

Refining the Diagnosis: Evolving Concepts in Urinary Tract Cytopathology

Chris VandenBussche MD PhD

Associate Professor of Pathology and Oncology
Associate Director, Cytopathology Division
Director, Pathology Residency Training Program
The Johns Hopkins University School of Medicine



**Ureteral washing specimen from a patient with both
low grade urothelial carcinoma and carcinoma in situ**

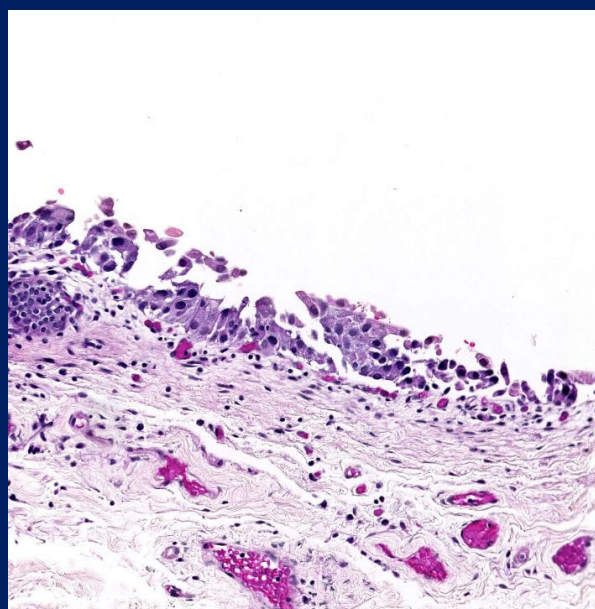
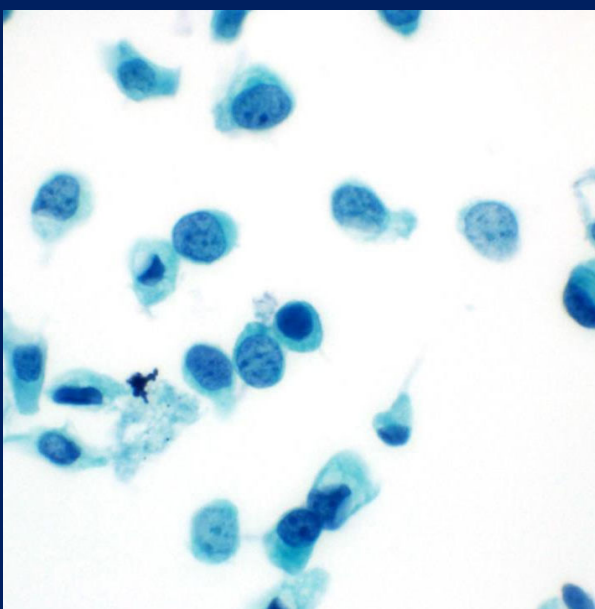


TABLE 1. Classification Scheme Proposed
by G. Papanicolaou

Class	Definition
1	Absence of abnormal or atypical cells
2	Atypical cells present but without abnormal features
3	Cells with abnormal features but not sufficiently pathognomonic
4	Fair number of pathognomonic cells and cell clusters
5	Large number of conclusive cells and cell clusters

Owens CL, Vandenbussche CJ, Burroughs FH, Rosenthal DL. A review of reporting systems and terminology for urine cytology. *Cancer Cytopathol.* 2013 Jan;121(1):9-14. doi: 10.1002/cncy.21253. Epub 2012 Nov 28. PMID: 23192885.

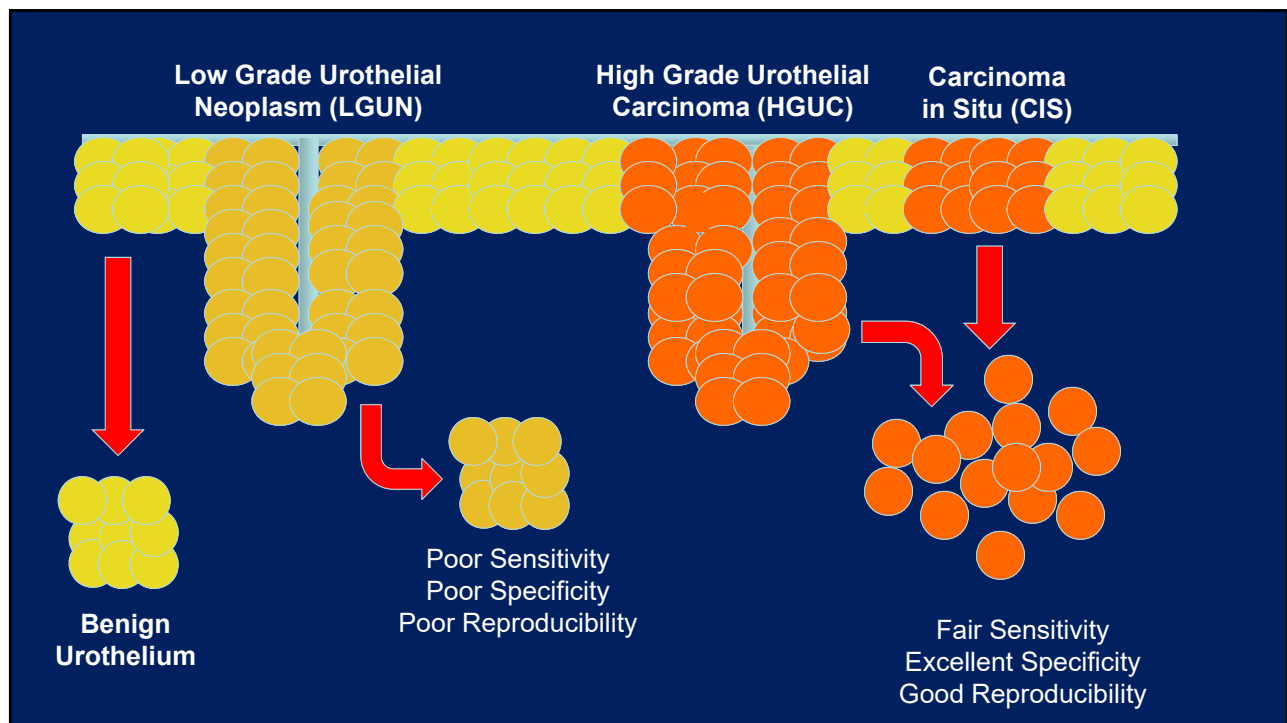
TABLE 2. Histopathologic Basis of Urine Cytology:
L. G. Koss

Histology	Cytopathology
Benign	Benign urothelial cells, few ATY 1 cells
Inflammatory conditions and instrumented urine	Bland clusters/fragments; ATY 1 cells
Papilloma, grade 1	Clusters, nuclear elongation
papillary carcinoma	
Grade 2 and 3 papillary carcinoma, CIS	Malignant cells; numerous ATY 2 cells

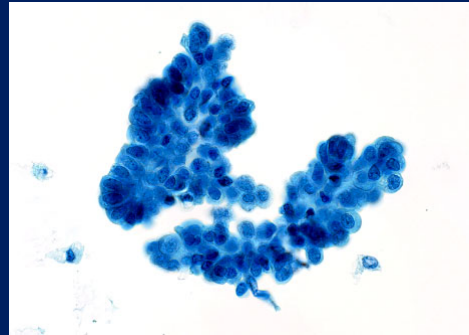
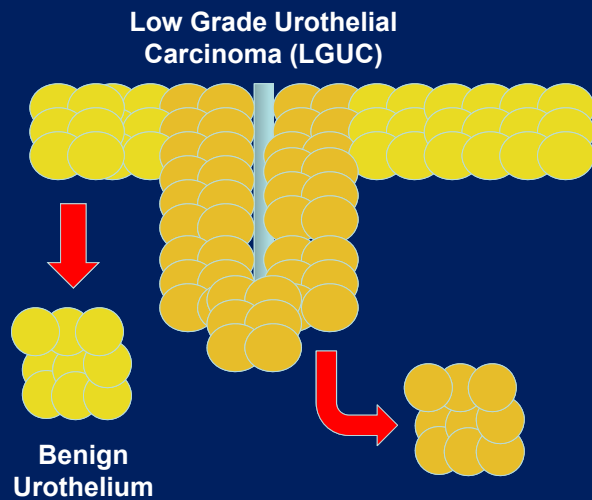
Abbreviations: ATY 1, atypical cells with hyperchromasia and predominantly round or oval contours; ATY 2, cells with hyperchromasia and nuclear membrane abnormalities; CIS, carcinoma in situ.

Owens CL, Vandenbussche CJ, Burroughs FH, Rosenthal DL. A review of reporting systems and terminology for urine cytology. *Cancer Cytopathol.* 2013 Jan;121(1):9-14. doi: 10.1002/cncy.21253. Epub 2012 Nov 28. PMID: 23192885.

Can we diagnose low grade urothelial neoplasms (LGUN)?



Fear of Missing Low Grade Urothelial Carcinoma



Benign-Appearing Urothelial Tissue Fragment (BUTF)

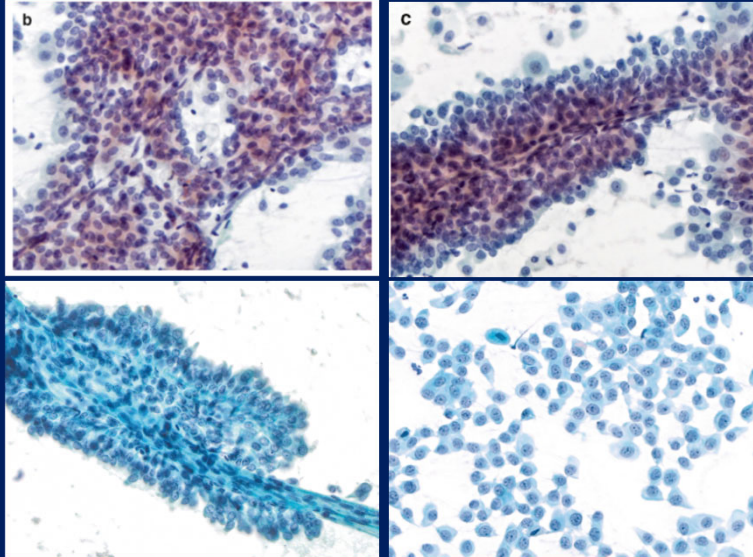
General Cytologic Diagnostic Categories

- Benign (Negative for Malignancy)
- Indeterminate
 - Atypical
 - Suspicious for Malignancy
- Malignant

