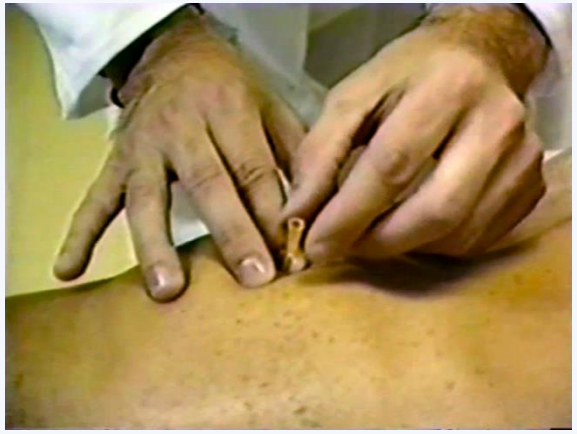
Torsten Löwhagen

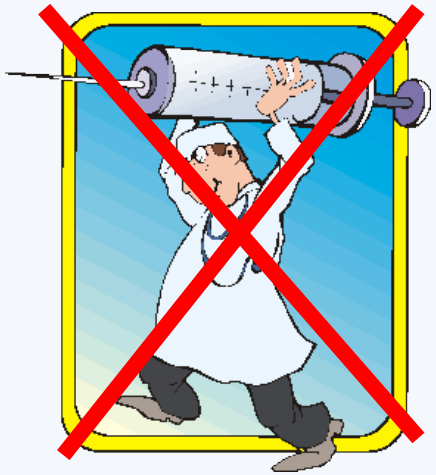
He was the member most responsible for introducing the visiting pathologists and clinicians to the aspiration method.
He carried out his teaching with thundering enthusiasm, stressing the fundamentals of palpation, proper aspiration, and the preparation and interpretation of excellent smears.

FNA in Europe

Antoine Zajdela
(Institut Curie - Paris)
In the 70's he proposed the use of the fine-needle without syringe to perform the FNA. It can be defined a kind of "*aspiration without aspiration*" to minimize the blood contamination of the diagnostic material.







Exfoliative Cytology

Spontaneous

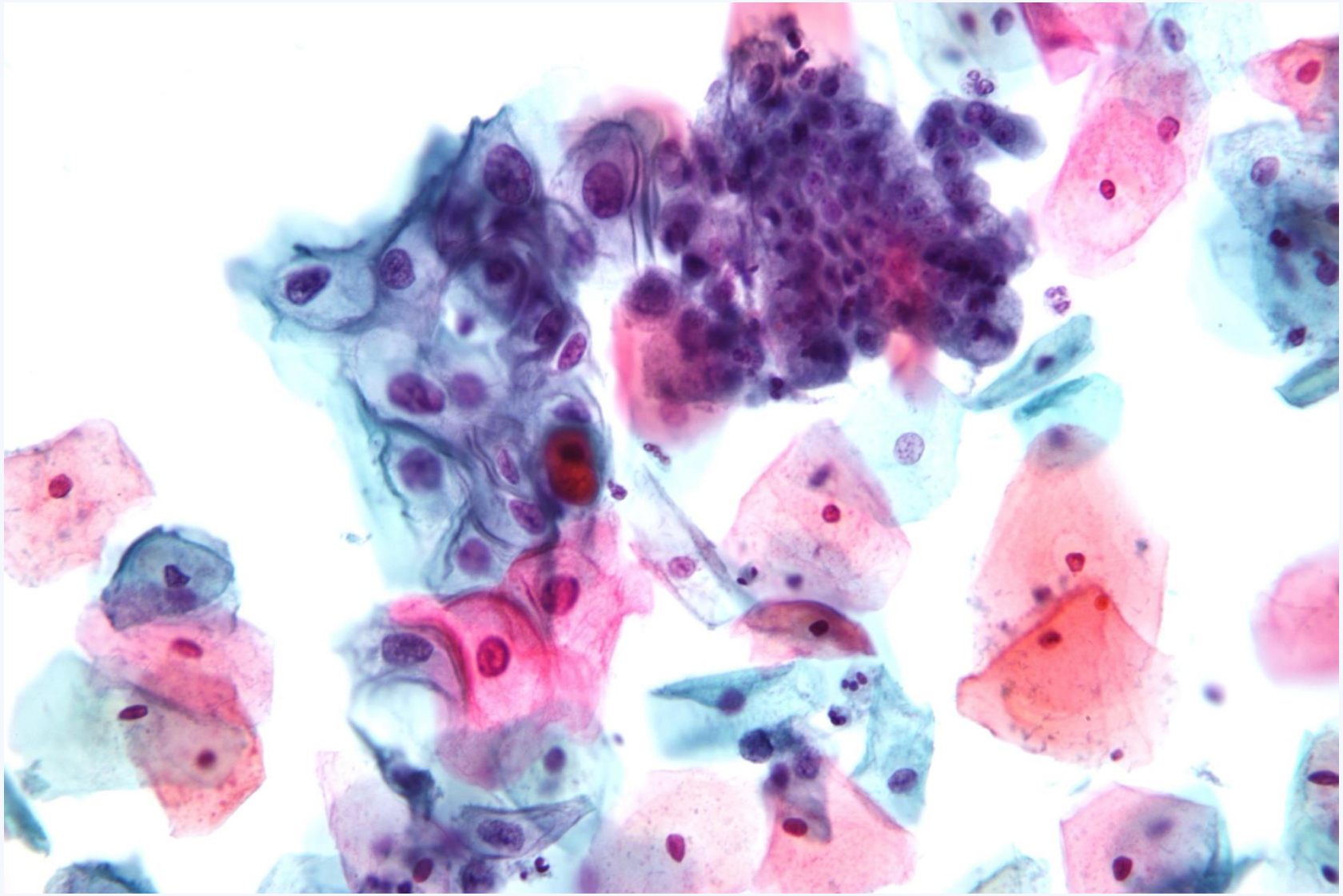
- Urinary tract
- Sputum
- Serous effusions
- Liquor

By **brushing** or **washing** of a body cavity or surface:

- Distal bronchial tree
- Hepato-biliary tree
- Nose
- Mouth
- Ear
- Skin

And obviously

Cervical Cytology



George Papanicolau

While studying the menstrual cycle of rodents, he identified changes in the maturation of squamous cells associated with ovulation.

Studying the same changes in women, he incidentally found cancer cells in asymptomatic patients.

In 1941 and 1943, in cooperation with the gynaecologist Herbert Traut, he published an article and a book describing the cytological changes in cervical and endometrial cancer.

Summarizing - 1

01 Diagnostic cytology faced **strong resistance** from leading pathologists well into the 1920s, who doubted the diagnostic value of cellular morphology

02 **FNA cytology** was pioneered in the US by **Martin Hayes** (Memorial Hospital, NY), then refined in Europe by the **Karolinska group** in Stockholm (Zajicek, Franzen, Esposti, Löwhagen) and **Zajdela** at Institut Curie, Paris

03 **Exfoliative cytology** expanded to urine, sputum, serous effusions, brushings, and cervical sampling

04 The landmark contribution came from **Papanicolaou** (1941–1943), not only because of his systematic description of cervical cancer cytology, but also **because he developed a method** for collecting cells and a suitable stain to identify them. We continue to use it today.

