HKIAP-HKSC Cytopathology Course
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The Paris System for Reporting Urinary Cytology: Evolution from TPS 1.0 to 2.0+

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Conflict of Interest: No Disclosures

Objectives

Understand	Review	Discuss
Understand rationale for standardized urinary cytology reporting system	Review terminology of The Paris System (TPS) and criteria for each category	Discuss updates in criteria described in evolution from first to second edition of TPS with recognition of recent studies

Background

Until recently, urine cytology was at risk of becoming obsolete

High atypia rates, inconsistent criteria, and unclear management directions led to poor performance and low confidence

TPS was introduced in 2016 to standardize reporting and improve detection of high-grade urothelial carcinoma (HGUC)

Wojcik EM, Kurtycz DFI, Rosenthal DL. We'll always have Paris The Paris System for Reporting Urinary Cytology 2022. J Am Soc Cytopathol. 2022 Mar-Apr;11(2):62-66

The Paris System (TPS) Origin

The International Academy of Cytology (IAC) at the 18th ICC in 2013, held in Paris, initiated the development of TPS

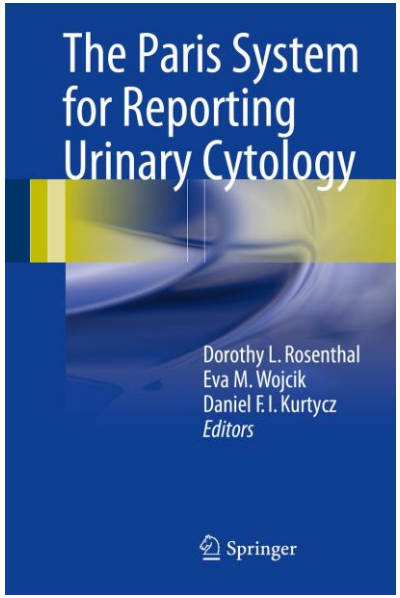
The primary aim of TPS is to detect HGUC

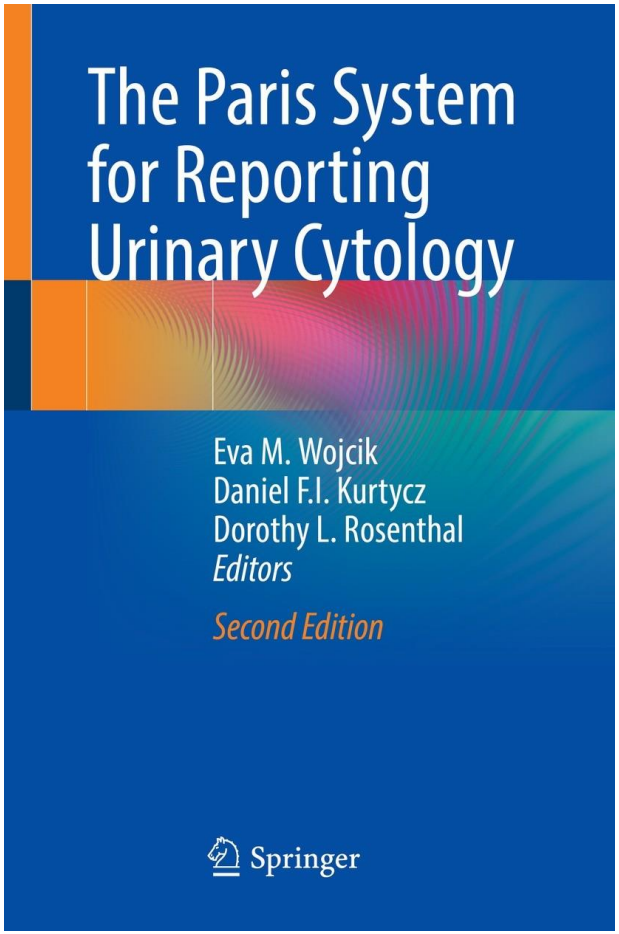
TPS 1.0 published in 2016 to lower atypia rates and standardize urine cytology

The Paris System for Reporting Urinary Cytology: The Quest to Develop a Standardized Terminology. Barkan GA, Wojcik EM, Nayar R, Savic-Prince S, Quek ML, Kurtycz DF, Rosenthal DL. Acta Cytol. 2016;60(3):185-97.

Evolution from TPS 1.0 to 2.0

Rosenthal DL, wojcik EM, Kurtycz DF. The Paris System for Reporting Urinary Cytology, 1st ed. Cham: Springer International Publishing Switzerland; 2016



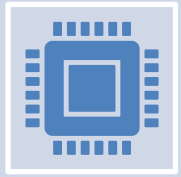


Wojcik EM, Kurtycz DF, Rosenthal DL. The Paris System for Reporting Urinary Cytology, 2nd ed. Cham: Springer Nature Switzerland AG; 2022

Goals of TPS

Main goal: Standardize reporting to lower atypia rates in urine cytology

Collect and utilize evidence-based data to guide patient management

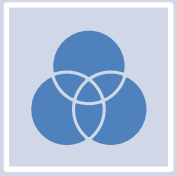


Report risk of malignancy (ROM) data for TPS categories; initial ROM estimates for TPS 1.0 based on pre-TPS 1.0 data, recognizing it would evolve with new data

TPS Evolution

TPS 1.0 recognized as needing revision and continuous evolution

An Afterword in TPS 1.0 listed research questions and knowledge gaps



Effectiveness relies on lab experience and expertise, reporting rates for TPS categories, and risk of high-grade malignancy (ROHM)

TPS 2.0 Enhancements

- TPS 2.0 addresses shortcomings of TPS 1.0
- Expanded discussion on:
  - Sample degeneration
  - Squamous atypia
  - Upper urinary tract cytology
- Main focus on HGUC detection remains unchanged
- LGUN incorporated into NHGUC category

Challenges Addressed

TPS 2.0 aims to reduce atypical and suspicious diagnoses

Supports research on low-grade urothelial neoplasia and its proper designation

Encourages ancillary method investigations and management outcome research

Morphologic Criteria

N:C ratio remains significant

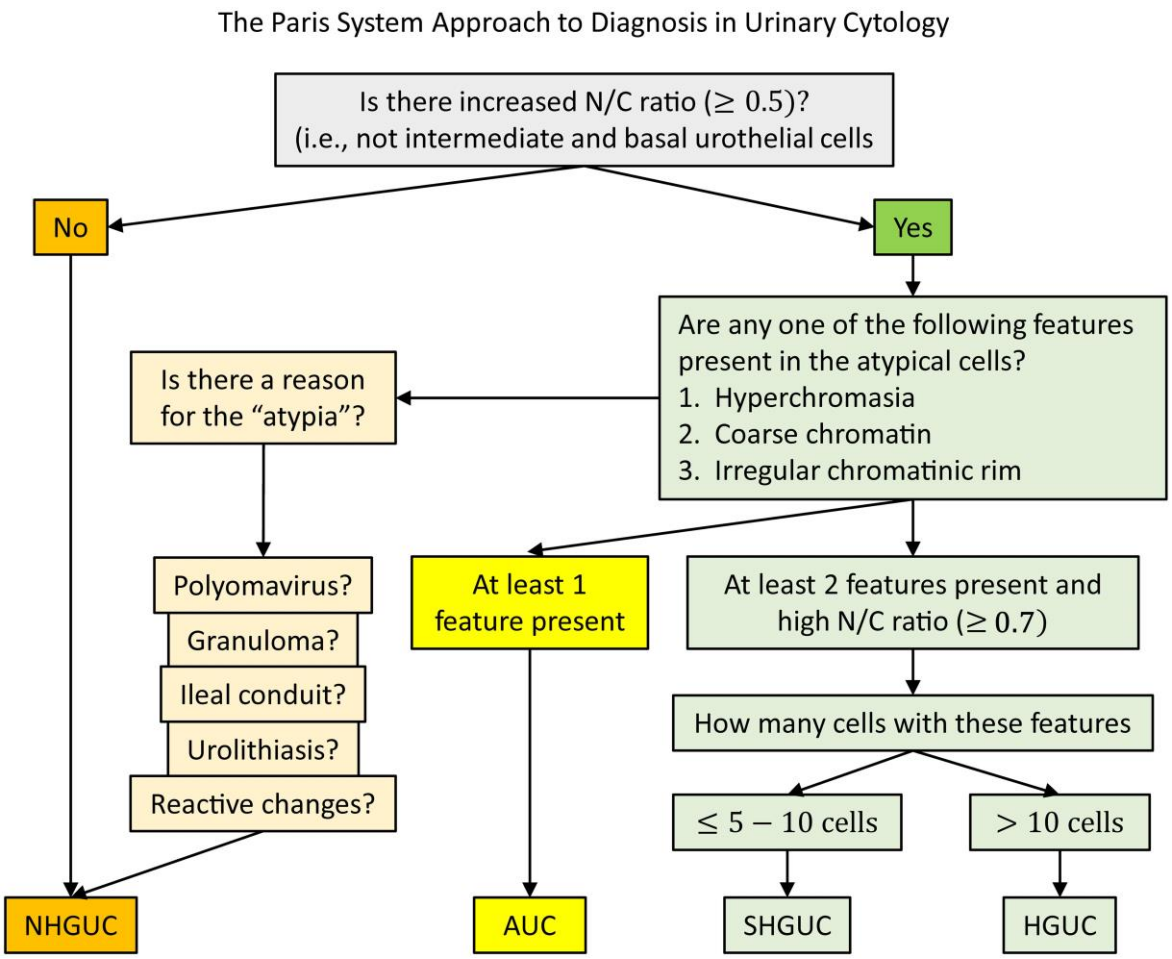
- - ≥0.5 triggers AUC diagnosis
- - ≥0.7 criterion for SHGUC and HGUC

TPS 2.0 de-emphasizes specific numbers

- Categorized as 'increased' (≥0.5) and 'high' (≥0.7)

Diagnostic algorithm emphasizes N/C ratio

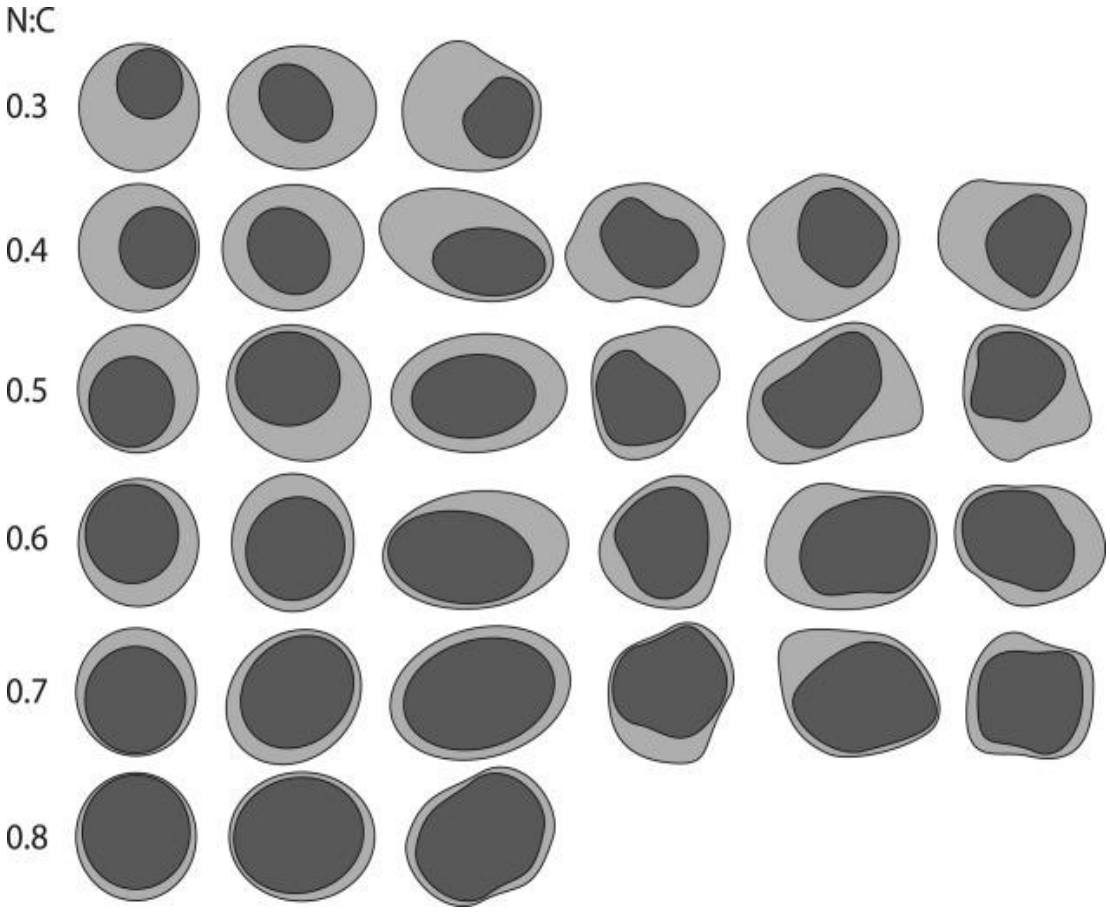
Graphic Algorithm of TPS for Reporting Urinary Cytology Decision Tree



Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. *J Clin Transl Pathol*. 2023;3(2):59-74.