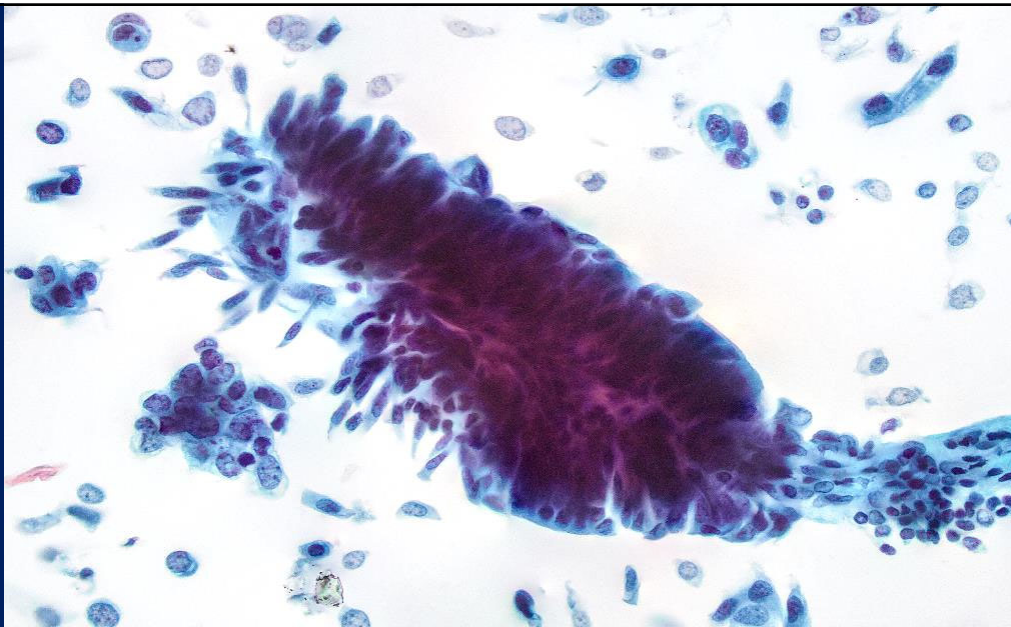
The Paris System for Reporting Urinary Cytology

- Negative for High Grade Urothelial Carcinoma
- Atypical Urothelial Cells (AUC)
- Suspicious for High Grade Urothelial Carcinoma
- High Grade Urothelial Carcinoma
- Other
- Non-Diagnostic

Low Grade Urothelial Neoplasms (LGUN)

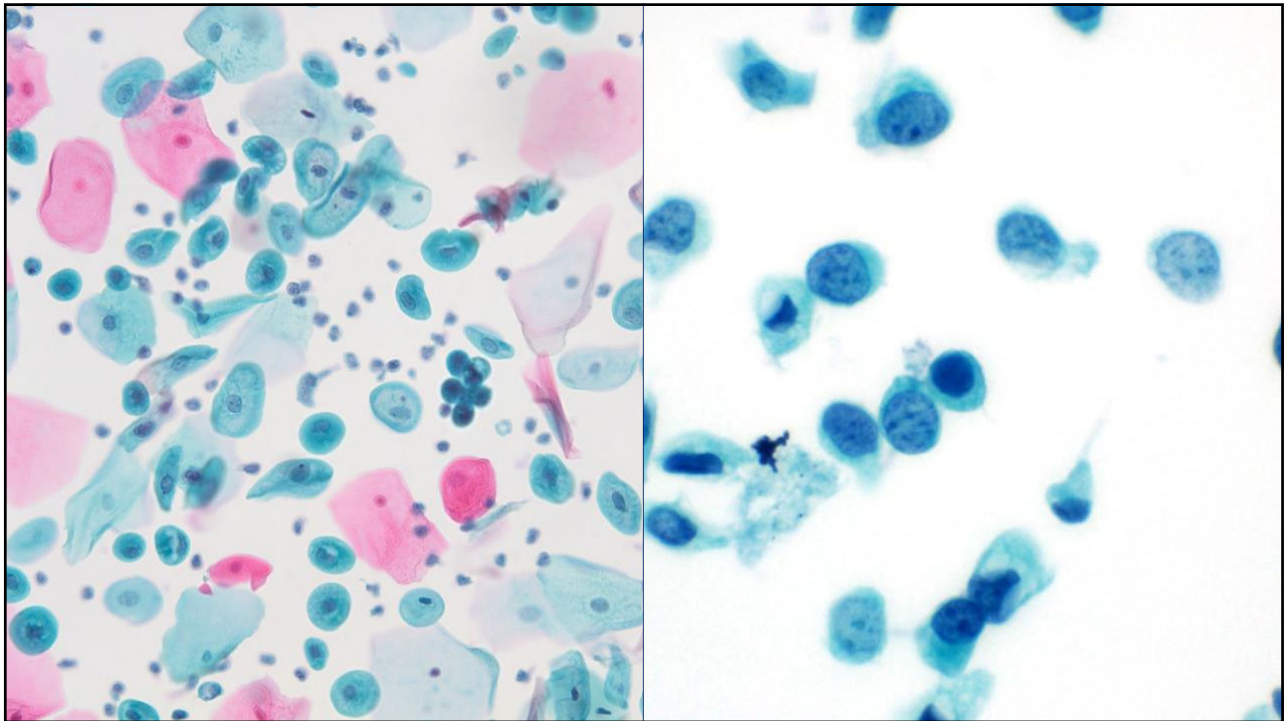


VandenBussche CJ, Chandra A, Heymann JJ, McCroskey Z, Owens CL, Schubert PT, Wang YH. Negative for high-grade urothelial carcinoma (NHGUC). In: The Paris System for Reporting Urinary Cytology 2022 Feb 3 (pp. 21-62). Cham: Springer International Publishing.



Ureteral washing specimen from a patient with both low grade urothelial carcinoma and carcinoma in situ

Can we diagnose high grade urothelial carcinoma (HGUC)?



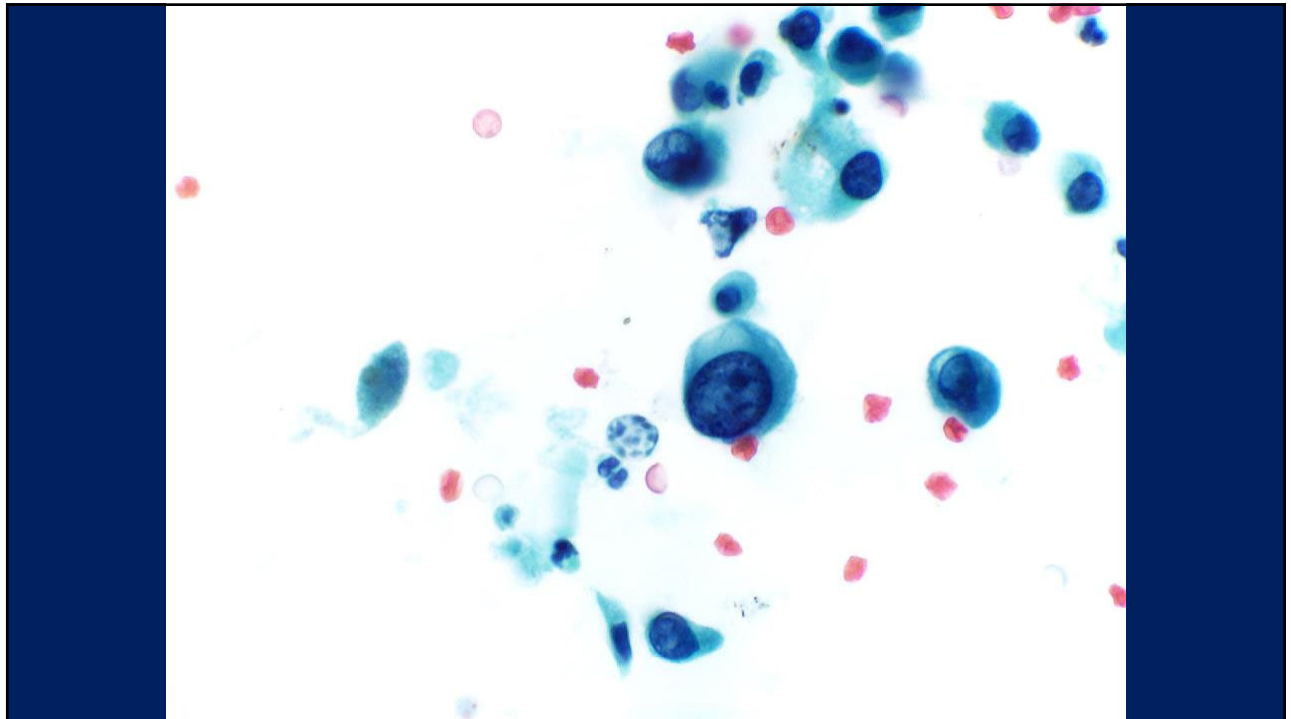
HGUC & Suspicious for HGUC [TPS 2.0]

Morphological Criteria (Required):

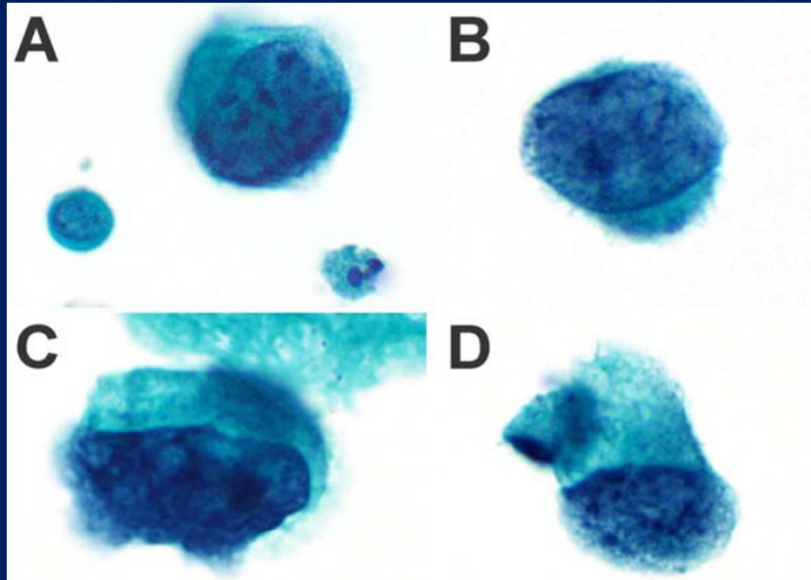
- ~~Non-degenerated~~, non-superficial cells
- **High N/C ratio (~>0.7)**

Morphologic Criteria (Two of Three):

- Irregular clumpy chromatin
 - Irregular nuclear membranes (marked)
 - Hyperchromasia (moderate to severe)
-
- SHGUC = <5-10 cells
 - HGUC = >5-10 cells

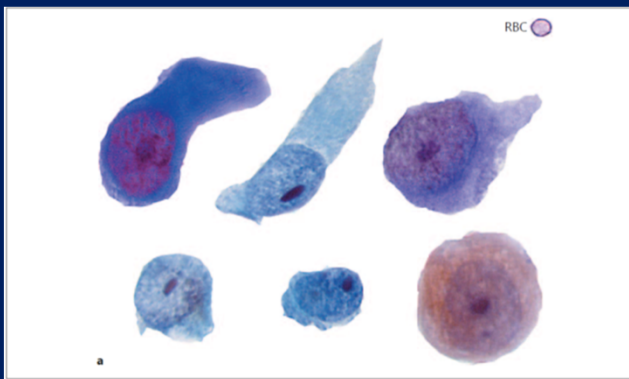


Diagnostic Dilemmas



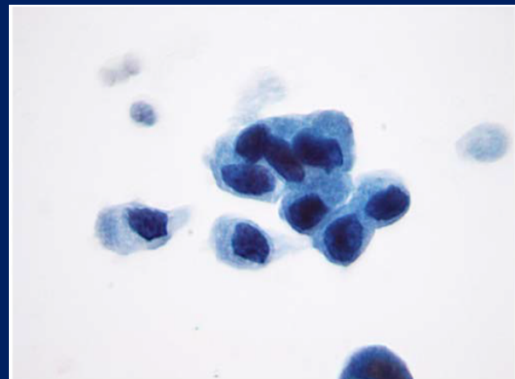
Cowan ML et al. Cancer Cytopathol. 2017 Jun;125(6):427-34.