2 - Standardization of Classifications in Diagnostic & Screening Cytology

From Papanicolaou (1948) to the Modern Organ-Specific Systems

The Original Problem: Papanicolaou's Class System (1948)

I	No atypical cells (normal)
II	Atypical or inflammatory, no malignancy
III	Suggestive of malignancy
IV	Strongly suggestive
V	Conclusive for malignancy

Limitations of the Class System

1. Numeric classes lacked morphological specificity
2. Class III meant different things in different labs
3. No direct link to clinical management
4. Extended to urine, sputum, effusions — without adaptation
5. No specimen adequacy criteria

Cervical Cytology: Four Decades of Terminology Evolution

1948 Pap Class	1953 WHO / Dysplasia	1966 CIN (Richart)	1988→2014 Bethesda (TBS)
Class I – Normal	Normal	Normal	NILM
Class II – Atypical	Mild dysplasia	CIN I	ASC-US / ASC-H
Class III – Suspicious	Moderate dysplasia	CIN II	LSIL
Class IV – Strongly susp.	Severe dysplasia	CIN III	HSIL
Class V – Malignant	CIS	(= severe dysp. + CIS)	SCC / AIS
	Invasive carcinoma	Invasive carcinoma	Adenocarcinoma

TBS 2014 remains the only cervical system with a histological counterpart (LAST terminology, College of American Pathologists)

The Bethesda System: Structural Innovations (1988)

Specimen Adequacy

Mandatory 'Satisfactory / Unsatisfactory' statement — the first formal quality standard in cytology reporting

ASC-US / ASC-H Category

Introduced the 'Atypical Squamous Cells' category — acknowledging diagnostic uncertainty without forcing misclassification

LSIL / HSIL Dichotomy

Replaced the 5-class numerical scale with a clinically actionable 2-tier squamous intraepithelial lesion model.

Management Recommendations

Each category explicitly linked to a recommended clinical action — colposcopy, repeat test, or routine screening

Model for Expansion

TBS became the template for all subsequent organ-specific cytology systems: thyroid, urinary tract, salivary glands, and beyond

Organ-Specific Standardised Reporting Systems

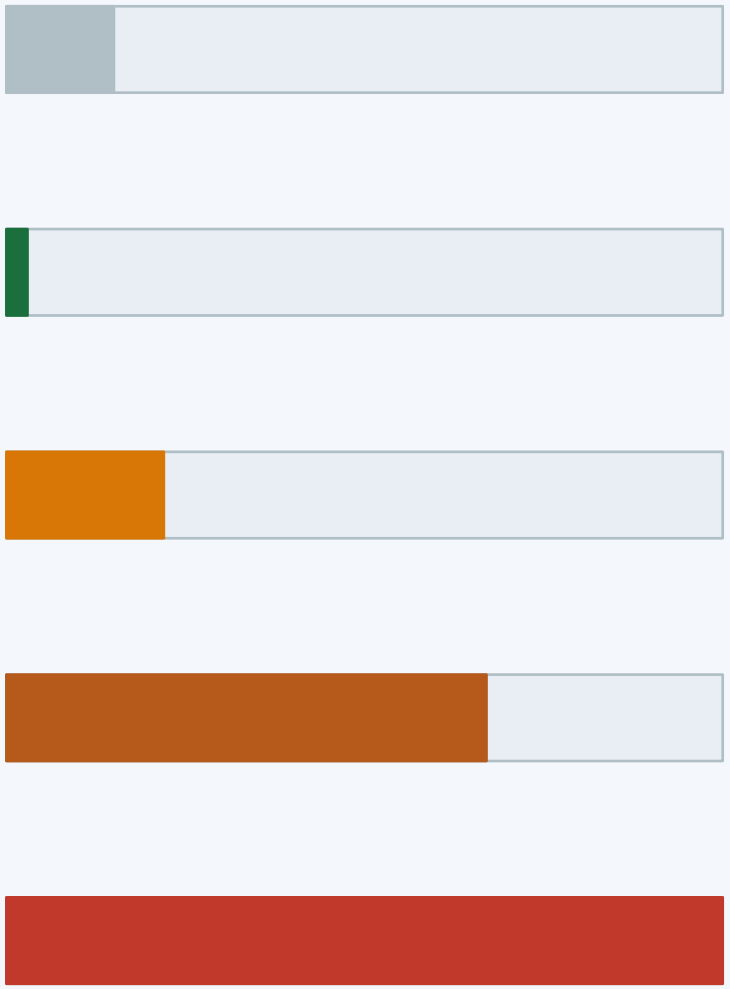
System	Site	Year	Categories	Sponsor	Key novelty
Bethesda (TBS)	Cervix / vagina	1988–2014	6	NCI	LSIL/HSIL; specimen adequacy
TBSRTC	Thyroid (FNA)	2007–2023	6	NCI / PSC	1st non-gyn Bethesda system; ROM-linked tiers
PSC Pancreaticobiliary	Pancreas / bile ducts	2014	6	PSC	EUS-FNA context; WHO-aligned terminology
Paris System (TPS)	Urine / urinary tract	2016	5	PSC / IAC	HGUC-focused; AUC replaces Class III
PSC Respiratory	Lung / bronchi (FNA+BAL)	2016	5	PSC	Ancillary testing (IHC, FISH) integrated
Milan System (MSRSGC)	Salivary glands (FNA)	2018	6	ASC / IAC	SUMP category; ROM quantified per tier
Yokohama System	Breast (FNA)	2019	5	IAC	International consensus; C1–C5 scale
TIS – Serous Fluids	Pleura / peritoneum / pericardium	2020	5	IAC / PSC	ND/NFM/AUS/SFM/MAL; mesothelioma criteria

Organ-Specific Reporting Systems: Category Comparison

Tier	TBSRTC Thyroid · 2007–2023	PSC Pancr. Pancreas/Bile · 2014	Paris (TPS) Urine · 2016	PSC Resp. Lung/Bronchi · 2016	Milan (MSRSGC) Salivary gl. · 2018	Yokohama Breast FNA · 2019	TIS Serous fluids · 2020
Non-diag.	ND (I)	ND	ND	ND	ND (I)	C1 – Insuff.	ND
Negative / Benign	Benign (II)	Negative	NFM Negative for malignancy	Negative	NFM (II)	C2 – Benign	NFM Negative for malignancy
Atypical / Indeterm.	AUS/FLUS (III) Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance	Atypical (III)	AUC Atypical Urothelial Cells	Atypical	AUS (III)	C3 – Atypical	AUS Atypical Cells of Undetermined Significance
Neoplasm / Suspicious	FN/SFN (IV) Follicular Neoplasm / Suspicious for Follicular Neoplasm Suspicious (V)	Neoplastic Suspicious (IV-V)	SHGUC Suspicious for High Grade Urothelial Carcinoma	Suspicious Neoplasm	Neoplasm ben. (IVa) SUMP (IVb) Uncert. Mal. Pot.	C4 – Suspicious	SFM Suspicious for Malignancy
Malignant	Malignant (VI)	Malignant (VI)	HGUC MAL	Malignant	Malignant (VI)	C5 – Malignant	MAL Malignant