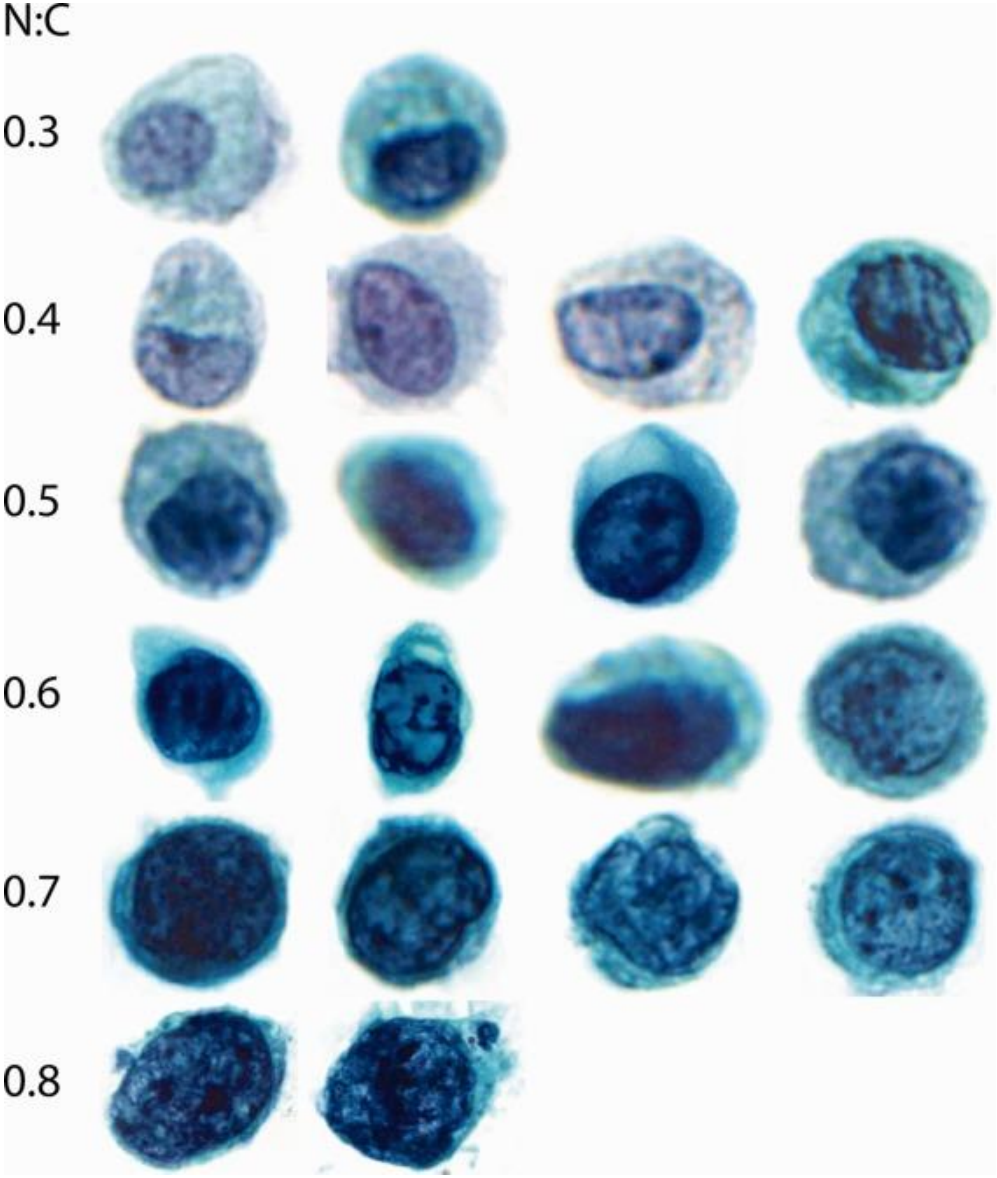
Wojcik EM, Kurtycz DFI, Rosenthal DL. We'll always have Paris The Paris System for Reporting Urinary Cytology 2022. J Am Soc Cytopathol. 2022 Mar-Apr;11(2):62-66

- Ideal cell images from the nuclear-to-cytoplasmic (N:C) ratio survey
- Cross-sectional area of the nucleus occupying a portion in relation to the cross-sectional area of the cell size



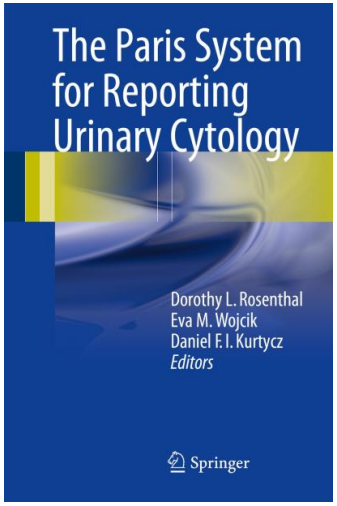
Morphologists overestimate the nuclear-to-cytoplasmic ratio. Mingjuan L. Zhang BS, Alan X. Guo PhD, Christopher J. VandenBussche MD, PhD ***Cancer Cytopathol*** **2016;124:669–77**

Real cell images from the nuclear-to-cytoplasmic (N:C) ratio survey



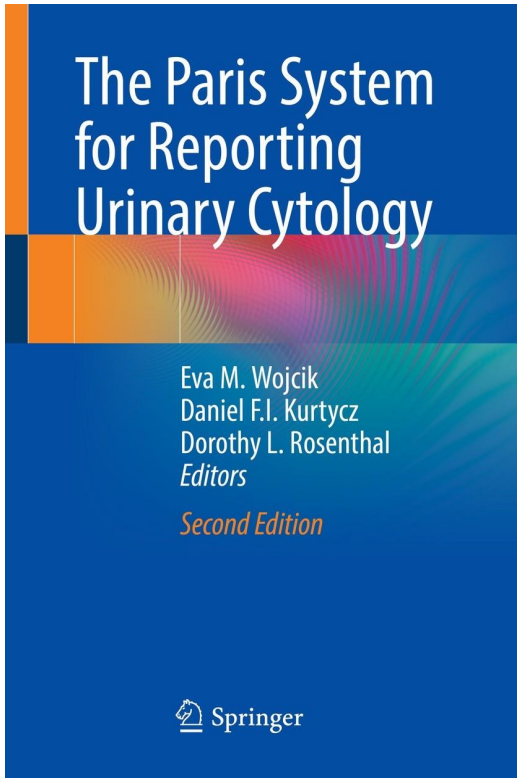
Morphologists overestimate the nuclear-to-cytoplasmic ratio. Mingjuan L. Zhang BS, Alan X. Guo PhD, Christopher J. VandenBussche MD, PhD ***Cancer Cytopathol*** **2016;124:669–77**

Evolution of TPS



TPS 2.0 comprises six diagnostic categories:

1. **Non-diagnostic (ND)**
2. **Negative for high-grade urothelial carcinoma (NHGUC; incl. LGUN)**
3. **Atypical urothelial cells (AUC)**
4. **Suspicious for high-grade urothelial carcinoma (SHGUC)**
5. **High-grade urothelial carcinoma (HGUC)**
6. **Other: Primary and secondary malignancies**



Wojcik EM, Kurtycz DF, Rosenthal DL. The Paris System for Reporting Urinary Cytology, 2nd ed. Cham: Springer Nature Switzerland AG; 2022

Bladder Cancer Epidemiology

- Bladder cancer incidence
  - Highest in higher-income regions of the world, including Europe, North America and western Asia, and is also
  - Increased in regions affected by Schistosoma parasites such as Northern Africa
- Bladder cancer incidence linked to
  - Tobacco use, occupational exposure, arsenic in drinking water

Dyrskjøt, L., Hansel, D.E., Efstathiou, J.A. *et al.* Bladder cancer. *Nat Rev Dis Primers* **9**, 58 (2023). https://doi.org/10.1038/s41572-023-00468-9

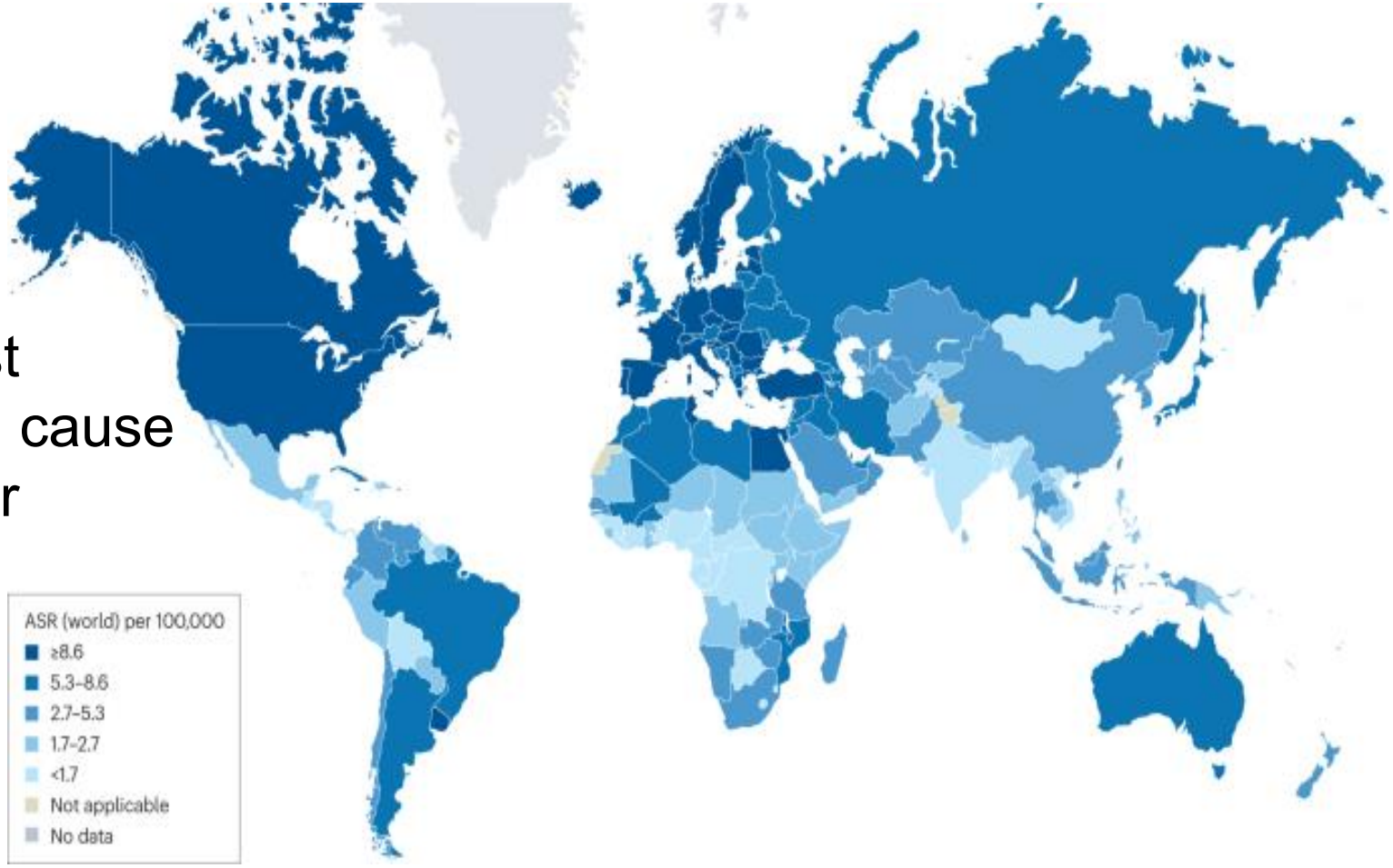
Bladder Cancer Epidemiology

- In 2020, nearly 600,000 people were diagnosed with bladder cancer globally
  - Predominantly affecting individuals >55 years of age and men
  - Number is expected to double by 2040 based on WHO predictions