Umbrella Cell Morphology



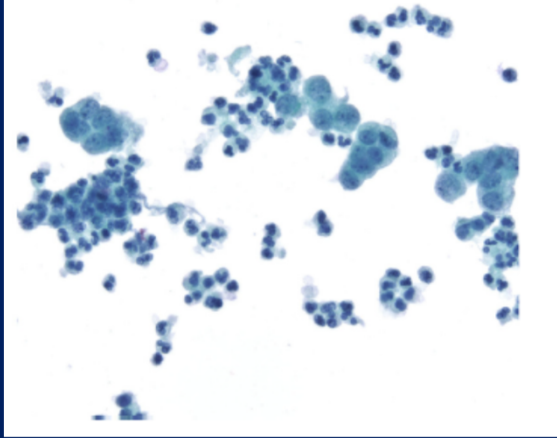
Renshaw AA, Gould EW. High-Grade Urothelial Carcinoma on Urine Cytology Resembling Umbrella Cells. Acta Cytol. 2018;62(1):62-67. doi: 10.1159/000481908.

Jet-Black Nuclei



Renshaw AA, Gould EW. High-grade urothelial carcinoma in urine cytology with jet black and smooth or glassy chromatin. Cancer Cytopathol. 2018 Jan;126(1):64-68. doi: 10.1002/ency.21947.

“Hypochromatic” HGUC



Xing J, Monaco SE, Pantanowitz L. Utility of The Paris System for Reporting Urinary Cytology in upper urinary tract specimens. J Am Soc Cytopathol. 2018 Nov-Dec;7(6):311-317. doi: 10.1016/j.jasc.2018.07.006.

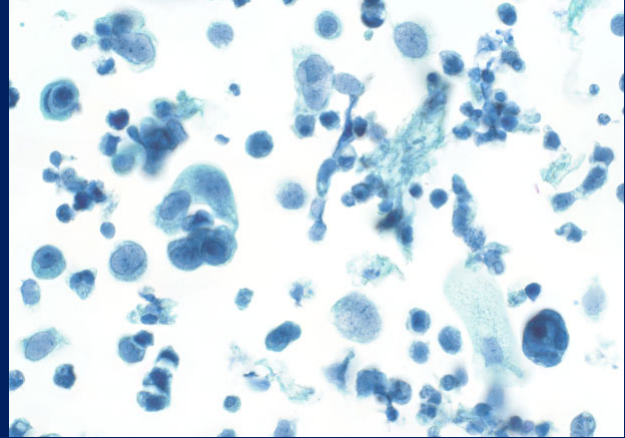
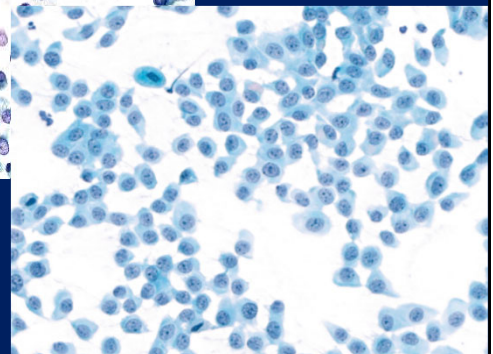
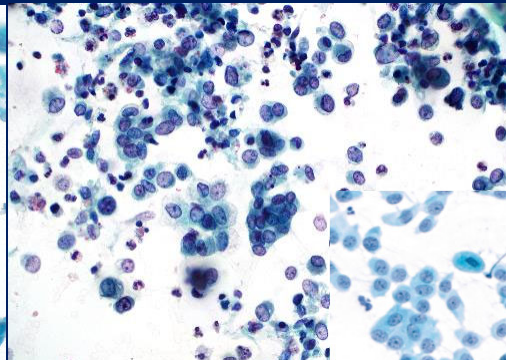
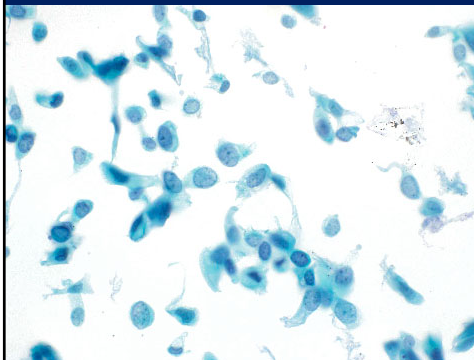


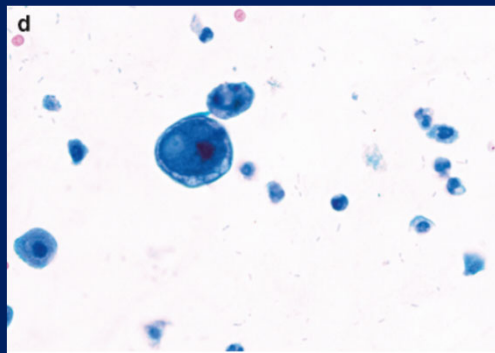
Image published in TPS 2.0.

LGUN vs. “Hypochromatic” HGUC

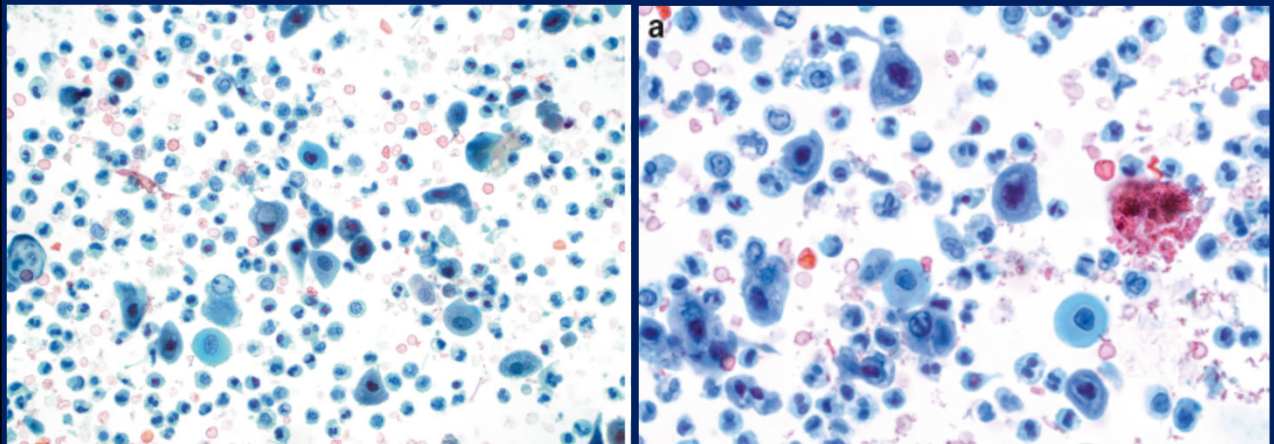


How to deal with degenerative changes?

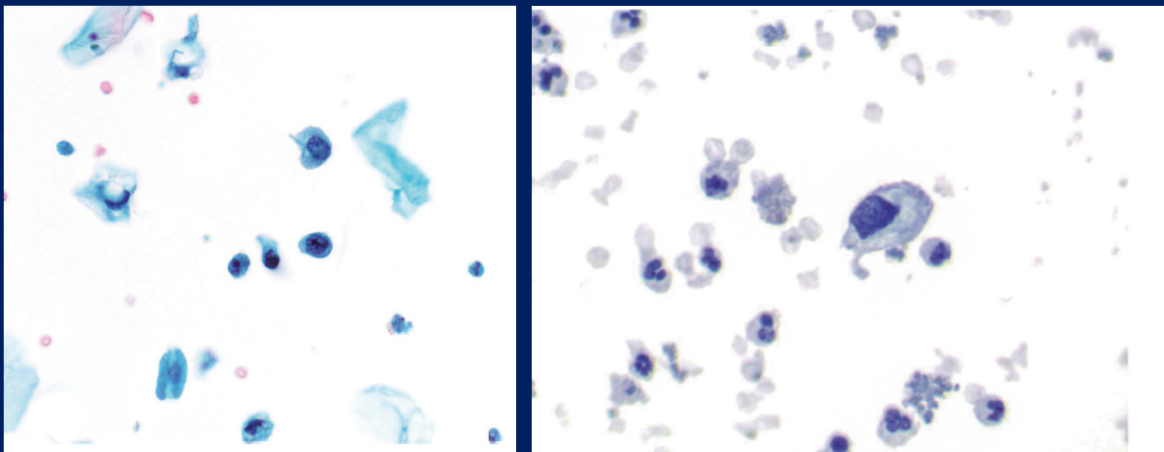
Indeterminate Degeneration (Do Not Assess)



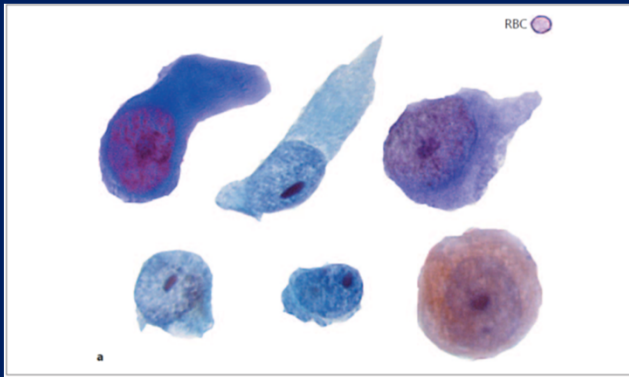
Benign Degeneration



Degenerated HGUC Cells

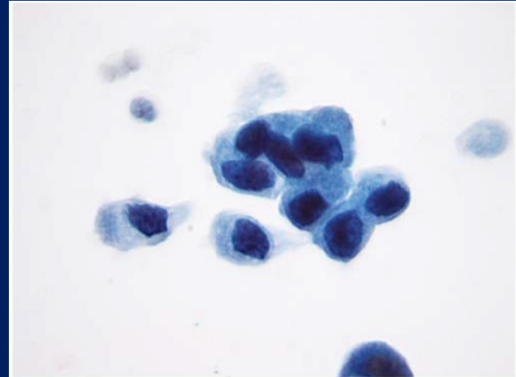


Umbrella Cell Morphology



Renshaw AA, Gould EW. High-Grade Urothelial Carcinoma on Urine Cytology Resembling Umbrella Cells. *Acta Cytol.* 2018;62(1):62-67. doi: 10.1159/000481908.