The Shared Architecture: Risk of Malignancy (ROM) as Clinical Driver

Category	ROM	Value	Default management
Non-diagnostic		~20–30 %*	Repeat / resample
Negative / benign		0–3 %	Routine follow-up
Atypia (AUS / AUC)		~15–30 %	Repeat / ancillary testing
Neoplasm / suspicious		60–75 %	Surgery / further workup
Malignant		97–100 %	Definitive treatment



** Non-diagnostic ROM varies widely by site; re-sampling strongly recommended. ROM values are cross-system approximations (TBSRTC, TPS, MSRSGC, TIS).*

The Atypical/Indetermined Category: The Achilles' Heel of All Systems

System	Atypical category	ROM	Reporting rate	Main diagnostic trap
TBS (Cervix)	ASC-US / ASC-H	5–10 % / 40–50 %	~3–5 %	ASC/SIL ratio monitoring required
TBSRTC (Thyroid)	AUS/FLUS (III)	10–30 %	~10 %	Single highest-variability category; repeat FNA often inconclusive
TPS (Urine)	AUC	~20 %	~8–12 %	Bladder washing samples vs voided — different cellularity
MSRSGC (Salivary)	AUS (IVa/IVb)	~20–35 %	~10 %	Oncocytic lesions — major source of atypical calls
PSC Respiratory	Atypical	~15–25 %	~7 %	Reactive atypia vs low-grade malignancy — key diagnostic trap
TIS (Serous)	AUS	~35 %	~5–8 %	Reactive mesothelial vs mesothelioma — IHC mandatory

Interobserver variability is highest in the atypical tier across all systems. Ancillary testing (IHC, FISH, molecular panels) is increasingly embedded in guidelines to reduce indeterminate rates.

Reporting Systems Key Features

- Adequacy criteria
- Atypical/Indeterminate classes
- Boundaries of acceptance for Atypical/Indeterminate reporting (Reporting Rate)
- Risk of Malignancy (ROM) concept for each class
- Management recommendations
- Role of ancillary testing

Summarizing - 2

01

Papanicolaou's classes were a starting point, not an endpoint

Numerical reporting was necessary but insufficient — clinical communication required morphological specificity.

02

Bethesda established the template

Specimen adequacy + tiered risk + management linkage — all subsequent systems follow this three-pillar structure.

03

ROM is the universal challenge

Every modern system is ultimately a risk-stratification tool: the label is secondary to the associated probability of malignancy.

04

The atypical/indeterminate category is where classifications live or die

Reproducibility, ancillary testing protocols, and institutional audit of indeterminate rates define system performance.

05

Integration with molecular pathology is non-negotiable

Cytology reporting in 2026 is a hybrid discipline — morphology provides the framework, ICC/molecular testing fills the gaps.

3 - Cytology in the Molecular & AI Era

From morphology-only diagnosis to integrated molecular, digital pathology and artificial intelligence — a field in transformation

Three Converging Revolutions Reshaping Cytopathology

I

1983 →

The Molecular Revolution

PCR, FISH, ISH, and next-generation sequencing transform cytological specimens from morphological samples into molecular repositories. Ancillary testing becomes standard of care.

II

2014 →

The Digital Pathology Revolution

Whole-slide imaging (WSI) approved for primary diagnosis. Liquid-based cytology scanned at 40×. Telepathology and remote sign-out become feasible. Metadata embedded in the image layer.

III

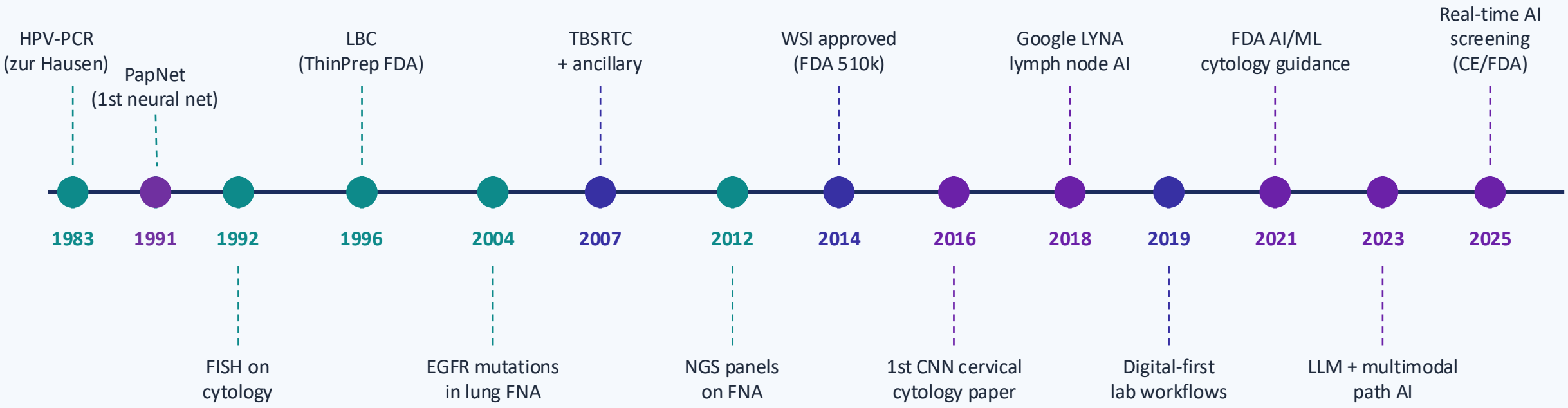
2017 →

The Artificial Intelligence Revolution

Deep Learning, CNNs and ViT match or surpass the sensitivity of cytopathologists and cytotechnologists for HSIL, thyroid atypia, and non-small cell lung cancer subtyping. Multimodal AI integrates image, genomic, and clinical data.

These revolutions are not sequential — they are now simultaneous and mutually reinforcing.

Master Timeline: Cytology + Molecular + Digital + AI



Molecular

Digital pathology

Artificial intelligence

Vårmöte i Patologi
UMEÅ 2026

1 - The Molecular Revolution: From HPV-PCR to NGS

1983 – 2012

~ 1980

Immunocytochemistry
The first effective change in cytological diagnosis

1983

HPV PCR [1-2]

Proof that HPV DNA is detectable in cervical cytology specimens by PCR. Nobel Prize 2008. Transforms a morphological diagnosis into a molecular-backed one.

1990

EGFR mutation detection in FNA [4]

First reports of EGFR hotspot mutations detected in non-small cell lung carcinoma FNA specimens. Opens the era of companion diagnostics on cytological material.