Dyrskjøt, L., Hansel, D.E., Efstathiou, J.A. *et al.* Bladder cancer. *Nat Rev Dis Primers* **9**, 58 (2023). https://doi.org/10.1038/s41572-023-00468-9

Global Incidence of Bladder Cancer

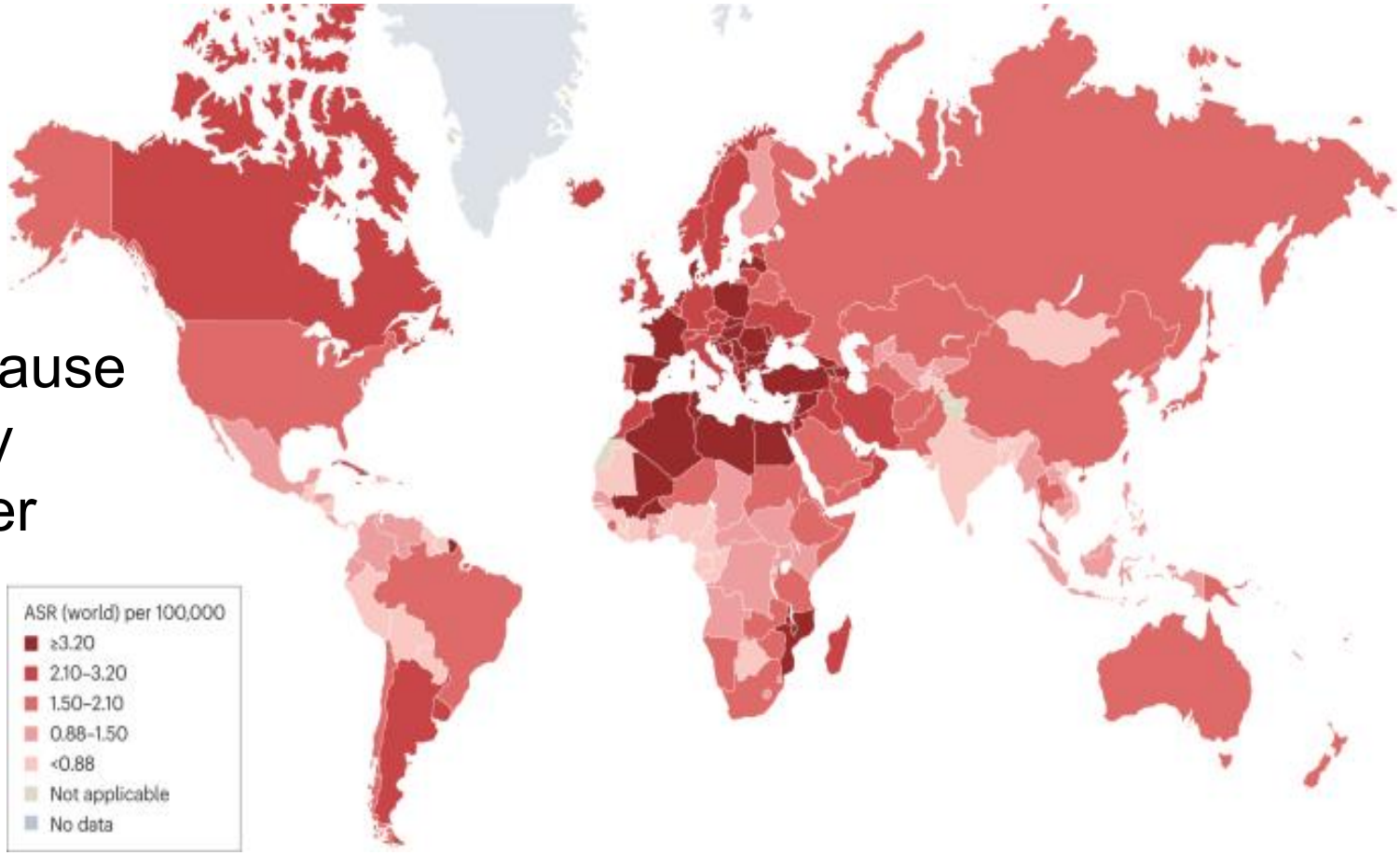
10th most common cause of cancer globally



Maps produced by the World Health Organization/International Agency for Research on Cancer (https://gco.iarc.fr/today).

Global Mortality of Bladder Cancer

13th most common cause of mortality from cancer



Maps produced by the World Health Organization/International Agency for Research on Cancer (https://gco.iarc.fr/today).

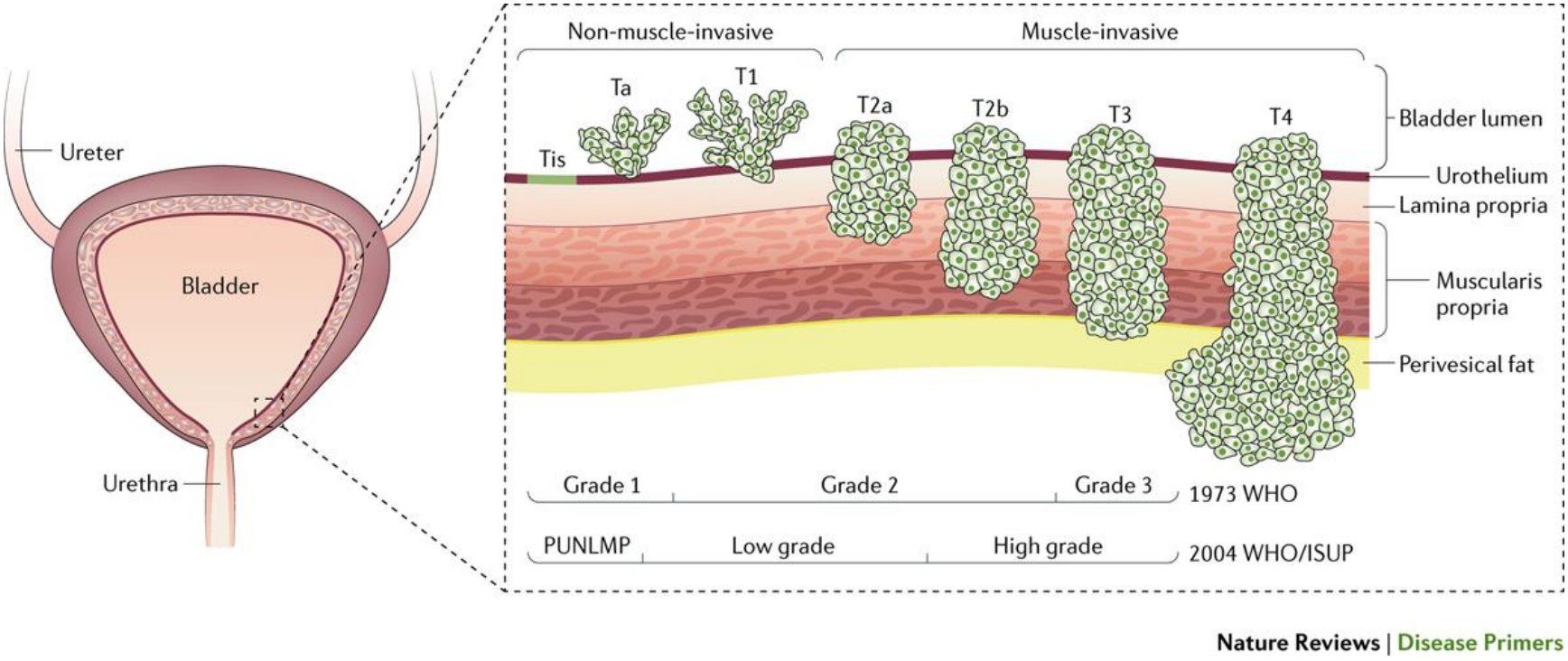
Bladder Cancer Epidemiology

- If detected early before muscle invasion, this disease is often treatable and can be managed with minimal effects on survival.
- Muscle-invasive disease can metastasize, predominantly to lymph nodes, bones, lungs and liver, and is associated with a median survival of ~15 months
- Ongoing efforts to mitigate risk factors, improve timely diagnosis and expand therapy have resulted in decreasing global rates of bladder cancer diagnoses and deaths

Dyrskjøt, L., Hansel, D.E., Efstathiou, J.A. *et al.* Bladder cancer. *Nat Rev Dis Primers* **9**, 58 (2023). https://doi.org/10.1038/s41572-023-00468-9

Types and Stages of Bladder Cancer

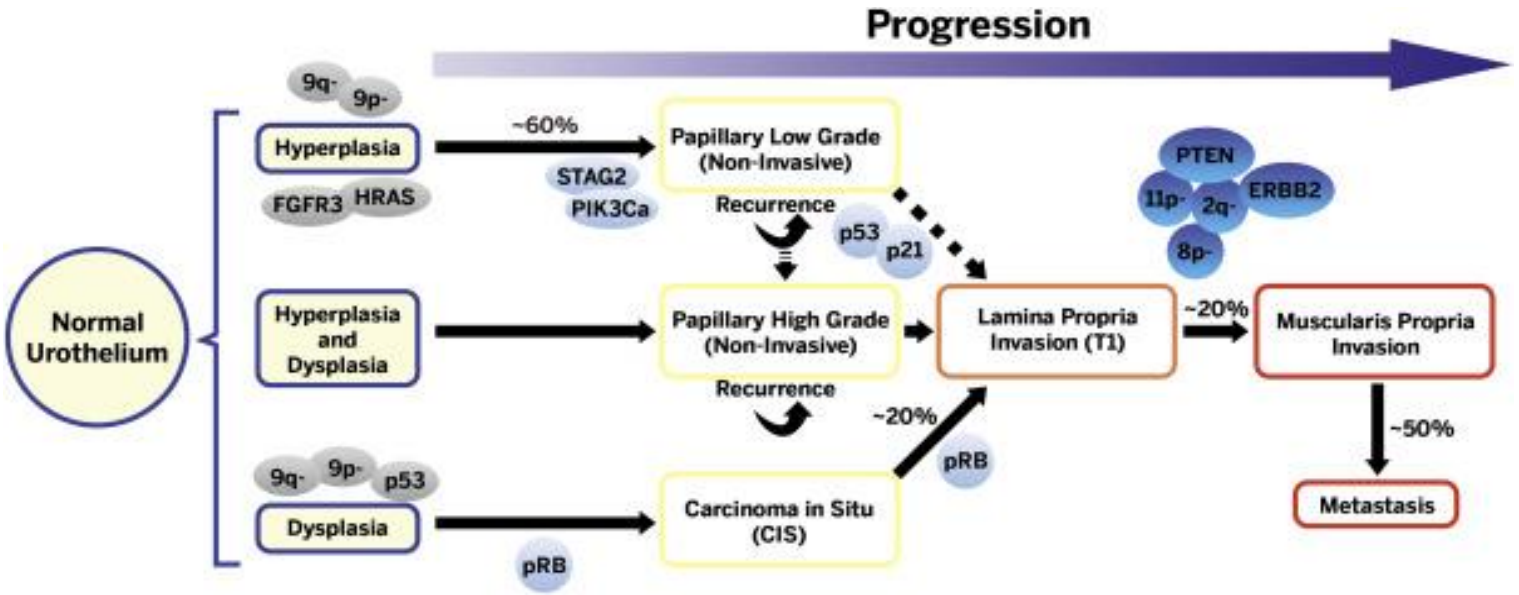
- **NMIBC: 80% of diagnosed bladder cancer**
- **MIBC: 20% of diagnosed bladder cancer**



Inset adapted with permission from Knowles, M. A. & Hurst, C. D. Molecular biology of bladder cancer: new insights into pathogenesis and clinical diversity. *Nat. Rev. Cancer* **15,** 25–41 (2015), Macmillan Publishers Limited

Sanli, O. *et al.* (2017) Bladder cancer. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2017.22

Molecular Pathways in Bladder Cancer



- Low-grade papillary UC: prognostically favorable urothelial carcinoma, stable in terms of molecular genetics, urothelial hyperplasia as premalignant lesion.