Jet-Black Nuclei



Renshaw AA, Gould EW. High-grade urothelial carcinoma in urine cytology with jet black and smooth or glassy chromatin. *Cancer Cytopathol.* 2018 Jan;126(1):64-68. doi: 10.1002/cncy.21947.

What is the point of “atypia”?

“Atypical” Category Performance in UTC

Table 4.1 Published reporting rates and the follow-up of atypical urothelial cells

Study	Year	Rate of AUC (%)	Follow-up HGUC (%)
Barasch et al. [6]	2013	5.7	14.3
Rosenthal et al. [7]	2013	31.0	18.0
Piaton et al. [8]	2014	<2	8.3
Muus et al. [9]	2012	8.1	21.0
Mokhtar et al. [10]	2010	2.1	37.5
Brimo et al. [11]	2009	26.0	37.0
Streeter et al. [12]	2008	N/A	30.9
Kapur et al. [13]	2008	6.9	33.0
Bhatia et al. [14]	2006	1.9	20.0
Deshpande et al. [15]	2005	N/A	13.0

AUC atypical urothelial cells, HGUC high-grade urothelial carcinoma, N/A not applicable

The Paris System for Reporting Urinary Cytology, 2016



- IAC/ASC/Springer Support
- Solicit Community Feedback / Surveys
- Urologist Input
- Committee Meetings & Teleconferences
- Inter-observer Survey
- Presentations at National & International Meetings



Atypical Urothelial Cells (AUC)

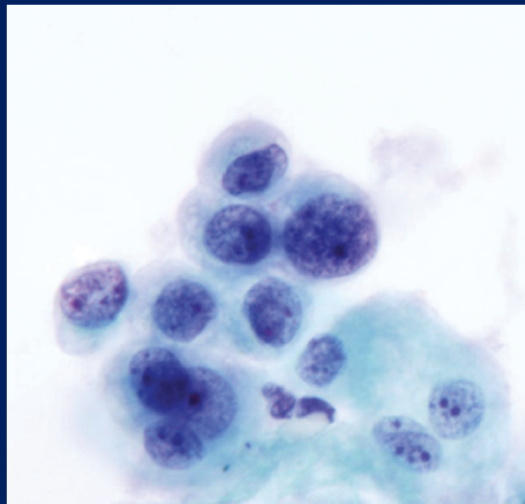
Morphological Criteria (Required):

- ~~Non-degenerated~~, non-superficial cells
- Elevated N/C ratio ($\sim >0.5$), due to increased nuclear size.

Morphologic Criteria (One of These):

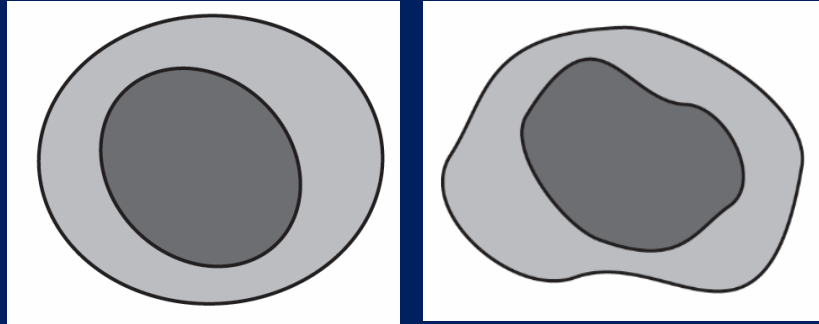
- Irregular clumpy chromatin
- Irregular nuclear membranes
- Hyperchromasia

Number of atypical cells is not a criterion.

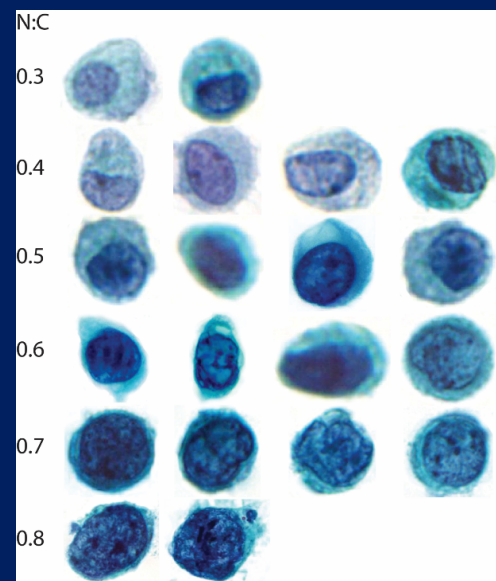
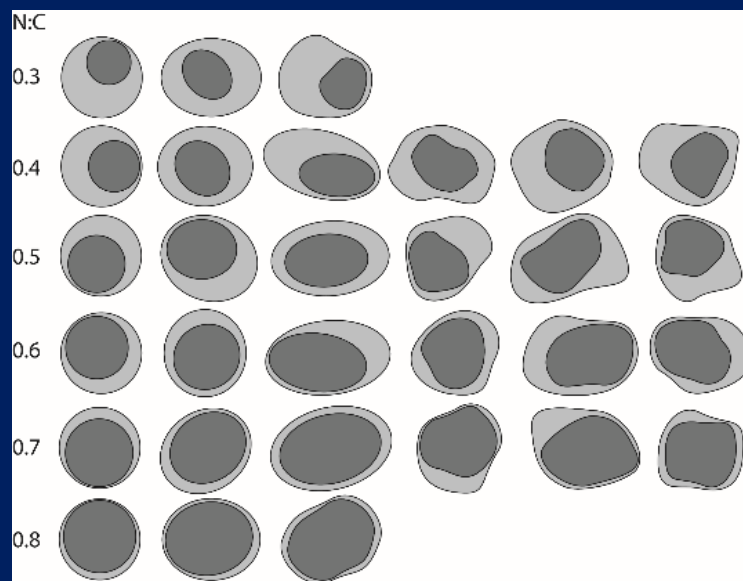


Barkan GA, Compton ML, Elsheikh TM, Ely KA, Kurtycz DF, Jorda M, Maleki Z, Minamiguchi S, Ohtani H, Piaton E, Ping B et al. Atypical Urothelial Cells (AUC). In: The Paris System for Reporting Urinary Cytology 2022 Feb 3 (pp. 63-83). Cham: Springer International Publishing.

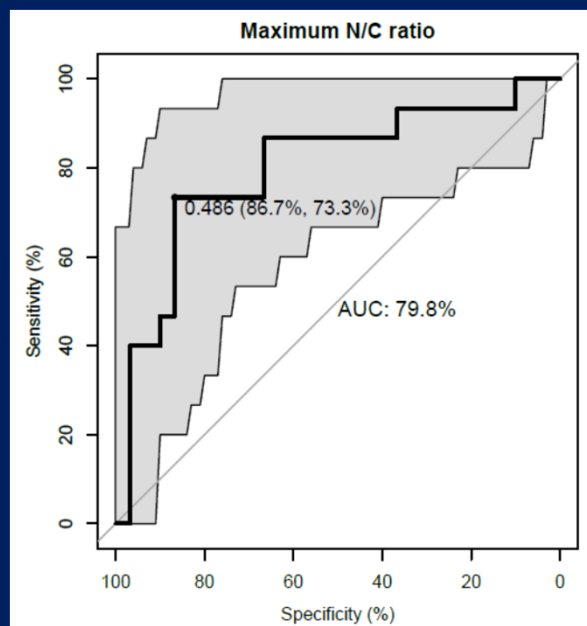
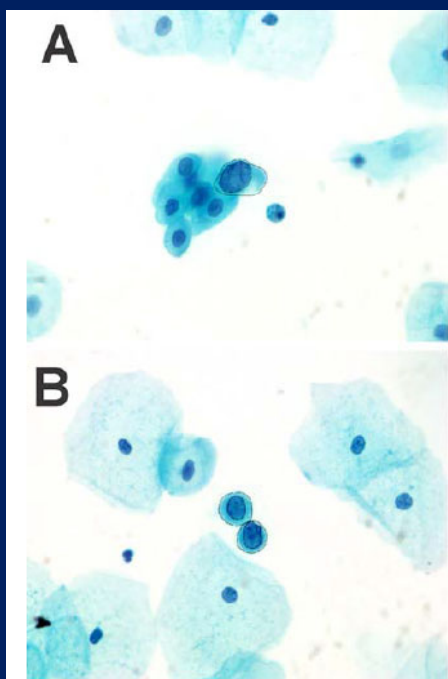
Estimate the N:C Ratio:



Zhang ML, Guo AX, VandenBussche CJ. Morphologists overestimate the nuclear-to-cytoplasmic ratio. *Cancer Cytopathol.* 2016 Sep;124(9):669-77. doi: 10.1002/cncy.21735. Epub 2016 May 9. PMID: 27159533.



Zhang ML, Guo AX, VandenBussche CJ. Morphologists overestimate the nuclear-to-cytoplasmic ratio. *Cancer Cytopathol.* 2016 Sep;124(9):669-77. doi: 10.1002/cncy.21735. Epub 2016 May 9. PMID: 27159533.



Hang JF, Charu V, Zhang ML, VandenBussche CJ. Digital image analysis supports a nuclear-to-cytoplasmic ratio cutoff value of 0.5 for atypical urothelial cells. *Cancer Cytopathol.* 2017 Sep;125(9):710-716. doi: 10.1002/cncy.21883. Epub 2017 Jun 5. PMID: 28581671.

Impact on Rate of Atypia

Table 1 Published changes in diagnosis rates by institution following institution of The Paris System for Reporting Urinary Cytology (TPS).

	Hassan et al		Torous et al		VandenBussche et al		Wang et al	
	Pre TPS, %	Post TPS, %	Pre TPS, %	Post TPS, %	Pre TPS, %	Post TPS, %	Pre TPS, %	Post TPS, %
Negative	NR	NR	64.3	70.7	64.9	66.1	75.4	80.0
Atypical	39	26	29.5	21.8	23.9	23.0	18.6	14.4
Suspicious	NR	NR	3.3	4.4	5.8	4.5	3.0	2.4
Malignant	NR	NR	2.9	3.0	3.8	5.0	3.0	3.2

Abbreviation: NR, not reported.