1992

FISH on cytological preparations [3]

Fluorescence in situ hybridisation applied to air-dried and alcohol-fixed smears. Chromosomal numerical aberrations detectable without histological sections.

(2004) 2009

BRAF V600E in thyroid FNA (Bethesda III–IV) [6-7]

BRAF V600E detection in AUS/FLUS thyroid FNA substantially increases pre-surgical malignancy risk stratification.

2012

ALK rearrangement (FISH) on cell blocks [5]

FISH for ALK gene rearrangement validated on cytological cell blocks, enabling reflex testing for targeted therapy without surgical biopsy.

2012

Multi-gene NGS panels on FNA [8-9]

Commercially available panels (e.g., ThyroSeq, Afirma) validated on thyroid FNA.

Molecular Ancillary Testing Integrated into Cytology Reporting

Site	Indeterminate category	Molecular test	Clinical impact
Thyroid FNA	AUS/FLUS (Cat. III)	ThyroSeq v3 / Afirma GSC / BRAF / RAS / RET fusions	Rule-out malignancy (NPV 97%) → avoid surgery in 50% of Cat. III
Lung FNA/bronch.	Atypical / suspicious	NGS: EGFR/ALK/ROS1/KRAS/BRAF/MET/RET/NTRK	Companion dx: direct reflex to targeted therapy without re-biopsy
Pancreas EUS-FNA	Atypical / suspicious	KRAS/GNAS (mucinous); SMAD4/TP53 (PDAC)	Differentiate serous vs mucinous; assess surgical candidacy
Serous effusions	AUS (TIS)	BAP1 IHC / MTAP IHC / CDKN2A FISH	Mesothelioma confirmation; avoids thoracoscopy in frail patients
Salivary glands	AUS IVb (SUMP)	MYB-NFIB / EWSR1 / PLAG1 fusions (FISH/RT-PCR)	Adenoid cystic vs low-grade mucoepidermoid — surgical planning
Urine (TPS)	AUC	FGFR3 mutation / UroSEEK panel	Recurrence monitoring in known bladder carcinoma — non-invasive

IHC = immunohistochemistry · FISH = fluorescence in situ hybridisation · NPV = negative predictive value · EUS = endoscopic ultrasound

Liquid Biopsy: The Convergence of Cytology and Circulating Tumour DNA

2013 →

ctDNA (cell-free DNA) [10]

Plasma-derived fragmented tumour DNA detectable by ddPCR or NGS. Single-nucleotide variants, copy-number alterations, methylation patterns — all informative without tissue.

Circulating Tumour Cells (CTCs) [11-12-13]

Intact tumour cells isolated from blood morphologically assessable. Two methods: immunomagnetic and superhydrophobic substrates. Combined CTC + ctDNA: >90% sensitivity in advanced carcinoma.

Exosomes & tumour-educated platelets [14-15]

Vesicle-borne RNA/miRNA profiles from plasma. Emerging diagnostic platforms for early NSCLC and pancreatic carcinoma, where conventional cytology has limited sensitivity.

Urine ctDNA — the natural liquid biopsy [16]

Urine supernatant ctDNA detectable in urothelial, renal, and even prostate cancer. Complements The Paris System cytology; potential for adjunct urine surveillance panels.

Where liquid biopsy HELPS cytology [17]

Residual indeterminate cases (AUS/AUC): ctDNA profiling can reclassify. Monitoring response to targeted therapy without repeat FNA. Detecting resistance mutations (e.g., T790M EGFR).

Where cytology is IRREPLACEABLE [18]

Morphological context, tumour heterogeneity assessment, direct specimen cellularity, and rapid on-site evaluation (ROSE) remain beyond the reach of cell-free assays.

2 - Digital Pathology: Whole-Slide Imaging in Cytology

2014 →

2013	The Pathology Dpt of the Linköping University Hospital was the first in the world to digitise 100% of histology
2014	FDA clearance for WSI in surgical pathology [19-20]
2019	Validation studies confirm non-inferiority of WSI vs glass for LBC cervical cytology [21-22-23]
2021	IARC/WHO guidelines accept digital review as equivalent to optical microscopy for cervical screening [24-25]
2023	Real-time AI-assisted pre-screening integrated into WSI viewers [26]
2025	Multi-site remote sign-out for FNA and effusion cytology — standard workflow in high-volume centres [27-28]

Key challenge in cytology WSI: sparse cellularity, 3-D clumps, and focus depth variation require z-stack capture or algorithms for single layer reduction.

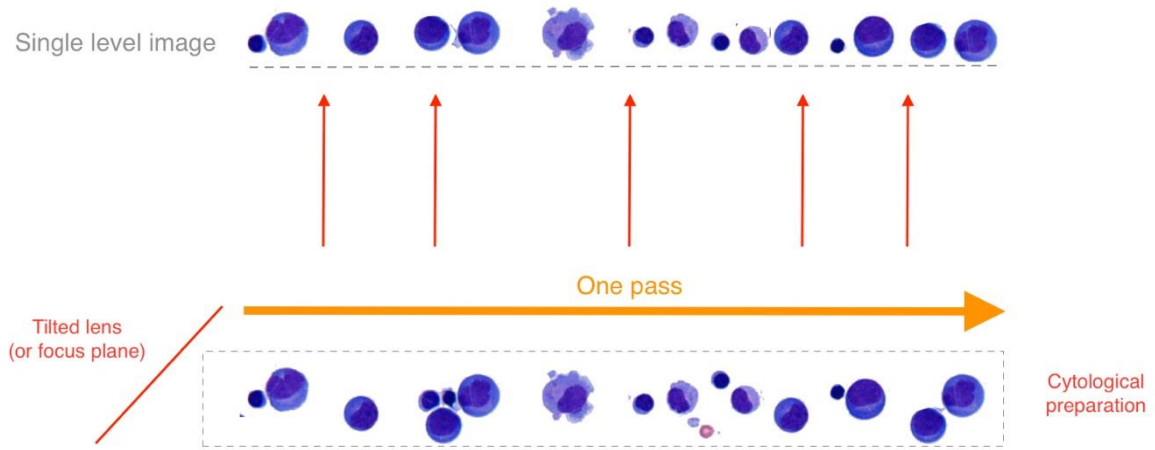
Digital Cytology

Digital cervical cytology is now an established fact.

Digital diagnostic cytology is rarely practised. Only a few examples exist worldwide.