- High-grade UC: prognostically unfavorable urothelial carcinoma, unstable in terms of molecular genetics, urothelial dysplasia as premalignant lesion

Lopez-Beltran A, Cimadamore A, Montironi R, Cheng L. Molecular pathology of urothelial carcinoma. Hum Pathol 2021;113:67-83

Pathogenesis of Urothelial Carcinoma

TPS 2.0

- Incorporation of The Cancer Genome Atlas (TCGA) molecular characterization into the pathogenesis of low-grade and high-grade urothelial carcinomas
- TCGA recognizes four molecular clusters based on differential gene expression by RNA sequencing

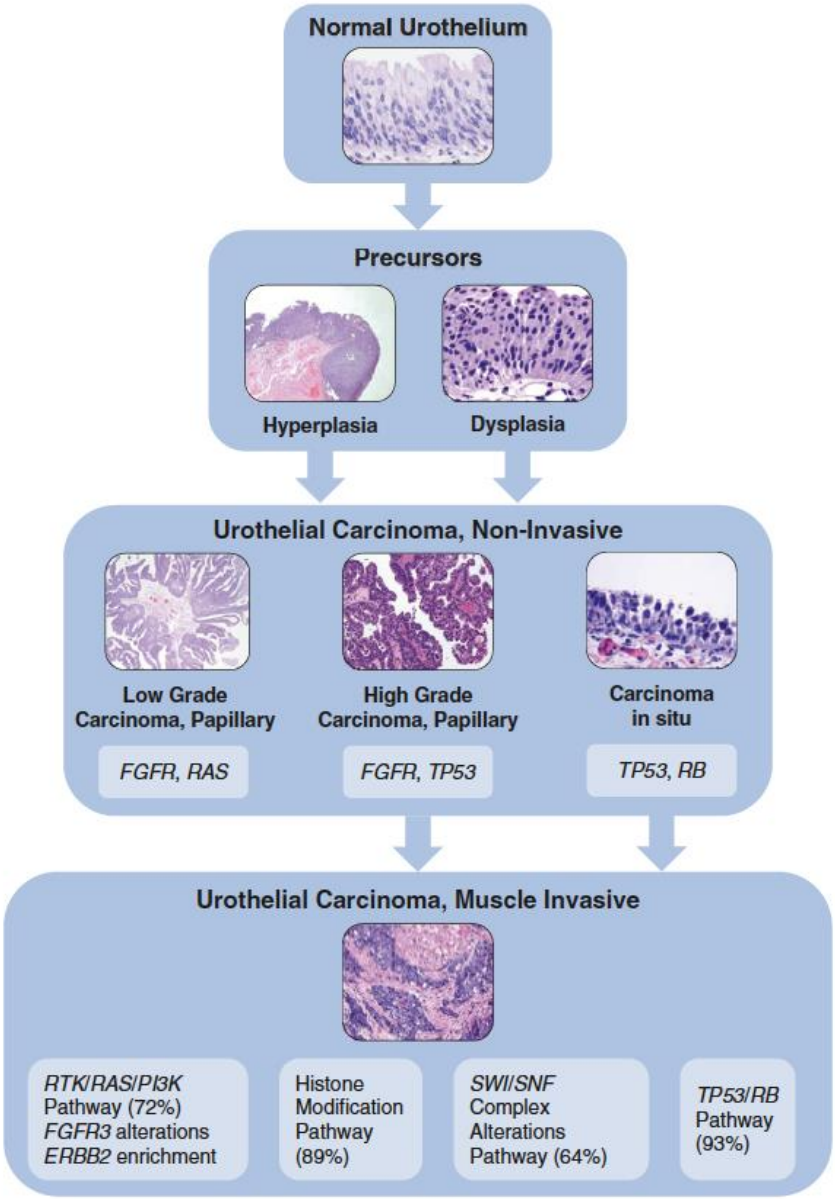


Fig. 1.1 Schematic representation of the major histologic findings in urothelial carcinogenesis. Key genetic alterations are noted in the noninvasive carcinomas, while pathway alterations from TCGA analysis are noted in muscle-invasive urothelial carcinomas. Note that there is overlap among the pathway and cluster designations, and the groupings are not mutually exclusive

Sunding et al., Chapter 1 in The Paris System for Reporting Urinary Cytology, 2nd ed. Cham: Springer Nature Switzerland AG; ***2022***

Adequacy Criteria

- Voided urine: >25-30 ml
- Instrumented urine urothelial cells:

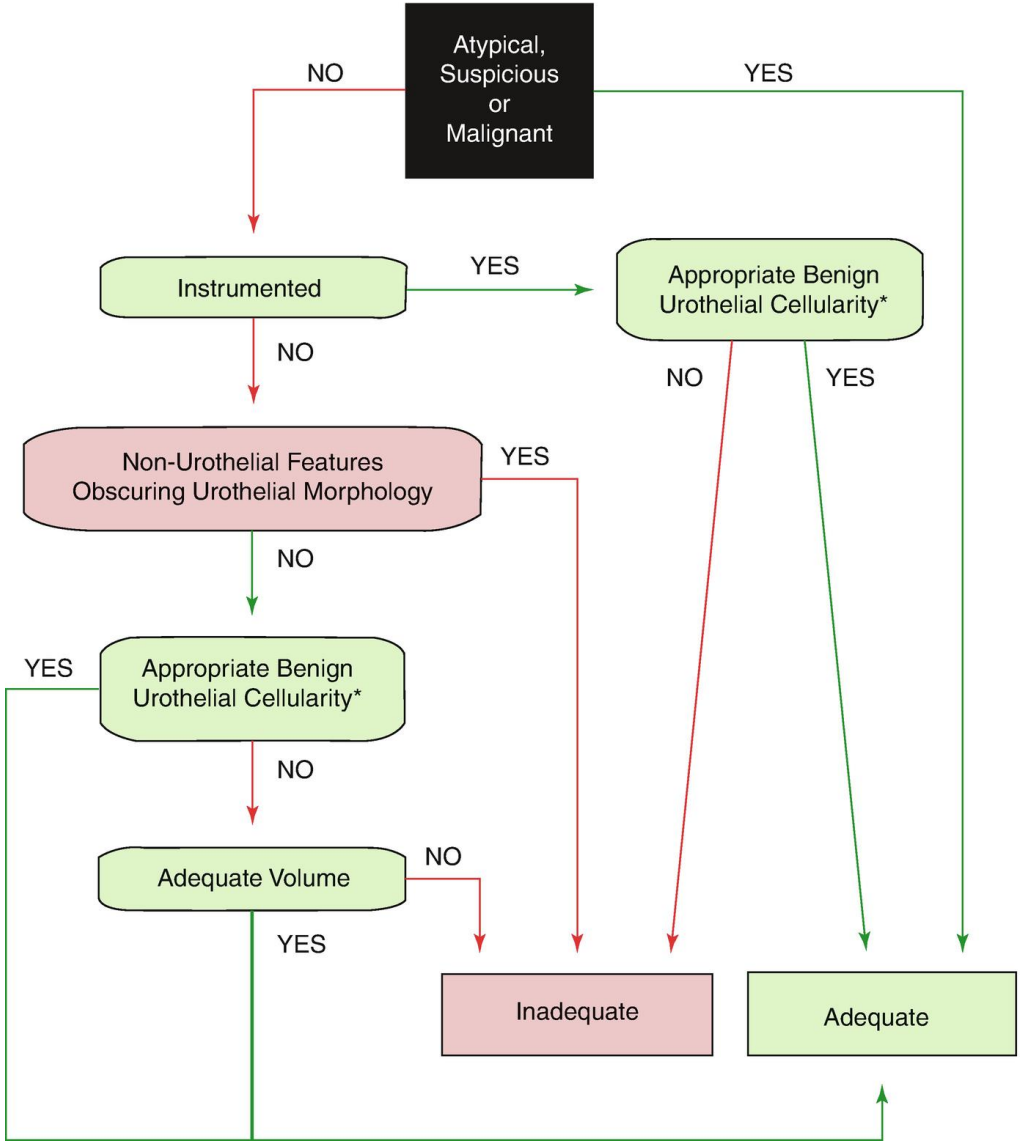
  Satisfactory: More than 20 cells per 10 high-power fields (HPFs).

  Satisfactory but limited: 10–20 cells per 10 HPFs.

  Unsatisfactory/non-diagnostic: Less than 10 cells per 10 HPFs
- *Less-than-optimal Adequacy:*

  Insufficient cells, adequate vol

  Additional studies needed



Rezaee N, Tabatabai ZL, Olson MT. Adequacy of voided urine specimens prepared by ThinPrep and evaluated using The Paris System for Reporting Urinary Cytology. J Am Soc Cytopathol. 2017 Jul-Aug;6(4):155-161.

Tabatabai, Z.L. *et al.* (2022). Adequacy of Urine Specimens (Adequacy). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Negative for high-grade urothelial carcinoma: Definition of NHGUC

- A urinary sample (voided or instrumented) can be categorized as NHGUC when:
  - It is Adequate AND
  - Lacks any cytomorphologic findings of HGUC
- NHGUC cases account for approximately 90% of voided urine specimens
  - Retrospective classification of TPS (n=1,240)
  - Cancer center population

VandenBussche, CJ. *et al.* (2022). Negative for High-Grade Urothelial Carcinoma (NHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Lobo J, Lobo C, Leça L, Rodrigues Â, Henrique R, Monteiro P. Evaluation of the Implementation and Diagnostic Accuracy of the Paris Classification for Reporting Urinary Cytology in Voided Urine Specimens: A Cyto-Histological Correlation Study in a Cancer Center. Pathobiology. 2023;90(4):233-240.