Cowan and VandenBussche. doi: 10.1016/j.jasc.2018.04.001

PRE/POST PARIS	PRE-TPS #	PRE-TPS%	POST TPS #	POST TPS %	DIFFERENCE	P-VALUE
UNSAT	67	0.42	93	0.45	5.51	> 0.05
NEG/NEG FOR HGUC	12832	81.22	18080	86.99	7.10	< 0.0001
ATYPICAL/AUC	2001	12.67	1770	8.52	-32.76	< 0.0001
SUSP/SUSP HGUC	360	2.28	407	1.96	-14.06	0.029
POSITIVE/POS HGUC	399	2.53	348	1.67	-33.70	< 0.0001
LOW GRADE UC/LGUN	0	0	2	0.01	N/A	N/A
OTHER/OTHER	8	0.05	3	0.01	0.01	N/A

Barkan et al.

Impact on Rate of Atypia

Table 1 Published changes in diagnosis rates by institution following institution of The Paris System for Reporting Urinary Cytology (TPS).

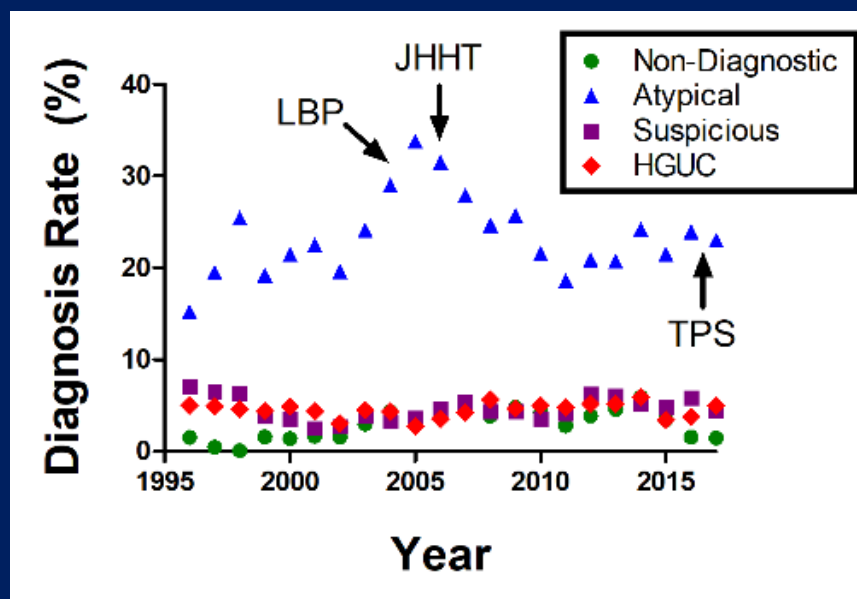
	Hassan et al		Torous et al		VandenBussche et al		Wang et al	
	Pre TPS, %	Post TPS, %	Pre TPS, %	Post TPS, %	Pre TPS, %	Post TPS, %	Pre TPS, %	Post TPS, %
Negative	NR	NR	64.3	70.7	64.9	66.1	75.4	80.0
Atypical	39	26	29.5	21.8	23.9	23.0	18.6	14.4
Suspicious	NR	NR	3.3	4.4	5.8	4.5	3.0	2.4
Malignant	NR	NR	2.9	3.0	3.8	5.0	3.0	3.2

Abbreviation: NR, not reported.

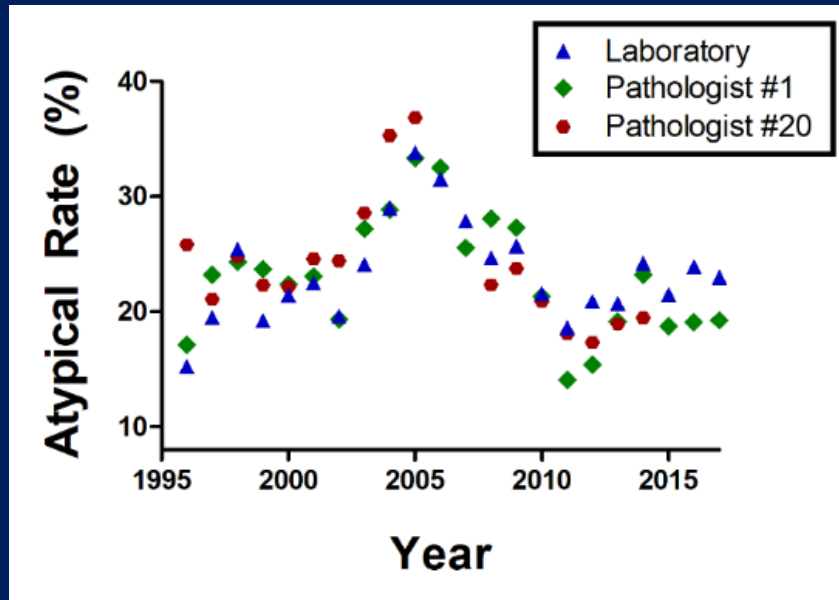
Cowan and VandenBussche. doi: 10.1016/j.jasc.2018.04.001

PRE/POST PARIS	PRE-TPS #	PRE-TPS%	POST TPS #	POST TPS %	DIFFERENCE	P-VALUE
UNSAT	67	0.42	93	0.45	5.51	> 0.05
NEG/NEG FOR HGUC	12832	81.22	18080	86.99	7.10	< 0.0001
ATYPICAL/AUC	2001	12.67	1770	8.52	-32.76	< 0.0001
SUSP/SUSP HGUC	360	2.28	407	1.96	-14.06	0.029
POSITIVE/POS HGUC	399	2.53	348	1.67	-33.70	< 0.0001
LOW GRADE UC/LGUN	0	0	2	0.01	N/A	N/A
OTHER/OTHER	8	0.05	3	0.01	0.01	N/A

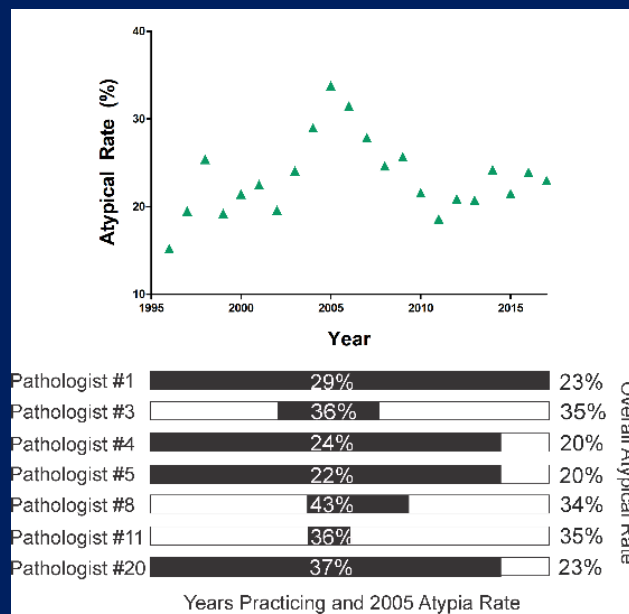
Barkan et al.



VandenBussche et al. Cancer Cytopathol. 2018.



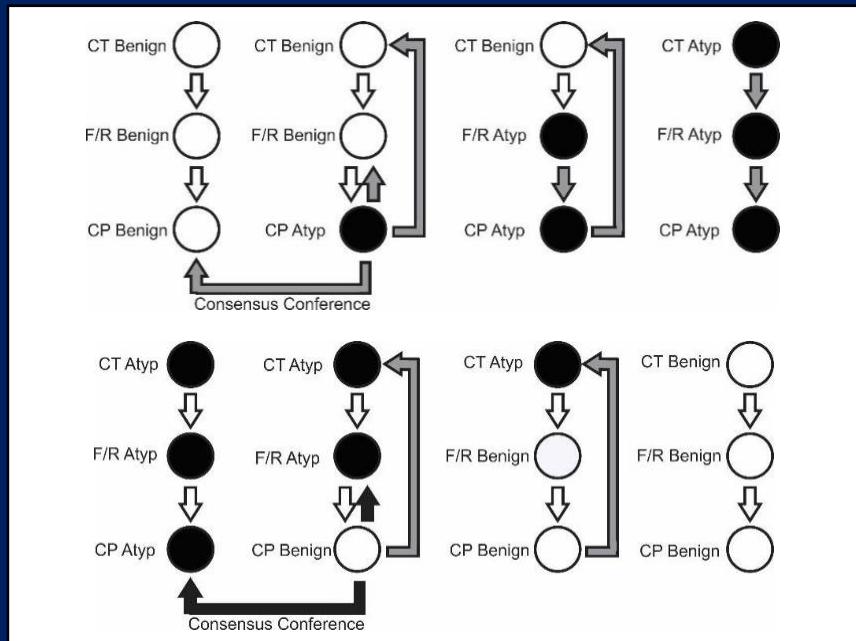
VandenBussche et al. Cancer Cytopathol. 2018.



VandenBussche et al. Cancer Cytopathol. 2018.

Passive Feedback:
The atypia rate drifts to
a laboratory baseline

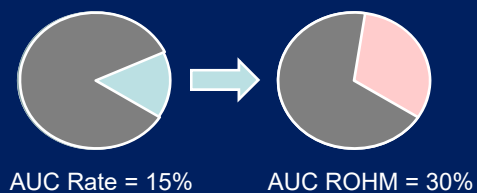
Active Feedback:
Individuals work together
to reinforce a new
laboratory baseline



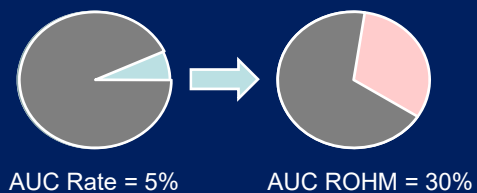
VandenBussche et al. Cancer Cytopathol. 2018.

Reducing Unnecessary AUC Diagnoses

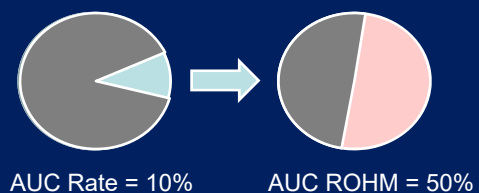
Laboratory Average



Pathologist A

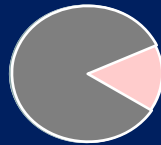


Pathologist B



What Is the Target AUC ROHM?