Nowadays, there are practical and effective solutions for all related problems:

- **Three-dimensionality of preparations**
- **Lack of standardization**
- **File size**
- **Scanning and screening speed**



3 - Artificial Intelligence

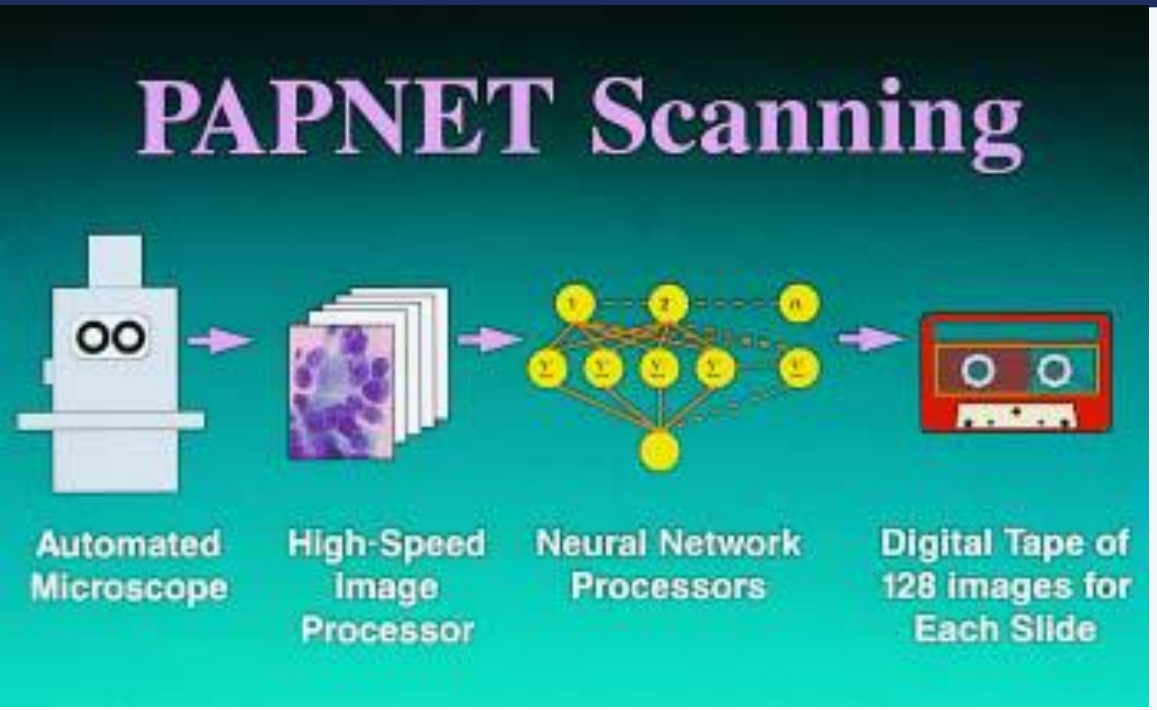
Two words synonymous with

Artificial Intelligence

Probability Calculation

3 - Artificial Intelligence in Cytopathology: PapNet's lonely experience

1991



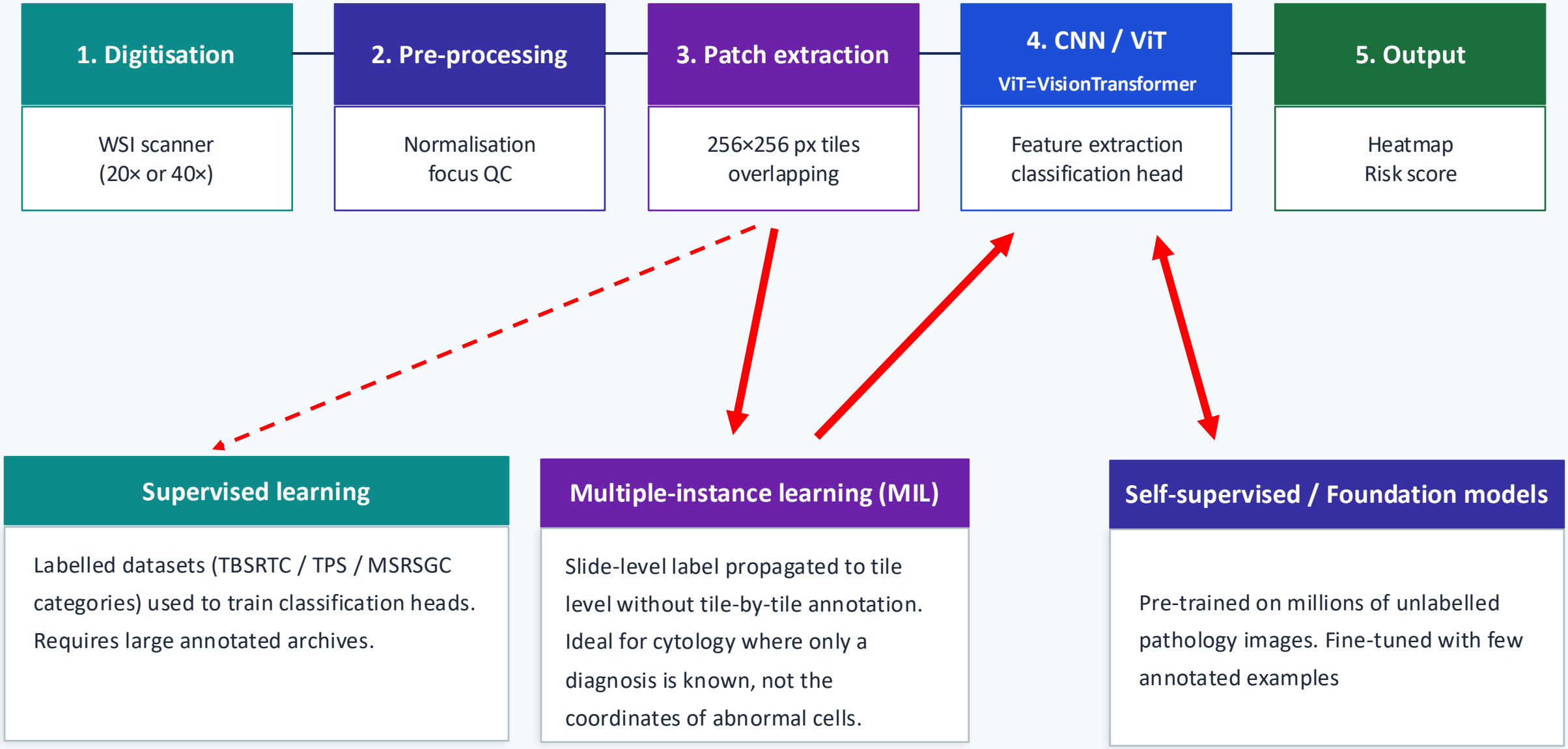
PapNet was a neural-network-based computer-assisted screening system for cervical cytology, developed by Neuromedical Systems Inc. and introduced commercially in the early to mid-1990s.

It scanned conventional glass slides, ranked cells by abnormality probability, and presented the 128 most suspicious images to a cytotechnologist for human review.

Neuromedical Systems filed for bankruptcy in 1999.