Negative for high-grade urothelial carcinoma: Criteria for NHGUC

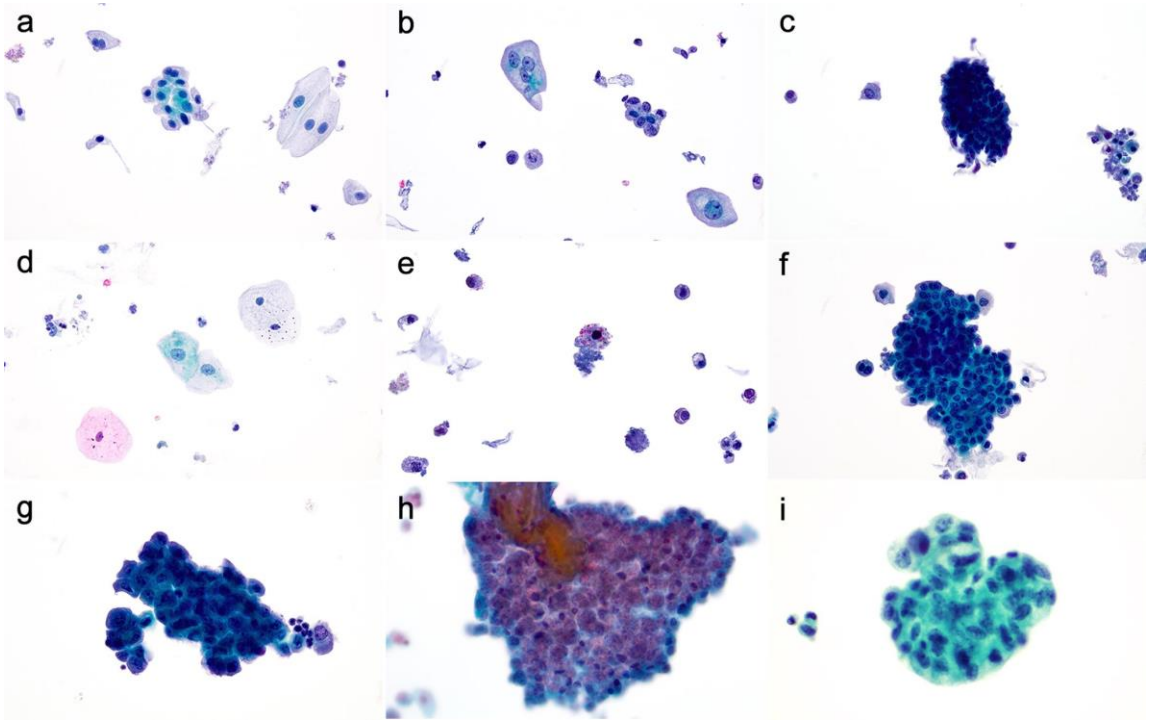
- Benign urothelial cells
  - Superficial umbrella cells – abundant cytoplasm
  - Intermediate (parabasal-like) cells - “fried egg” appearance
  - Deep urothelial cells (basal cells) - higher N:C, sheets
- Benign squamous cells
  - Not required to report in TPS incl. parakeratotic, anucleate

Negative for high-grade urothelial carcinoma: Criteria for NHGUC

- Glandular cells
  - In women from uterine cervix – endometrial cells
  - In men – prostatic cells (SV cells)
  - From urinary tract - vacuolated cytoplasm (dome or trigone)
  - Cystitis cystica/glandularis, intestinal metaplasia, endometriosis
- Renal tubular cells
  - Degenerated, small, high N:C, clusters, low power evaluation

Negative for high-grade urothelial carcinoma: NHGUC

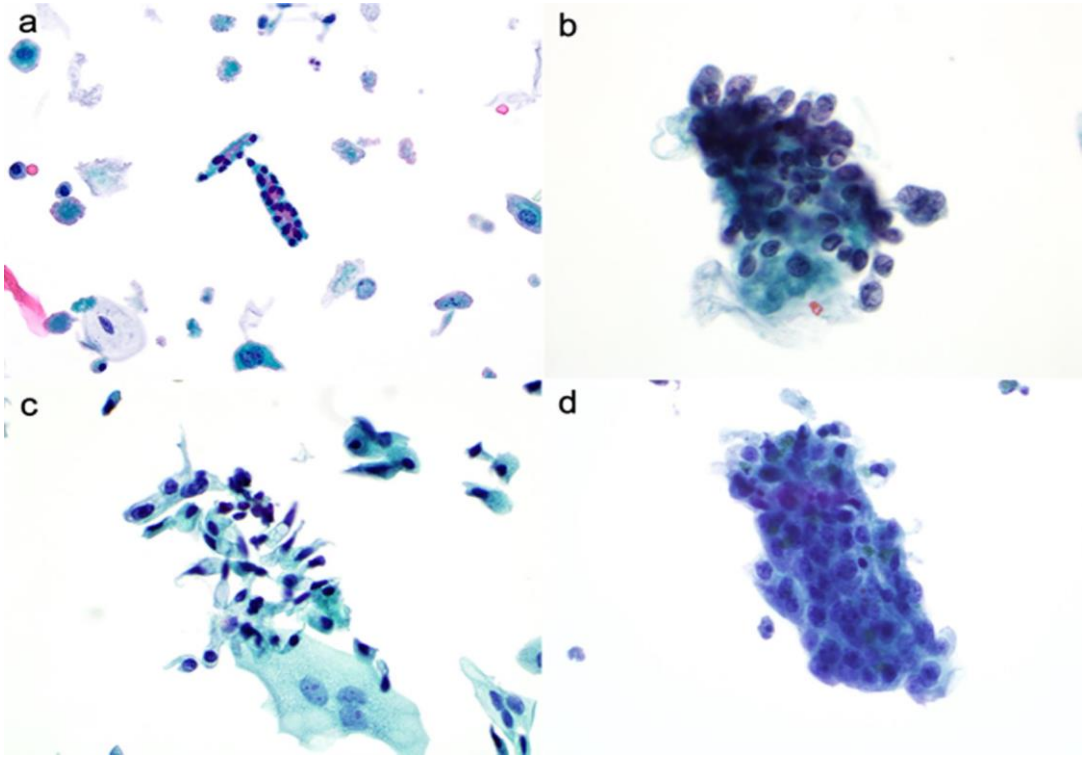
a. Intermediate cells
b. Umbrella cells
c. Bladder washing
d. Squamous cells
e. Degenerated cells
f. BUTF
g. AUTF
h. LGPUC
i. Urolithiasis



Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. J Clin Transl Pathol. 2023;3(2):59-74.

Negative for high-grade urothelial carcinoma: NHGUC

a. Renal tubular cells
b. Endometriosis
c. Cystitis glandularis
d. Prostatic cells



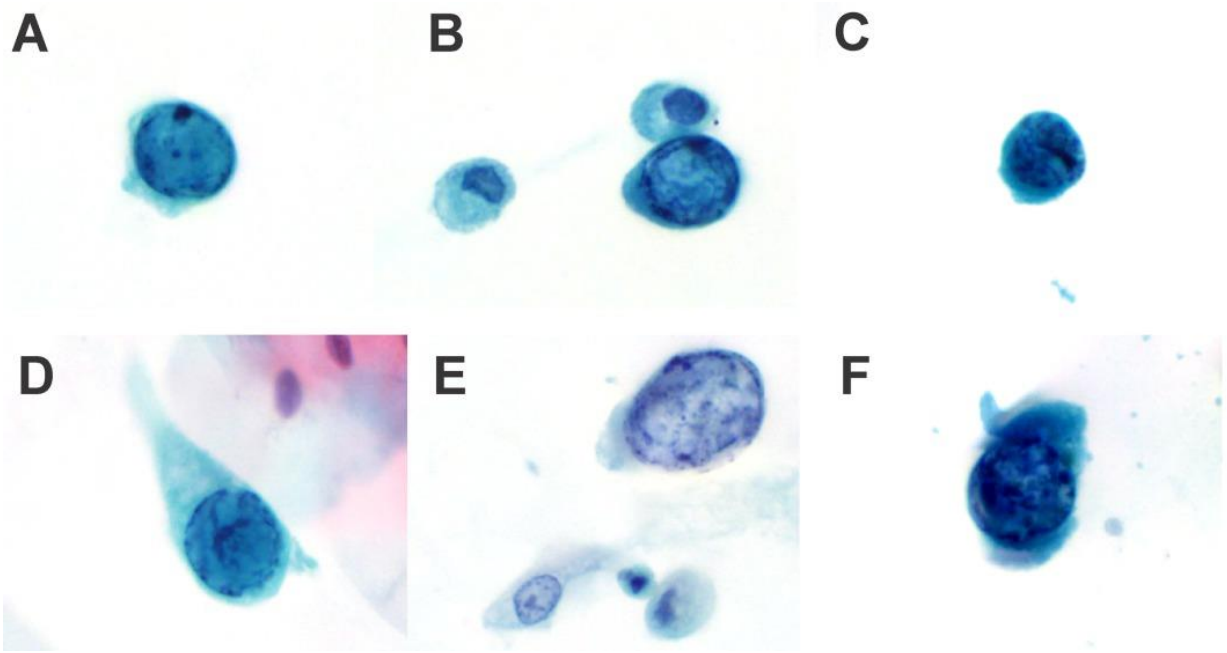
Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. J Clin Transl Pathol. 2023;3(2):59-74.

Negative for high-grade urothelial carcinoma: Criteria for NHGUC

- Degenerative Changes
  - Pyknotic/smudged nuclei, granular/vacuolated cytoplasm
  - Eosinophilic intracytoplasmic inclusions
  - Loss of nuclear-cytoplasmic border
- Infectious processes
  - Polyomavirus (BK and JC) – “decoy cells”; aneuploid by FISH
  - Other viral cytopathic effects – HSV, CMV, HPV
  - Bacteria, Parasites rare (Shistosoma haematobium ova)
- Treatment effects
  - Radiation, immunotherapy (BCG), chemotherapy
- Bladder Diversion specimen
  - Degenerated glandular cells, necrosis, bacteria, inflammation

Negative for high-grade urothelial carcinoma: NHGUC

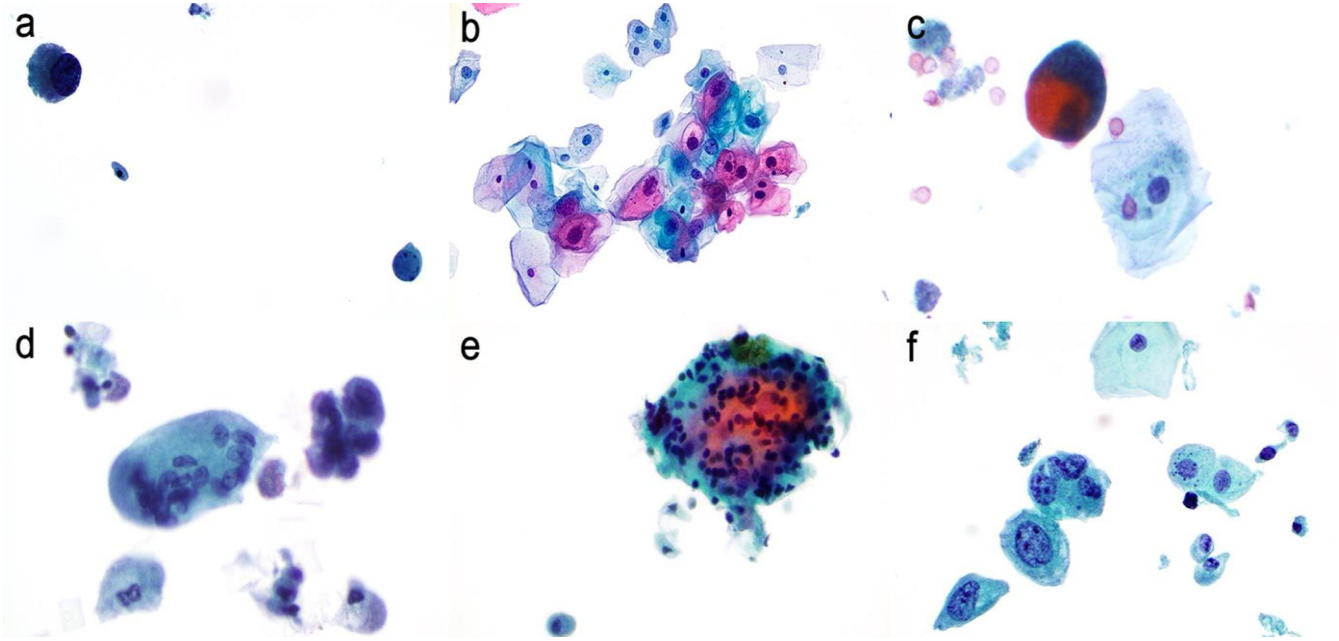
BK cytopathic effect
"decoy cells"



Allison DB, Olson MT, Lilo M, Zhang ML, Rosenthal DL, VandenBussche CJ. Should the BK polyomavirus cytopathic effect be best classified as atypical or benign in urine cytology specimens? Cancer Cytopathol. 2016 Jun;124(6):436-42.