Laboratory Average



AUC ROHM = 30%

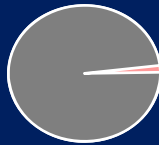


SHGUC/HGUC Rate = 5%

Pathologist A



AUC ROHM = 80%



SHGUC/HGUC Rate = 2%

Pathologist B



AUC ROHM = 50%



SHGUC/HGUC Rate = 5%

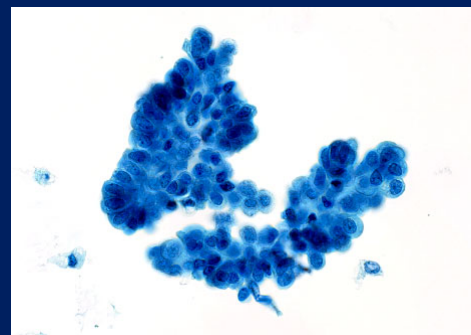
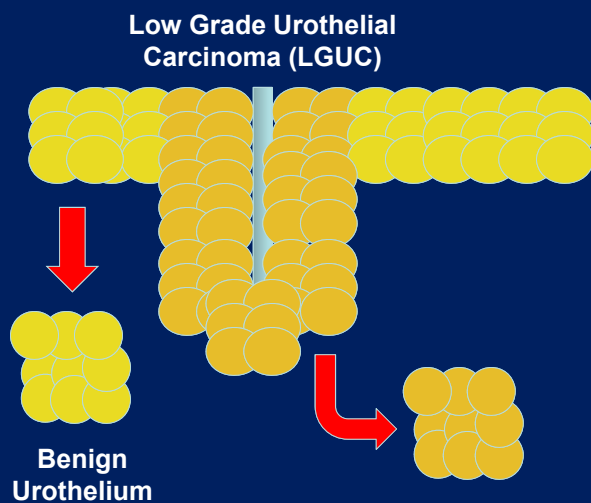
Published ROHMs for AUC (Prospective)

Author, year	Study cohort	Number of cases with available histology	ROHM (%)			
			NHGUC	AUC	SHGUC	HGUC
Stanzione et al, 2020	P	294	14.4	44.3	88.9	97.4
de Paula et al, 2019	P	499	11	32.6	80	92.3
Wang et al, 2018	P	167	17.7	50	76.4	89.1
Meilleroux et al, 2018	P	229	8.7	49	87	91
Xing et al, 2018	P	150	27	59	93	100

Rosenthal DL, Wojcik EM, Kurtycz DF, editors. The Paris system for reporting urinary cytology 2nd edition. Cham, Switzerland: Springer International Publishing; 2022.

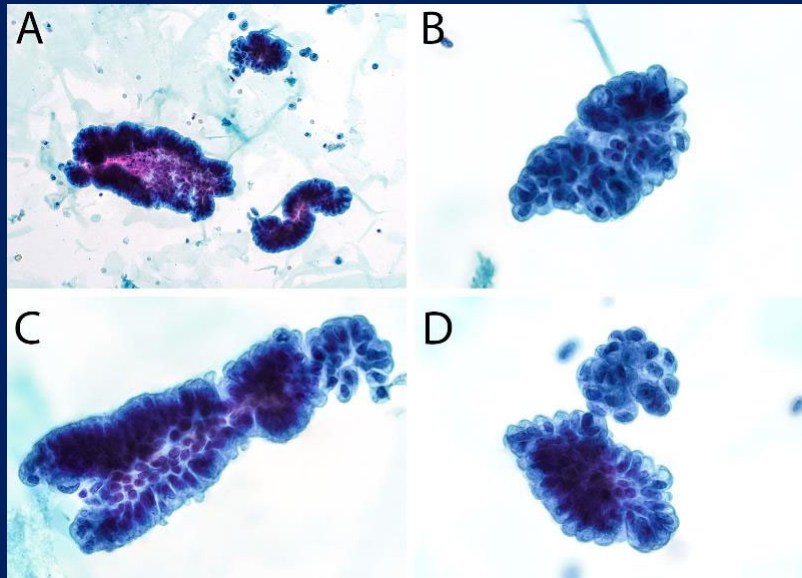
How to deal with tissue fragments?

Fear of Missing Low Grade Urothelial Carcinoma



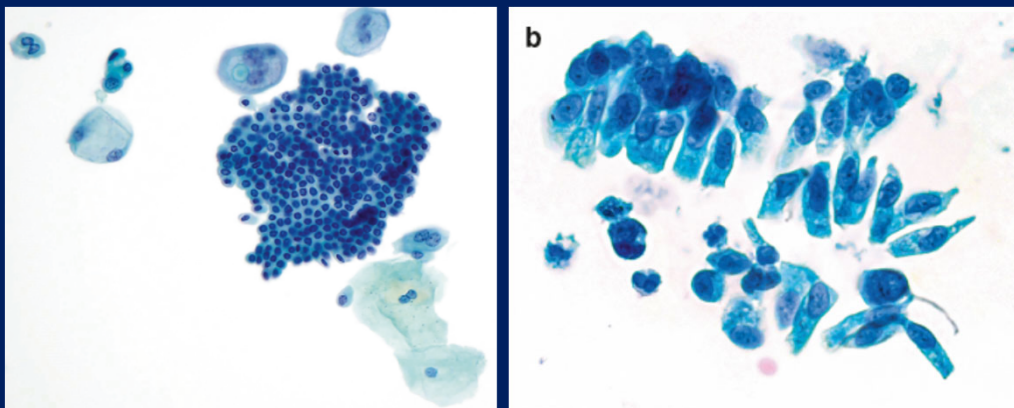
Benign-Appearing Urothelial Tissue Fragment (BUTF)

Benign Urothelial Tissue Fragments (BUTF)



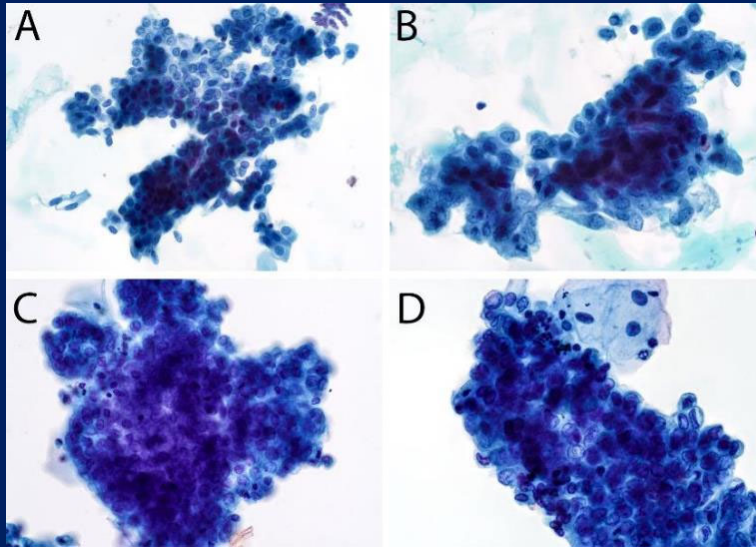
Allison DB, Zhang ML, Vohra P, VandenBussche CJ. The Diagnostic Dilemma of Urothelial Tissue Fragments in Urinary Tract Cytology Specimens. *Diagnostics (Basel)*. 2022 Apr 8;12(4):931. doi: 10.3390/diagnostics12040931. PMID: 35453979; PMCID: PMC9025489.

Benign Glandular Cells



VandenBussche CJ, Chandra A, Heymann JJ, McCroskey Z, Owens CL, Schubert PT, Wang YH. Negative for high-grade urothelial carcinoma (NHGUC). *InThe Paris System for Reporting Urinary Cytology* 2022 Feb 3 (pp. 21-62). Cham: Springer International Publishing.

Atypical Urothelial Tissue Fragments (AUTF)



Allison DB, Zhang ML, Vohra P, VandenBussche CJ. The Diagnostic Dilemma of Urothelial Tissue Fragments in Urinary Tract Cytology Specimens. *Diagnostics (Basel)*. 2022 Apr 8;12(4):931. doi: 10.3390/diagnostics12040931. PMID: 35453979; PMCID: PMC9025489.

Urothelial Tissue Fragments

Table 3.1 Significance of benign urothelial tissue fragments (BUTFs) and atypical urothelial tissue fragments (AUTFs) in voided urines (Onur I, Rosenthal DL, VandenBussche CJ. Atypical urothelial tissue fragments in noninstrumented voided urine specimens are associated with low but significantly higher rates of urothelial neoplasia than benign-appearing urothelial tissue fragments [20])

Follow-up diagnosis	No. (%) BUTF	No. (%) AUTF
Histopathologic	29 (10.6)	24 (14.1)
Benign	17 (6.2)	6 (3.5)
Urothelial neoplasia	12 (4.4)	17 (10.0)
PUNLMP	1 (0.4)	0 (0.0)
LGUC	9 (3.3)	2 (1.2)
HGUC	2 (0.7)	15 (8.8)
Cytopathology	45 (16.4)	25 (14.7)
Benign/AUC		
Urolithiasis (clinical/radiologic/gross)	45 (16.4)	49 (28.8)
No follow-up	25 (9.1)	10 (5.9)

Onur I, Rosenthal DL, VandenBussche CJ. Atypical urothelial tissue fragments in noninstrumented voided urine specimens are associated with low but significantly higher rates of urothelial neoplasia than benign-appearing urothelial tissue fragments. *Cancer Cytopathol*. 2015 Mar;123(3):186-92. doi: 10.1002/cncy.21519. Epub 2015 Jan 13. PMID: 25588888

Urothelial Tissue Fragments

Differential Diagnosis:

- Benign urothelial fragments
- Low grade urothelial neoplasms (LGUN)
 - Papilloma
 - PUNLMP
 - LGUC
- Reactive/Stone atypia
- High grade urothelial carcinoma/CIS
- True papillary fragments are rare but strongly suggestive of a papillary urothelial neoplasm!

Urothelial Tissue Fragments

Differential Diagnosis:

- Benign urothelial fragments
- Low grade urothelial neoplasms (LGUN)
 - Papilloma
 - PUNLMP
 - LGUC
- Reactive/Stone atypia
- High grade urothelial carcinoma/CIS

BUT

- True papillary fragments are rare but strongly suggestive of a papillary urothelial neoplasm!

Urothelial Tissue Fragments

Differential Diagnosis:

- Benign urothelial fragments
- Low grade urothelial neoplasms (LGUN)
 - Papilloma
 - PUNLMP
 - LGUC
- Reactive/Stone atypia
- High grade urothelial carcinoma/CIS

BUTF

AUTF

- True papillary fragments are rare but strongly suggestive of a papillary urothelial neoplasm!

Sample Reports

1. Urine cytology (voided): Satisfactory for evaluation

Negative for high-grade urothelial carcinoma
Low-grade urothelial neoplasm (LGUN)

2. Urine cytology (voided): Satisfactory for evaluation

Negative for high-grade urothelial carcinoma. (See note)

Note: The sample contains singly dispersed and groups of urothelial cells including an occasional group with a fibrovascular core. The urothelial cells in the groups as well as those singly dispersed show bland nuclear features with no hyperchromasia, chromatin, or membrane abnormalities to suggest high-grade urothelial carcinoma. The findings may represent a low-grade urothelial neoplasm.