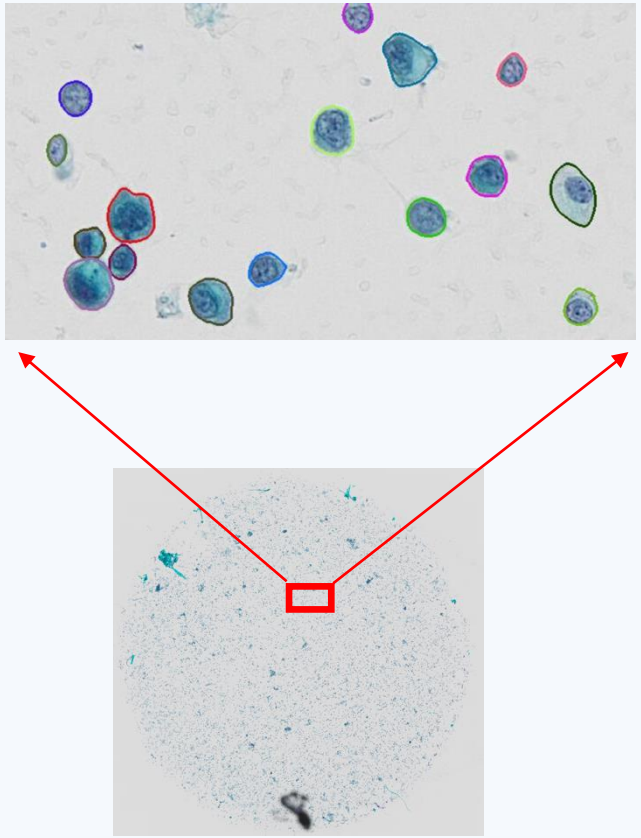
Despite its short commercial lifespan, PapNet is widely regarded as the first real-world deployment of a neural-network-based image-analysis tool in clinical pathology and as a **direct conceptual precursor to today's AI-assisted cytology and digital pathology workflows.**

How AI Works in Cytology: Architecture & Pipeline



Features extraction

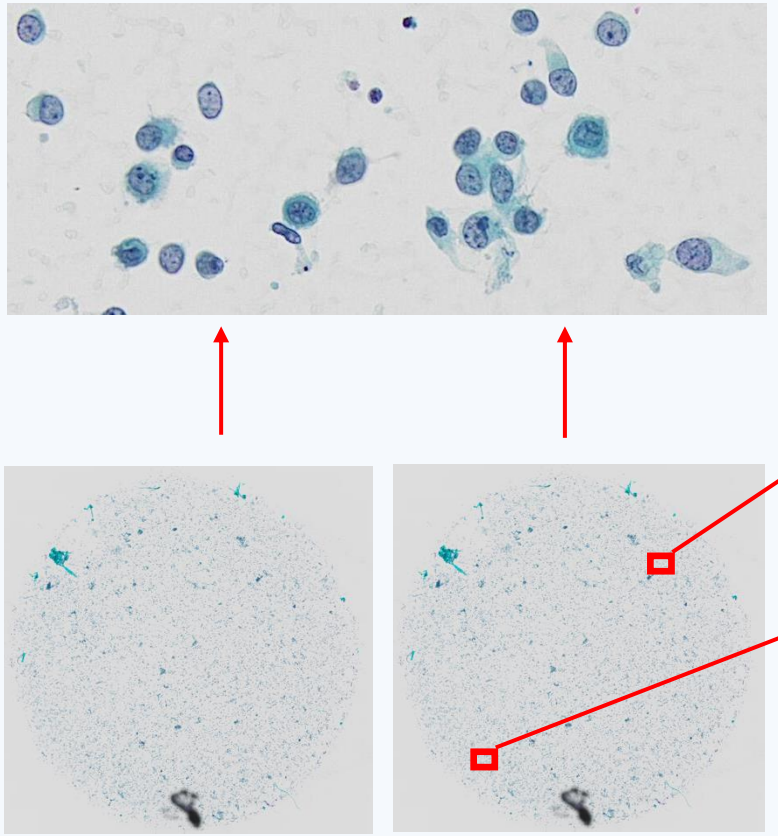
Supervised learning



Benign or malignant

Multiple-instance learning (MIL)

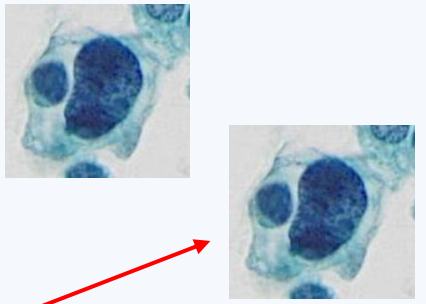
CNNs analyse the image piece by piece, building understanding from the small to the large



Benign

Malignant

ViT takes in the entire image at once and learns to recognise that two distant regions are connected.



Like an expert pathologist who, at a single glance at a slide, already knows where to look.

Foundation Models

The term was coined by Bommasani et al. (Stanford, 2021) to describe

AI models trained on massive amounts of unlabelled data through self-supervised learning,
not optimised for a single specific task, but
adaptable to many tasks with minimal fine-tuning.

A biological analogy is the innate immune system:
it has no prior knowledge of a specific antigen,
but possesses a generalised competence that allows it to mount a rapid and effective response
to virtually any antigen with little additional exposure.

In digital pathology, this translates as follows:
rather than training a separate model to classify thyroid FNA cells
and an entirely different one to detect cervical HSIL,
We have a single large model that is pre-trained on many cytological images without any annotations and then fine-tuned for any specific diagnostic task using only a few hundred labelled examples.
The advantage is substantial in settings where annotated datasets are scarce, as in cytopathology.

From morphology to risk stratification by AI

Cancer Cytopathology
An American Cancer Society Journal

Original Article | Free Access

Scrutinizing high-risk patients from ASC-US cytology via a deep learning model

Xiang Tao MD, PhD, Xiao Chu MD, Bingxue Guo MD, Qiuzhi Pan BS, Shuting Ji BS, Wenjie Lou MD, Chuanfeng Lv MD, PhD, Guotong Xie MD, PhD, Keqin Hua MD, PhD

First published: 15 March 2022 | https://doi.org/10.1002/cncy.22560

Dataset:
1,967 ASC-US cytology smears from which over 60,000 digital images were obtained to train the system

AI Technique:
Deep Learning applied to Whole Slide Images (WSIs) in cytology
Feature extraction at the cellular and slide level
No molecular data required

Clinical comparison:
In 622 cases, hrHPV test results were also available for direct comparison

Parameter	AI-Based Triage System	High-Risk HPV (hrHPV) Testing
Sensitivity (CIN2+)	92.9% (95% CI: 75.0–98.8%)	89.3% (95% CI: 70.6–97.2%)
Specificity (CIN2+)	49.7% (95% CI: 45.6–53.8%)	34.3% (95% CI: 30.6–38.3%)
Method agreement (κ)	κ = 0.138 (very low agreement)	—
Additional testing	Not required	Yes (requires HPV DNA test)

From morphology to targeted therapy by AI

Personalized Medicine

Diagnostic hypothesis
(Histological-Cytological-Radiological-Clinical)

Complementary tests
(molecular or any other type)