Negative for high-grade urothelial carcinoma: NHGUC

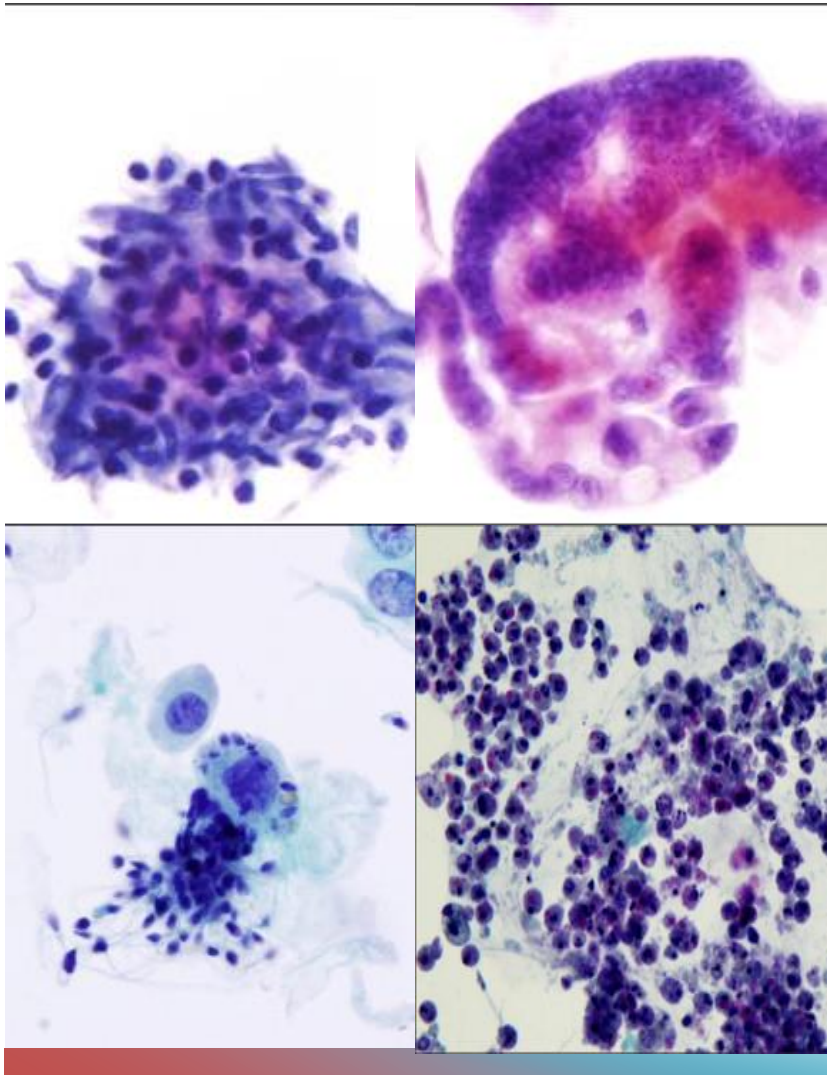
a. Polyomavirus
b. HPV
c. Radiation
d. BCG
e. BCG - granuloma
f. Chemotherapy



Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. J Clin Transl Pathol. 2023;3(2):59-74.

Negative for high-grade urothelial carcinoma: NHGUC

- Clockwise:
  - Granuloma (BCG therapy)
  - Radiation
  - Urinary diversion
  - Seminal Vesicle cells



Wojcik EM. What should not be reported as atypia in urine cytology. J Am Soc Cytopathol. 2015 Jan-Feb;4(1):30-36.

Negative for high-grade urothelial carcinoma: Category Performance for NHGUC

- NHGUC category
  - ROHM of 8.7–36.7%
  - False-negative rate of 3.3%
  - Negative predictive value (NPV) of 96.7%
- Limitations
  - Studies from both retrospective classification of TPS and prospective classification of TPS
  - Majority of patients with NHGUC do not have concurrent or follow up biopsies (3-6%)

VandenBussche, CJ. *et al.* (2022). Negative for High-Grade Urothelial Carcinoma (NHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Atypical Urothelial Cells: AUS
Background

- Prior to TPS reported “atypical” rates highly variable and excessive reaching up to 50% →poor screening tool
- In addition to standardized reporting, a main objective of TPS is to reduce the atypia rate and improve clinical utility of urine cytology

Barkan, GA. *et al.* (2022). Atypical Urothelial Cells (AUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

AUS 2.0

- Many studies have shown standardized criteria have reduced "atypia" comparing: post-TPS vs. pre-TPS rate.
- TPS goal: <15%→ <10%

			Pre-TPS % (n)	Post-TPS % (n)
Author	Year	Study location	Atypia	AUC
Vosoughi et al.	2021	USA (Miami)	16 (249)	9 (56)
Compton et al.	2021	USA (Nashville)	N/A	12.5 (199)
Stanzione et al.	2020	USA (Los Angeles)	59.8 (52)	41.5 (122)
Anbardar et al.	2020	Iran	26	1.2 (22)
Rai et al.	2019	India	16.7 (15)	11.1 (10)
Bakkar et al.	2019	USA (Los Angeles)	44 (44)	23 (23)
Vallamreddy et al.	2019	India	21.6 (16)	9.5 (7)
Wang et al.	2018	Canada	18.6 (442)	14.4 (345)
Meilleroux et al.	2018	France	6.1 (100)	5.2 (94)
VandenBussche et al.	2018	USA (Baltimore)	23.9 (568)	23.0 (589)
Xing et al.	2018	USA (Pittsburgh)	34 (52)	24 (37)
Rohilla et al.	2018	India	54.3 (73)	8.5 (114)
Zare et al.	2018	USA (San Diego)	24.2 (47)	11.9 (23)
Torous et al.	2017	USA (Boston)	29.5 (328)	21.8 (302)
Roy et al.	2017	India	41.2 (40)	11.3 (11)
Granados et al.	2017	Spain	4.7(7)	20.1 (30)
Suh et al	2017	Korea	25.4 (36)	14.8 (21)
Hassan et al.	2016	Canada	38.7 (48)	25.8 (32)

From TPS2.0, AUC Chapter by Barkan et al.

Barkan, GA. *et al.* (2022). Atypical Urothelial Cells (AUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Atypical Urothelial Cells: AUS

- TPS has caused cases interpreted as atypical to be more meaningful → measured by ROHM
- ROHM is significantly increased in the TPS AUC category
- Mean ROHM in weighted meta-analyses (n=2292) with histologic follow up: 38%
  - Retrospective re-classification 32%
  - Prospective classification 43%

Saieg, M,. *et al.* (2022). Risk of High-Grade Malignancy (ROHM). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Atypical Urothelial Cells: AUS

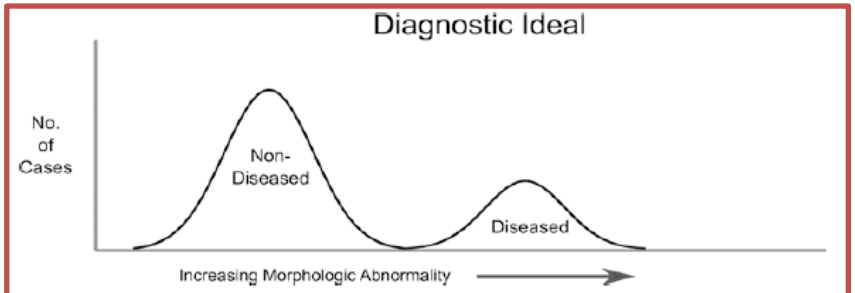


Fig. 4.1 Diagnostic ideal: in the ideal testing situation, the values derived from a test, be they numeric or a morphologic impression, would clearly separate the non-diseased population from a diseased population

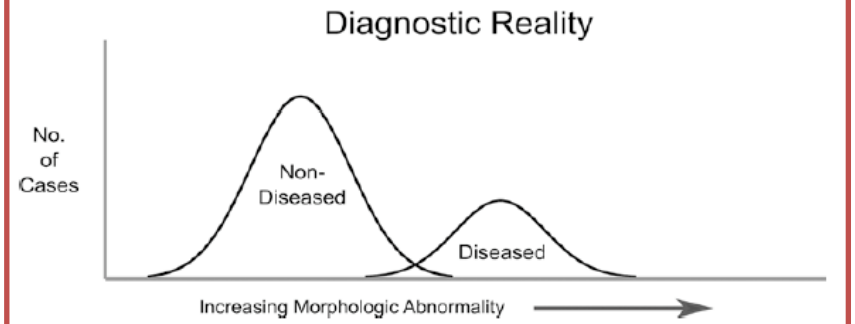


Fig. 4.2 Diagnostic reality: in the usual testing situation, some benign states yield values or features that overlap with those found in a diseased population

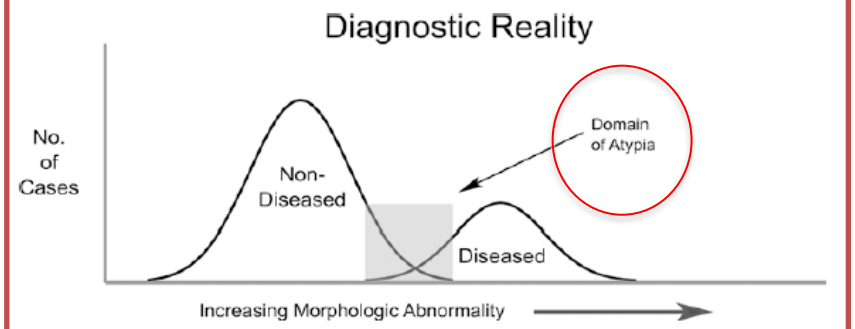


Fig. 4.3 Diagnostic reality: the area of overlap between benign states and diseased states constitutes a region of diagnostic uncertainty and provides a conceptual representation of the domain of atypia

Barkan, GA. *et al.* (2022). Atypical Urothelial Cells (AUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Atypical Urothelial Cells: AUS
Definition

- A specimen that contains urothelial cells with

  mild-to-moderate cytologic (not architectural) change concerning for HGUC
- In a 2023 study, AUC accounted for 5.6% of voided urine specimens

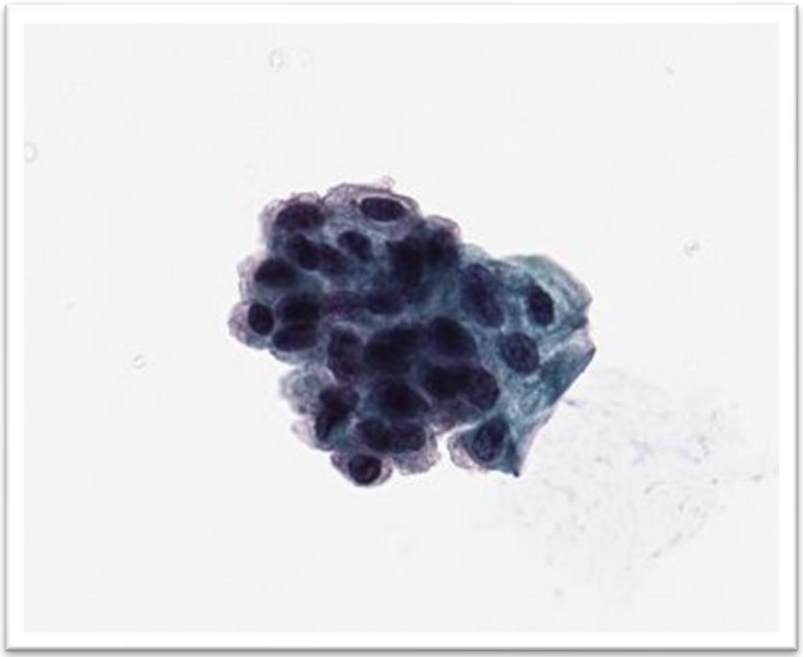
Lobo J, Lobo C, Leça L, Rodrigues Â, Henrique R, Monteiro P. Evaluation of the Implementation and Diagnostic Accuracy of the Paris Classification for Reporting Urinary Cytology in Voided Urine Specimens: A Cyto-Histological Correlation Study in a Cancer Center. Pathobiology. 2023;90(4):233-240.