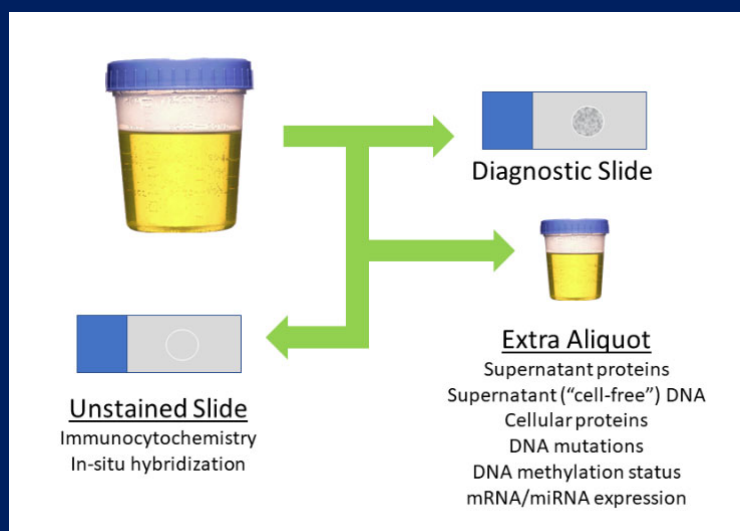
3. Bladder washings: Satisfactory for evaluation

NEGATIVE FOR HIGH-GRADE UROTHELIAL CARCINOMA

Note: Numerous groups include pseudopapillary structures lacking fibrovascular cores. Urothelial cells show bland nuclear features with no hyperchromasia, chromatin, or membrane abnormalities to suggest high-grade urothelial carcinoma.

Is molecular testing useful?

Ancillary Test Methodologies

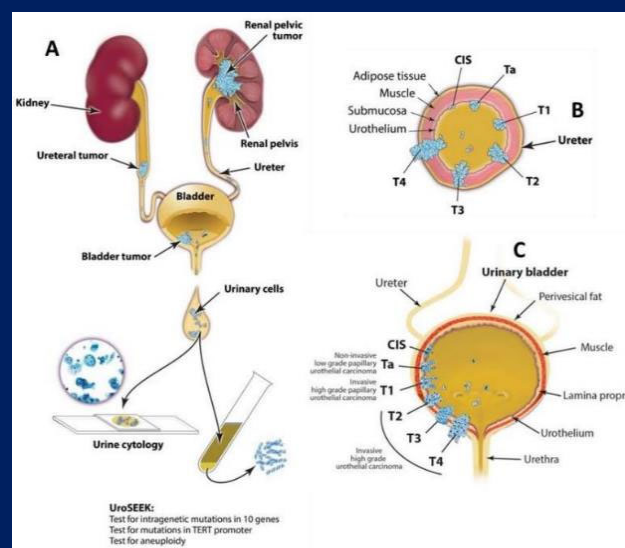


Ancillary Test Performance

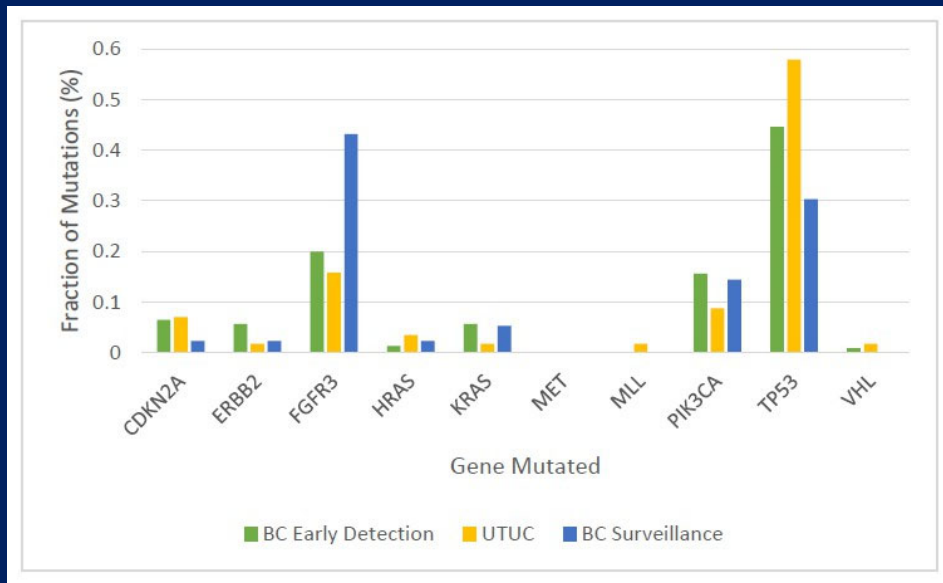
	Studies	# Pts	Sens	Range	# Pts	Spec	Range
BTA stat	17	1377	58	29-74	2084	73	56-86
NMP22	16	1018	69	47-100	1325	73	55-98
NMP22 POCT	2	159	62	50-86	654	86	77-87
uCyt +	8	626	77	N/A	2109	74	62-82
FISH	7	256	65	30-86	311	83	66-95
MSI	7	192	73	58-92	884	76	73-100
Cytology	26	2213	35	13-75	3322	94	85-100

Mod. from van Rhijn BWG et al. Eur Urol Suppl 2009 8:536-541

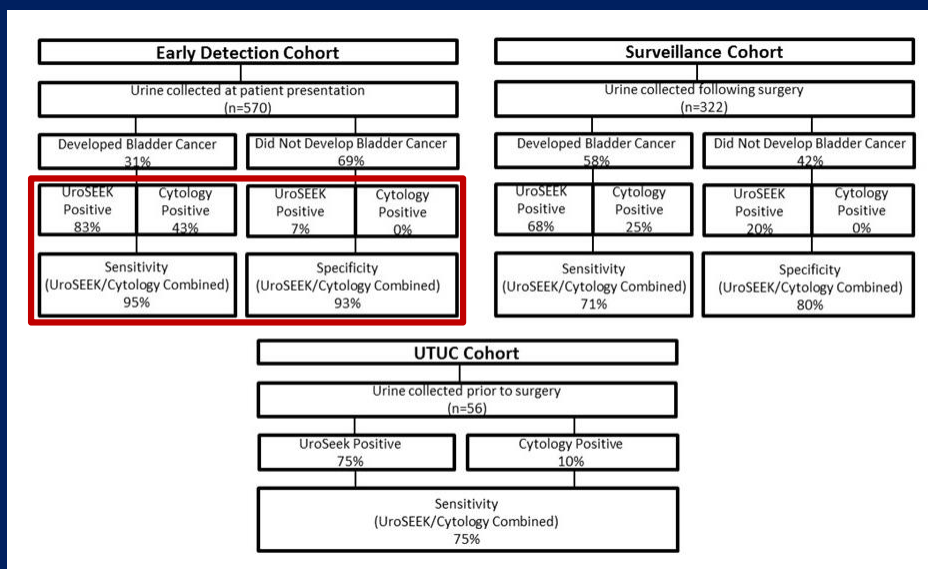
Slide-Free Example: UroSEEK



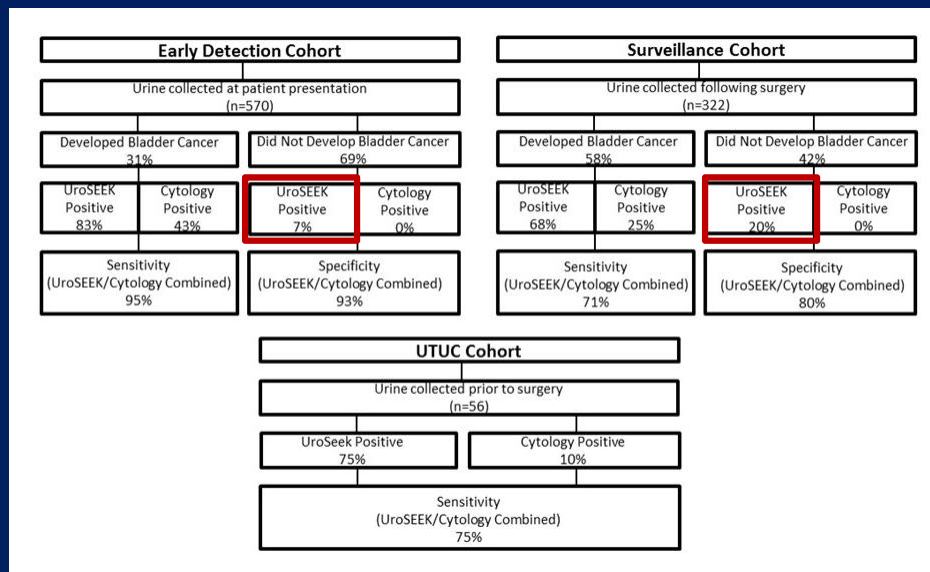
Springer SU et al. eLife. 2018 Mar 20;7:e32143.



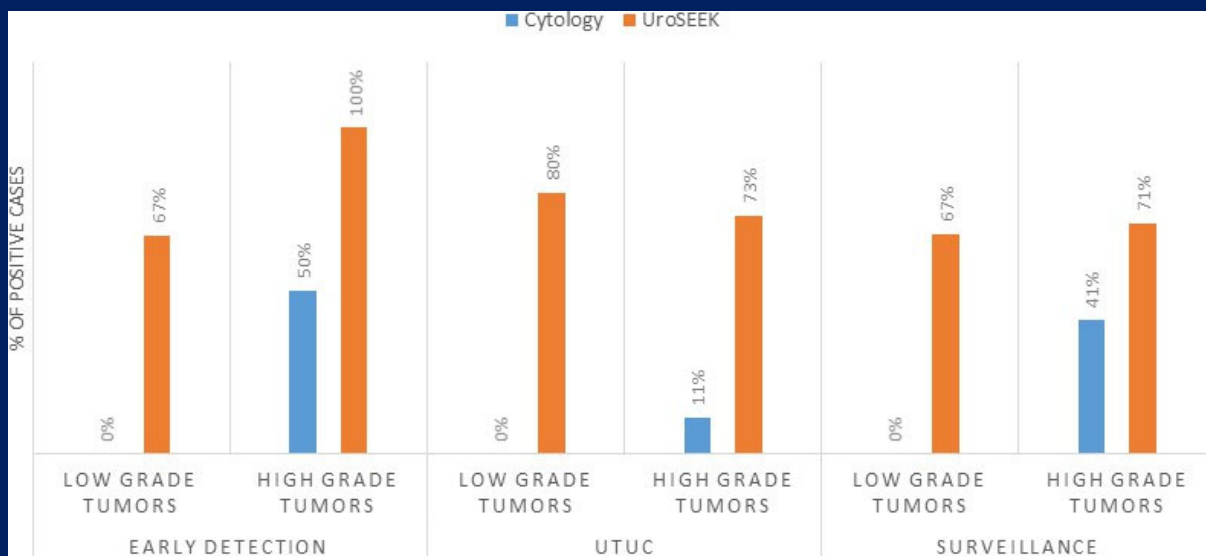
Springer SU et al. eLife. 2018 Mar 20;7:e32143.