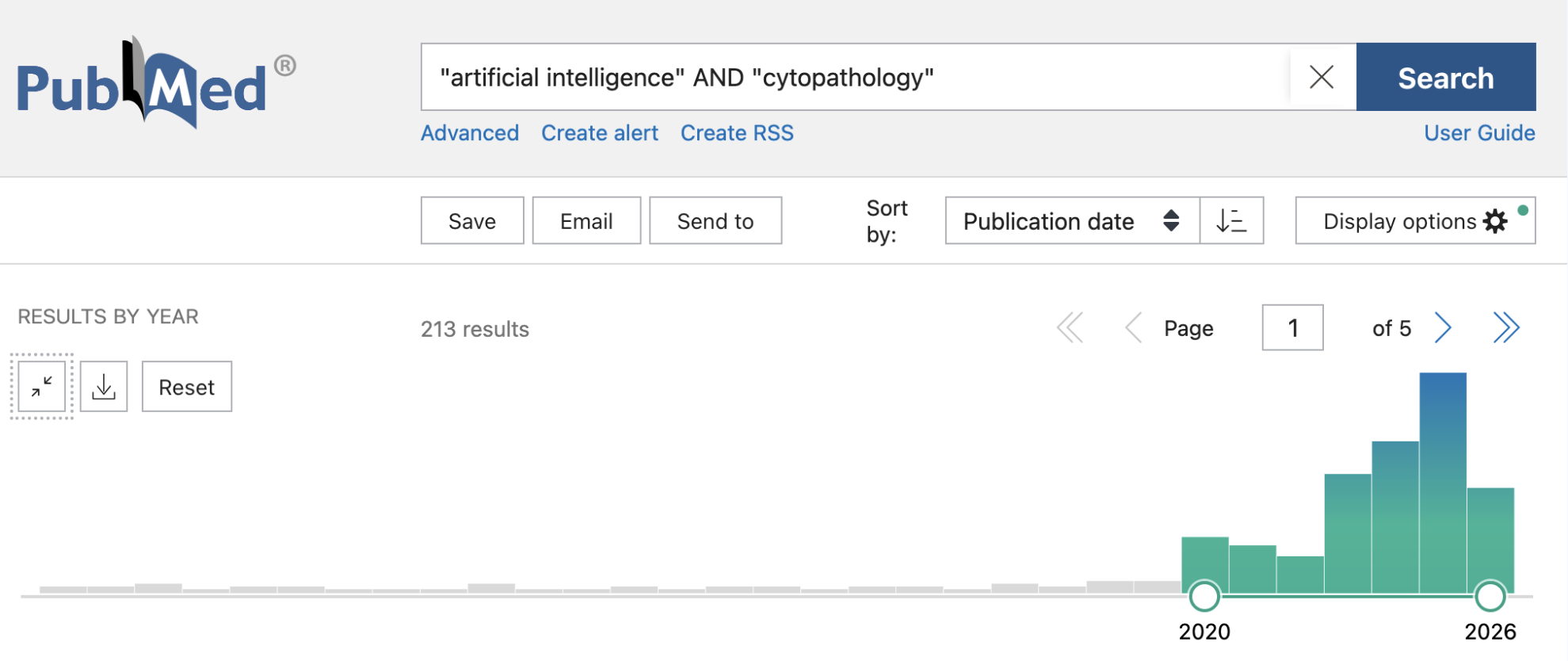
Personalized Therapy

Diagnostic hypothesis
(Histological-Cytological-Radiological-Clinical)

AI

Personalized Therapy

AI application in cytopathology



AI in Cytology: Companies & Products (1/3)

Country	Company	Product	Site	Status	Notes
US USA	**Hologic**	*Genius® Digital Dx*	Cervical LBC	FDA	First & only FDA-cleared digital cytology system. AI + volumetric imaging. ~50% less review time per case.
US USA	**BD (Becton Dickinson)**	*FocalPoint™ GS*	Cervical conv./LBC	FDA	Legacy neural network pre-screener. Widely installed globally. Pre-dates deep learning era.
US USA	**PathAI**	*AISight® Dx*	Pathology WSI	FDA	510(k) FDA clearance June 2025 for primary diagnosis image management. Cytology modules in development.
US USA	**Paige.AI**	*Paige Cervical*	Cervical LBC	BTD	FDA Breakthrough Device Designation. Deep learning pre-screener for HSIL on LBC slides.
US USA	**Paige.AI**	*PanCancer Detect*	Multi-site	BTD	FDA Breakthrough Device Designation (April 2025). AI tool targeting common and rare cancers across multiple tissue types.

FDA — cleared/approved RUO — Research Use Only BTD — Breakthrough Device CE — European conformity

AI in Cytology: Companies & Products (2/3)

Country	Company	Product	Site	Status	Notes
US USA/TW	**AIxMed**	*AIxURO™*	Urine (TPS)	RUO	Only commercial AI product for urinary cytology. Paris System-based. CE marking in progress. Expanding in Europe.
US USA/TW	**AIxMed**	*AIxTHY (dev.)*	Thyroid FNA	RUO	In development. Extension of the AIxURO platform to TBSRTC-based thyroid FNA classification.
US USA/TW	**AIxMed**	*AIxPUL (dev.)*	Lung cytology	RUO	In development for lung cytology. NSCLC subtyping on cytological material. Pipeline product.
US USA	**Deepcell**	*Deepcell Platform*	Body fluids	RUO	Microfluidic AI sorting of malignant cells from effusions. Morphology-based, label-free. NGS-ready (Mavropoulos et al., Mod Pathol 2023).
FR France EU EU	**VitaDx**	*VisioCyt Screening*	Urine (TPS)	CE	CE-marked AI for urinary cytology. Also offers VisioCyt Thyroid. Based in Lyon.

FDA — cleared/approved

RUO — Research Use Only

BTD — Breakthrough Device

CE — European conformity

AI in Cytology: Companies & Products (3/3)

Country	Company	Product	Site	Status	Notes
FR France EU EU	**VitaDx**	*VisioCyt Thyroid*	Thyroid FNA	CE	CE-marked. AI classification of thyroid FNA on Papanicolaou-stained slides. TBSRTC-aligned categories.
FR France EU EU	**Ibex Medical Analytics**	*GALEN™ suite*	Histo + cytol.	CE	Most widely deployed AI pathology platform globally. CE-marked, IVDR-compliant. Integrated with Roche Navify DP.
IL Israel EU EU	**Owkin**	*AI diagnostics*	Onco research	CE	AI for translational oncology and diagnostics. Cytology component in development. Franco-American.
FR France EU EU	**Visiopharm**	*AI image analysis*	Histo + cytol.	CE	European leader in quantitative image analysis. Modules for cytology. Partner of major IVD manufacturers.
DK Denmark EU EU	**Aiforia**	*Cloud AI platform*	Histo + cytol.	CE	Cloud-based CE-marked platform. Pathologist-configurable AI modules. Used in European academic centres.
FI Finland EU EU	**Qritive**	*AI pathology suite*	Multi-site	CE	Asia-Pacific leader. AI tools for cytology and histology. Expanding globally with CE marking.