Atypical Urothelial Cells:
Criteria for AUS

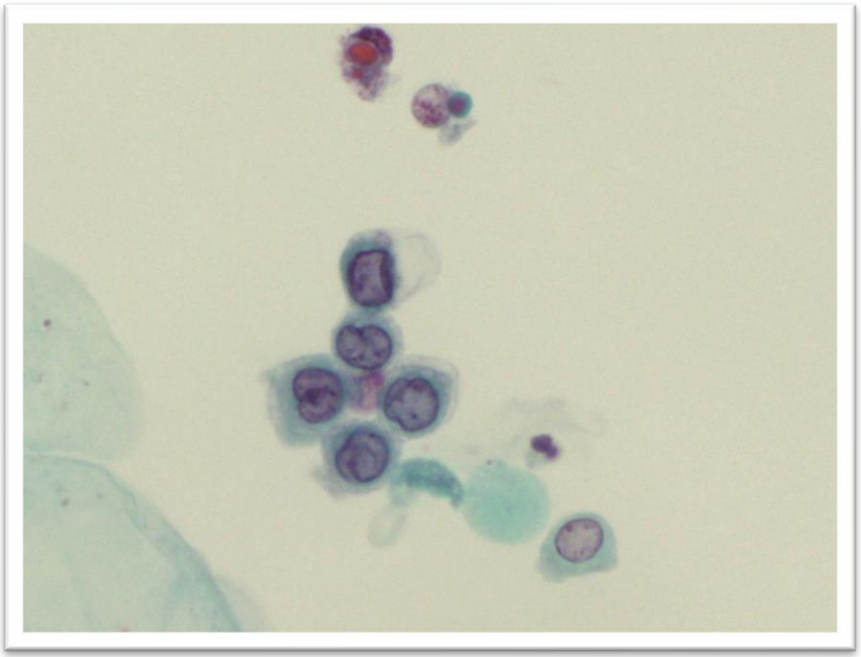
- Major criterion (required):
  - **Increase in N/C ratio of ≥0.5** due to nuclear enlargement
- AND
- Minor criteria (one required):
  - **Nuclear hyperchromasia**
  - **Irregular nuclear membranes** (chromatinic rim or nuclear contour);
  - **Irregular, coarse and clumped chromatin**
- Applies to all specimen types and preparations

Barkan, GA. *et al.* (2022). Atypical Urothelial Cells (AUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Atypical Urothelial Cells



N:C = 0.5
HYPERCHOMASIA
CLUMPY CHROMATIN



N:C > 0.5
NO HYPERCHROMASIA
IRREGULAR MEMBRANES

Suspicious for High-Grade Urothelial Carcinoma: SHGUC

Definition

- Restricted to cases with abnormal urothelial cells that **quantitatively** fall short of a definitive diagnosis of high-grade urothelial carcinoma (HGUC)

Brimo F. *et al.* (2022). Suspicious for High-Grade Urothelial Cacinoma (SHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Suspicious for High-Grade Urothelial Carcinoma: SHGUC

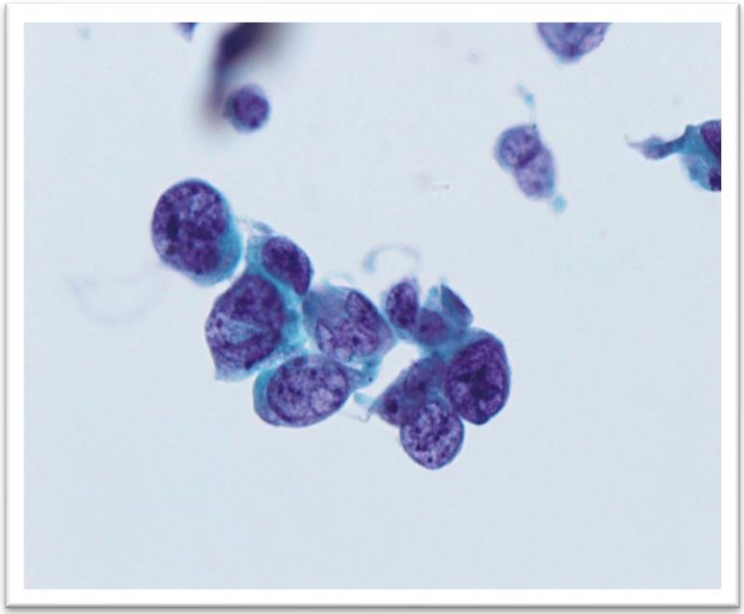
Criteria for all specimen types

Major criteria:

- Increase in N/C ratio to ≥0.7 due to nuclear enlargement (non-degenerated cell)

AND two of three features below:

- Moderate to severe hyperchromasia
- Irregular clumpy chromatin
- Irregular nuclear membrane



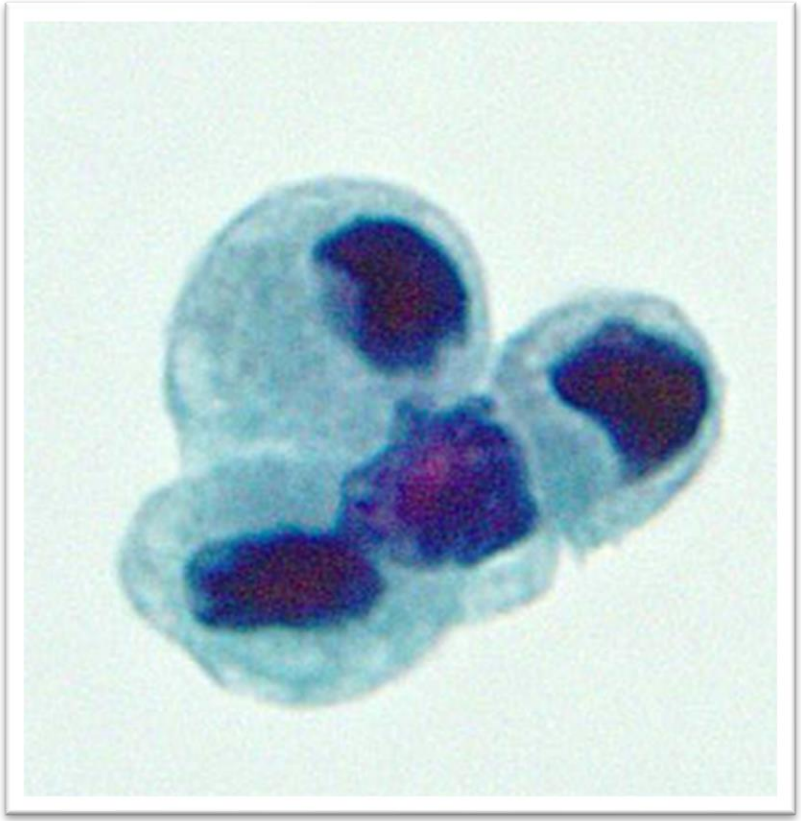
Brimo F. *et al.* (2022). Suspicious for High-Grade Urothelial Cacinoma (SHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Suspicious for High-Grade Urothelial Carcinoma: SHGUC

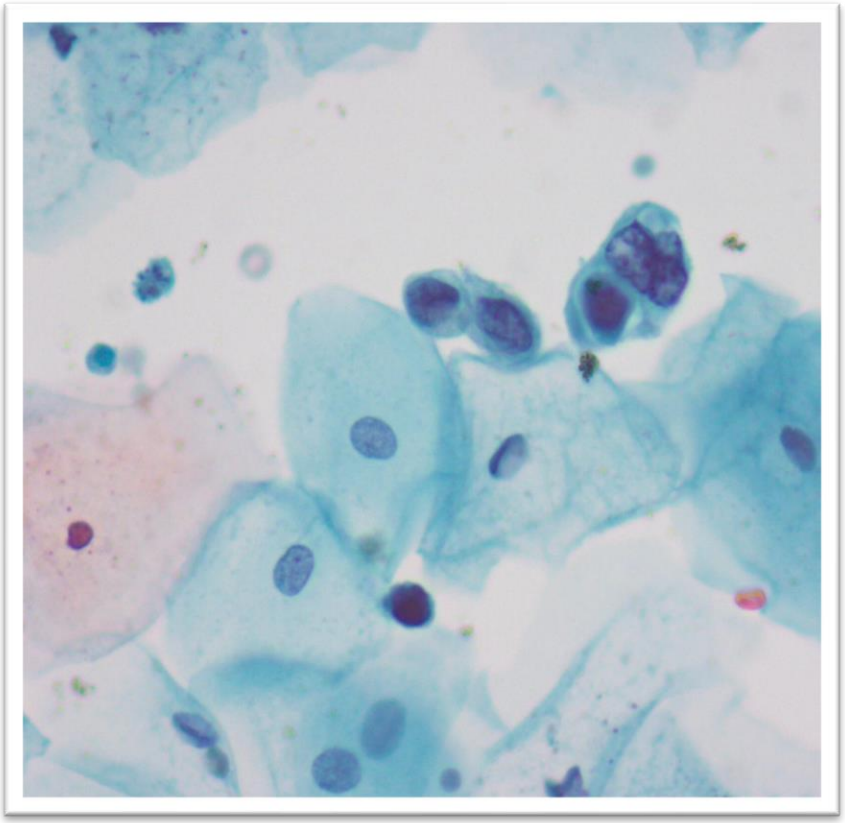
- The decision to assign a case to SHGUC vs. HGUC is based on the **number of abnormal cells** fulfilling the criteria
- A cut-off range of *at least 5–10 abnormal cells for lower tract (LT) specimens and ≥10 cells for upper tract (UT) specimens is recommended for HGUC*
- Studies have confirmed that a diagnosis of SHGUC reveals a risk for HGUC that falls between AUC and HGUC justifying it as a separate diagnostic category

Brimo F. *et al.* (2022). Suspicious for High-Grade Urothelial Cacinoma (SHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Suspicious HGUC



↑N/C
HYPERCHROMASIA
IRREGULAR MEMBRANES



↑N/C
HYPERCHROMASIA
CLUMPY CHROMATIN
IRREGULAR MEMBRANES

High-Grade Urothelial Carcinoma: HGUC

- The primary purpose of TPS is to have the highest positive predictive value (PPV) for HGUC
- TPS criteria for HGUC has resulted in a very high specificity with decreased false positives (FP)
- High specificity for HGUC results in improved risk stratification for patients based on future risk of malignancy
- In large cohorts with follow up ROHM for HGUC >90%

Pastorello RG, Barkan GA, Saieg M. Experience on the use of The Paris System for Reporting Urinary Cytopathology: review of the published literature. J Am Soc Cytopathol. 2021 Jan-Feb;10(1):79-87.