Springer SU et al. eLife. 2018 Mar 20;7:e32143.

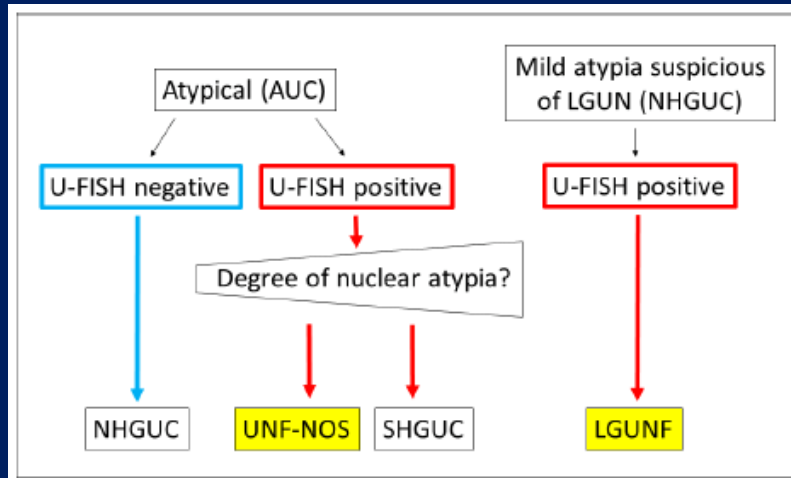


Springer SU et al. eLife. 2018 Mar 20;7:e32143.



Springer SU et al. eLife. 2018 Mar 20;7:e32143.

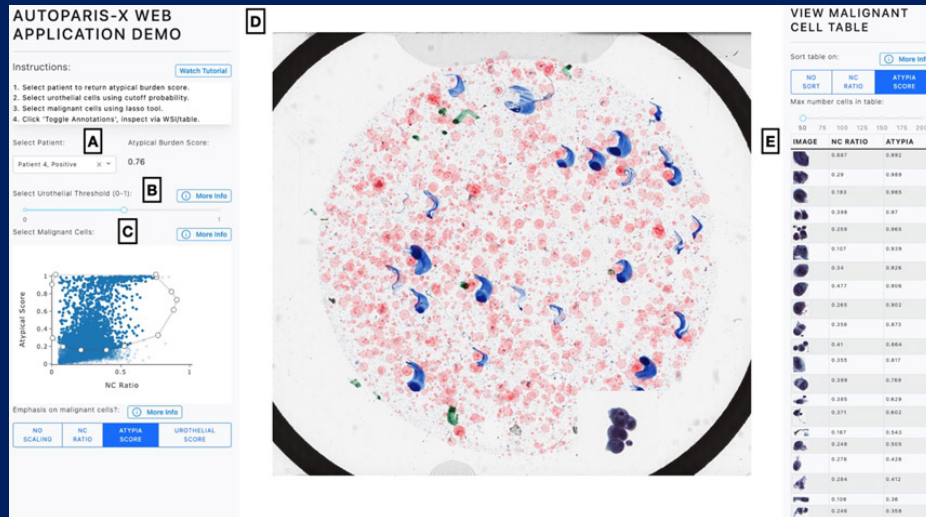
Combining Ancillary Test Result and TPS Diagnosis



Vlajnic T, et al. *J Clin Pathol* 2019;0:1–6. doi:10.1136/jclinpath-2019-206109

What's the deal with "A.I."?

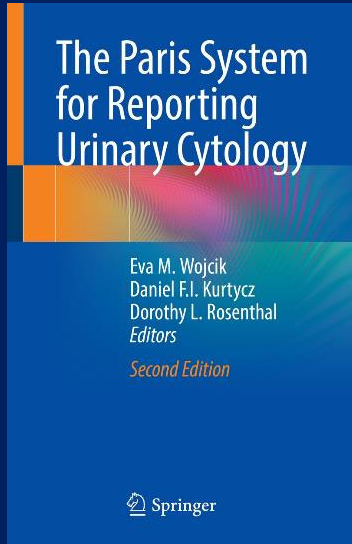
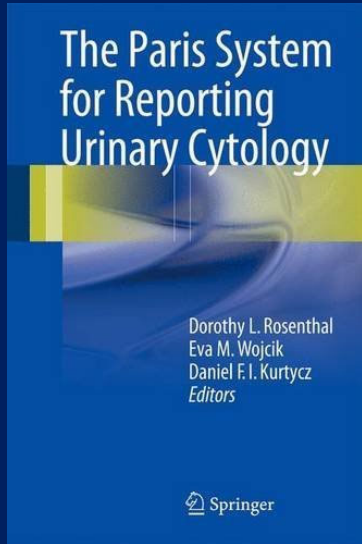
AutoParis-X



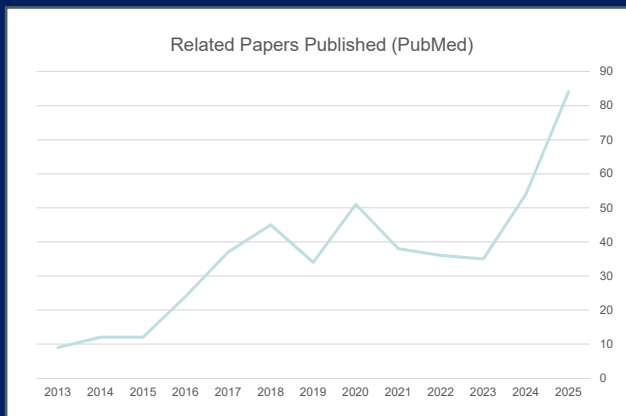
Levy JJ, Chan N, Marotti JD, et al. Large-scale validation study of an improved semiautonomous urine cytology assessment tool: AutoParis-X. *Cancer Cytopathol.* 2023;131(10):637-654. doi:10.1002/cncy.22732

What's next?

What's Next?

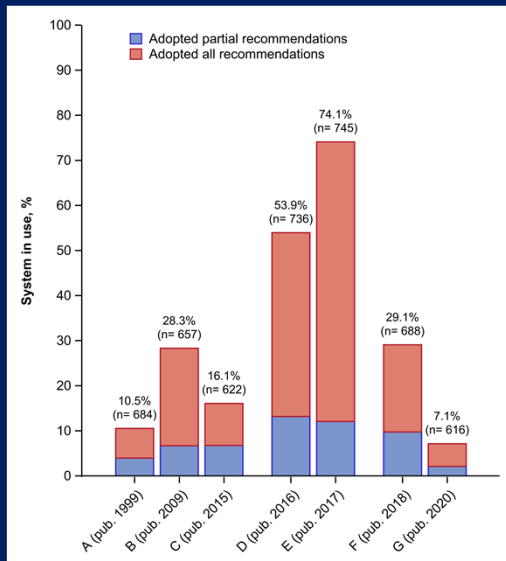
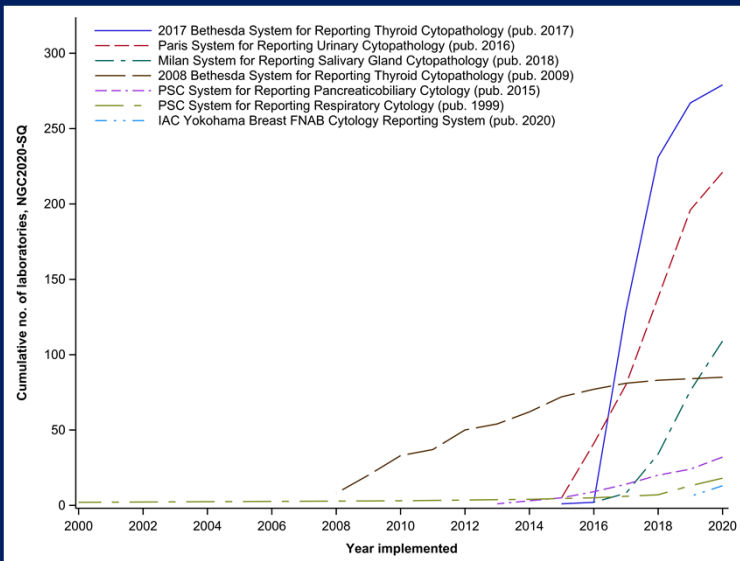


What's Next?



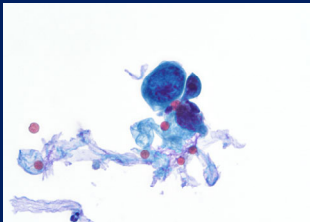
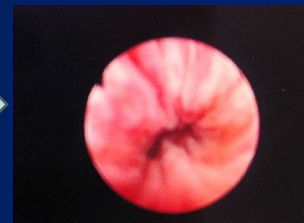
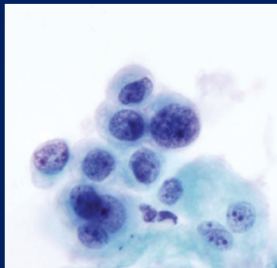
Driven By:

- Standardization & Clinical Adoption
- Release of TPS 2.0 (2022)
- Focus on HGUC Detection
- Integrating Molecular/Ancillary
- Global Acceptance
- Validation Studies
- Educational & Training Needs
- Technological Advancements



VandenBussche CJ, Nwosu A, Souers R, Sundling KE, Brainard J, Goyal A, Lin X, Masood S, Nguyen L, Roberson J, Tabbara SO, Booth C. The Implementation of Nongynecologic Reporting Systems in Cytopathology Laboratories Is Highly Variable: Analysis of Data From a 2020 Supplemental Survey of Participants in the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology. Arch Pathol Lab Med. 2023 Aug 22. doi: 10.5858/arpa.2023-0010-CP. Epub ahead of print. PMID: 37603681

What's Next?



Summary

Several reporting systems for urinary cytology have been proposed; The Paris System (TPS) is the first one to have been widely adopted

A primary objective of TPS is to reduce the number of diagnoses in the “atypical” category. As a result:

- LGUN and related changes are classified as NHGUC
- Tissue fragments are placed under NHGUC unless features of HGUC are present

Prospective studies have shown that implementation of TPS can decrease the utilization and increase the predictive value of the atypical category

Summary

The second edition of TPS:

- Identifies additional HGUC morphologies (e.g., hypochromatic)
- Streamlines the diagnosis of SHGUC vs HGUC
- Provides additional guidance regarding the assessment of tissue fragments and cellular degeneration
- Recommends classification of non-urothelial atypia under the “Other” category
- Includes sections and photographs on newly defined findings
- Includes an increased number of sample reports

Thank you!