FDA — cleared/approved

RUO — Research Use Only

BTD — Breakthrough Device

CE — European conformity

AI vs Cytopathologist: Complementary, Not Competitive

Dimension	AI / Deep learning	Human cytopathologist
Throughput	10,000+ slides/day	~80–120 slides/day
Rare lesions	Underperforms (sparse training data)	Expert pattern recognition, clinical context
Consistency	Zero intraobserver variability	Fatigue, lighting, slide order effects
Morphol. nuance	Misses architectural / 3D patterns	Gestalt: architecture, cohesion, background
Ancillary integration	Multimodal AI: image + molecular + clinical	Limited by cognitive load
Accountability	Regulatory / liability frameworks evolving	Clear professional responsibility
Cost (marginal)	Near-zero per slide once trained	Specialist time scales with volume
Unknown unknowns	Blind to out-of-distribution findings	Can recognise 'something is wrong'

Advantage

The Next Decade: Cytology 2.0 — Emerging Frontiers

Spatial transcriptomics on cytological specimens

10x Visium and Slide-seq adapted for LBC.
Gene expression mapped at single-cell resolution without tissue sectioning. Higher molecular resolution than standard histology.

Single-cell multi-omics from FNA

scRNA-seq (transcriptome), which genes are actively transcr.
scATAC-seq (epigenome), DNA open regions
Proteomics, what the cell is actually producing

Autonomous AI screening in LMICs

Portable scanners + edge-AI inference for cervical cancer screening in resource-limited settings.
WHO pilot programmes underway in sub-Saharan Africa and South/Southeast Asia.

Digital twins (Flying Simulator) of cytological specimens

Computational models reconstructing 3-D cellular architecture from 2-D images + AI + genomic data. Predictive simulation of tumour behaviour pre-treatment.

LLM-integrated cytology reports

Large language models parse morphological descriptions + molecular reports + clinical context to generate structured, guideline-consistent cytology reports with ROM quantification and management recommendations.

The cytopathologist of 2036

No longer a primary screener — an interpretive specialist validating AI outputs, integrating molecular data, and functioning as a 'molecular tumour board' participant. Demand for subspecialty expertise in cytomolecular pathology will increase, not decrease.

Summarizing - 3

01

Cytology specimen = molecular repository

Every FNA pass, LBC vial, and effusion sample is simultaneously a morphological and molecular substrate. ROSE now serves needle adequacy for NGS, not just diagnosis.

02

The ROM concept is molecularly calibrated

Modern organ-specific systems pair the morphological category with a molecular panel that narrows probabilistic ROM to an actionable binary. The indeterminate tier shrinks.

03

Digital pathology is the enabling platform

AI cannot function without digitisation. WSI, DICOM metadata, and LIS integration are prerequisites — not optional upgrades — for AI implementation in cytology.

04

AI augments, does not replace, the cytopathologist

AI excels at throughput and consistency; the human excels at rare lesions, architectural gestalt, and accountability. The optimal unit is human-AI collaboration.

05

Regulation and equity must keep pace

CE/FDA frameworks are evolving but lag behind technical capability. Global equity — ensuring AI-assisted screening reaches LMICs — is the defining ethical challenge of the next decade.

Morphology (1948) → LBC (1996) → Molecular ancillary (2004) → Digital WSI (2014) → AI pre-screening (2020) → Multimodal AI (2026 →)

Conclusions (1) — The Integration Is Underway and Irreversible

The cytological specimen is simultaneously three things.

I

A morphological substrate

Cell architecture, nuclear features, background, cohesion — the irreplaceable visual gestalt that only a trained human eye can integrate in its full complexity.

II

A molecular repository

Every LBC vial, every FNA pass, every effusion sample contains DNA, RNA, and protein. The needle that makes the diagnosis also collects the molecular profile that guides treatment.

III

A training dataset for AI

Every annotated slide, every labelled case, every structured report is a data point that trains the next generation of diagnostic algorithms. The specimen does not change — its informational value multiplies.

These three dimensions cannot be separated. The integration is structural, not optional. And it is irreversible.

Conclusions (2) — Reliable AI Requires Data. Only Pathologists Have It.

We are not only the “end-users” of AI. We are its primary source.

01

AI does not emerge from algorithms alone

Every image required a human expert to acquire, prepare, and label.

02

The knowledge in an AI model comes from pathologists’ expertise

When an algorithm correctly identifies an HSIL or flags an atypical mesothelial cell, it is applying a pattern learned from a cytopathologist's annotation.

03

No engineer can build reliable diagnostic AI without us

Data scientists provide architecture. Computing centres provide power. But the ground truth — the labelled, validated, clinically correlated image — can only come from the cytopathologist at the microscope.

04

Our expertise is the rate-limiting step

The bottleneck in AI development for cytopathology is not computational power or algorithmic sophistication. It is the scarcity of expert-annotated data. We are both the problem and the solution.

The knowledge embedded in every AI model is, at its core, the distilled expertise of pathologists.

Conclusions (3) — We Lack Repositories. Only We Can Fill This Gap.

The data gap is our problem to solve — and we are the only ones who can.

Field	Reference dataset	Scale	Cytology equivalent
Histopathology	TCGA (The Cancer Genome Atlas) BigPicture (European Repository)	~50,000 WSI, 33 cancer types	—
Radiology	ImageNet / RSNA datasets	Millions of images	—
Dermatology	ISIC Archive	>600,000 dermoscopy images	—
Cytology	No equivalent exists	Scattered, proprietary	**This is the gap**

What is needed: federated biobanks · annotated image archives · structured reporting with data export · international consortia

Building the data infrastructure this field requires is not a task for industry alone. It requires the active, coordinated engagement of cytopathologists worldwide.

The European Repository of Cytological cases for Educational Quality Control and Research Purposes

Conclusions (4) — Evolution Has Never Stopped. It Will Not Stop Now.

Ignoring change is not a neutral act. It is a choice to become irrelevant.

1943	**Cervical smear for cancer diagnosis**	'Speculative' → now: universal standard of care
1988	**Replacing numeric classes with terminology**	'Unnecessary complexity' → now: global standard
1991	**Neural network pre-screening (PapNet)**	'Will never replace the cytotechnologist' → now: FDA-cleared AI
2004	**Molecular testing on FNA material**	'Insufficient material' → now: companion diagnostic standard
2014	**Whole-slide imaging for primary diagnosis**	'Cannot replace the microscope' → now: ISO/FDA/CE validated
2024	**Foundation models in cytopathology**	'Too early, not validated' → actively entering clinical workflows

The history of cytopathology is a history of people who looked further than their contemporaries thought reasonable.

https://www.mutotheinkcat.com/

As previously said, we are at the same time the problem and the solution.

This attitude doesn’t help and puts us and all cytology out of history.

We must be brave, proactive,
aware of our present experience,
open to prospects.
Because only

Those who sow utopia reap reality.

(Carlín Petrini)

Thank You

Cytology: From Morphology to AI and Beyond.

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