Siddiqui MT. *et al.* (2022). Suspicious for High-Grade Urothelial Cacinoma (SHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

High-Grade Urothelial Carcinoma: HGUC Criteria

Cellularity:

- At least 5–10 malignant cells are required for LT specimens
- ≥10 cells are required for UT specimens

N/C ratio:

- **≥0.7** (XS area of nucleus occupying 70% of XS area of cell)
- most restrictive and recommended benchmark for HGUC

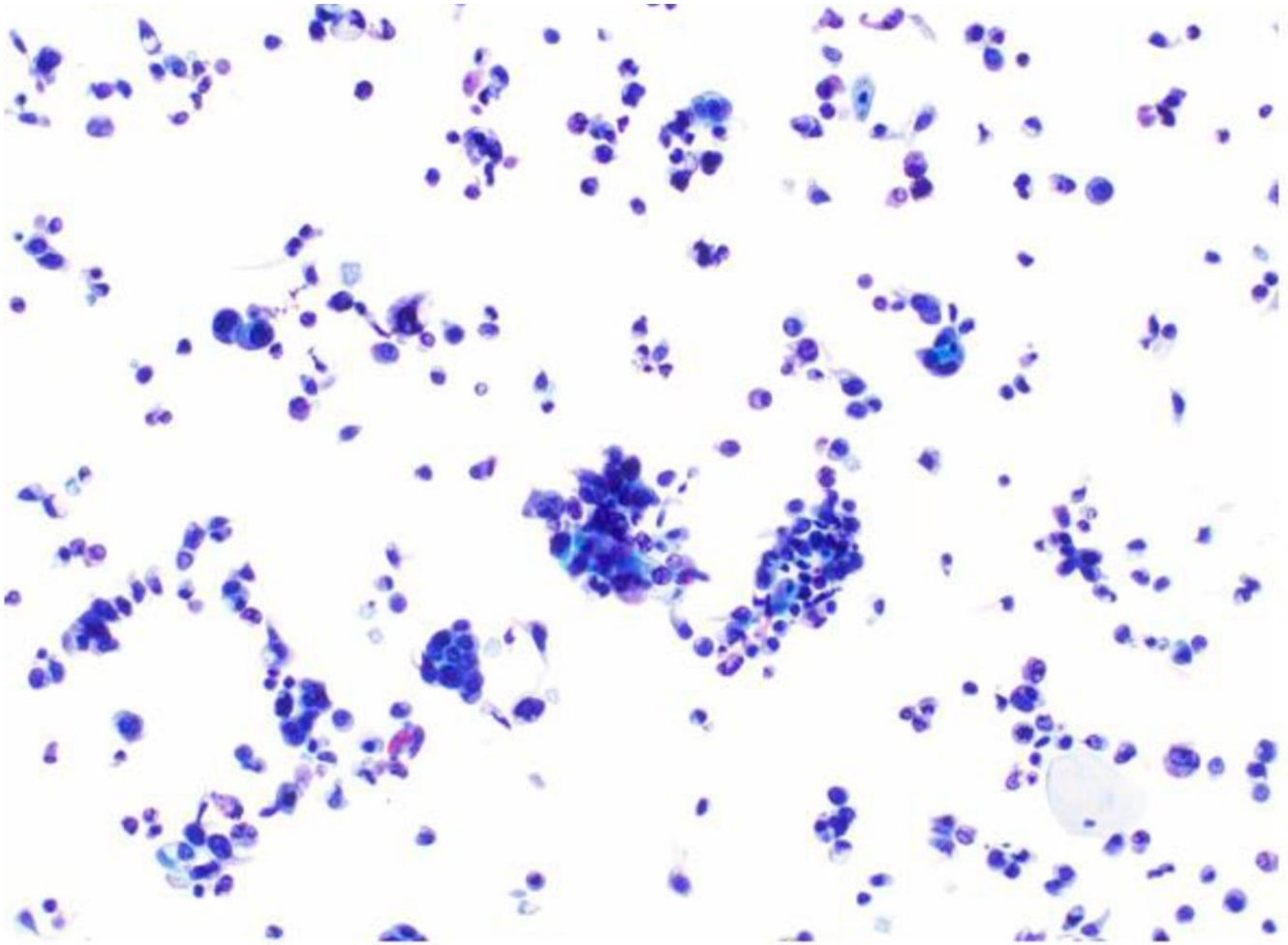
Nucleus: Moderate-to-severe hyperchromasia

Nuclear membrane: Irregular outline

Chromatin: Coarse/clumped

Siddiqui MT. *et al.* (2022). Suspicious for High-Grade Urothelial Cacinoma (SHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

High-Grade Urothelial Carcinoma: HGUC

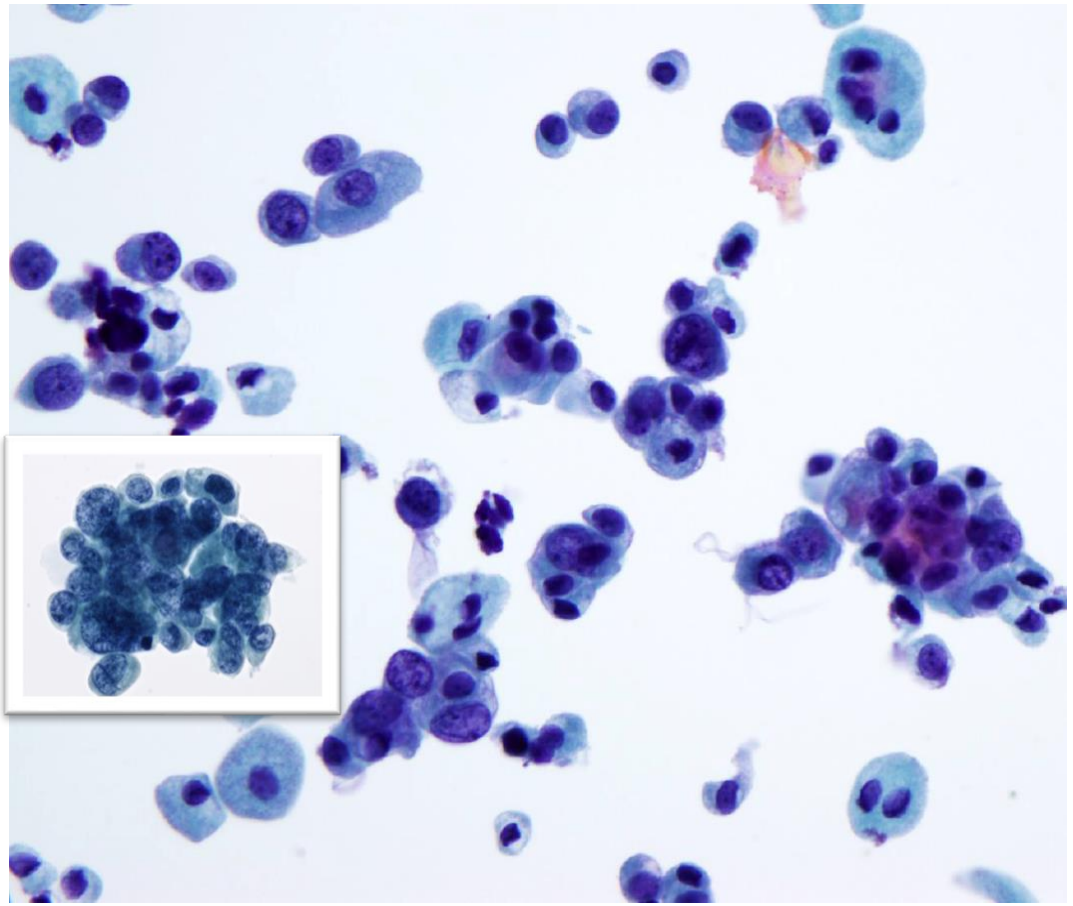


Olawunmi S. Folarin, Momin T. Siddiqui, Are we on track for diagnosing high-grade urothelial carcinoma with a minimum quantity of five malignant cells in lower tract specimens? Critical analysis of The Paris System Quantitation Criteria, Cancer Cytopathology, 10.1002/cncy.22749, **131**, 11, (708-715), (2023)

High-Grade Urothelial Carcinoma: HGUC

Additional cytomorphologic features:

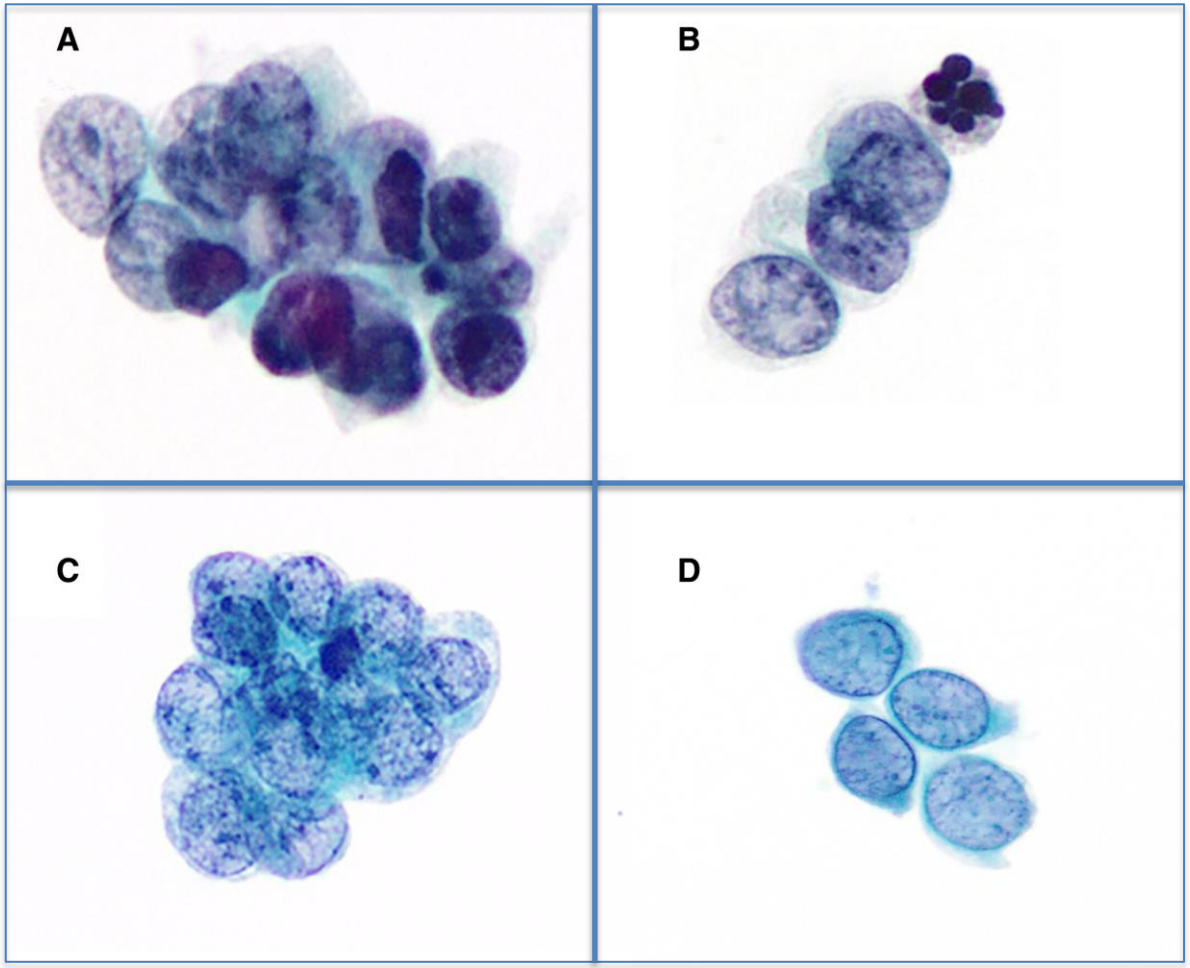
- Cellular pleomorphism
- Dense or vacuolated cytoplasm
- Prominent nucleoli
- Mitoses
- Necrosis
- Inflammation
- Hypochromasia*
  → potential pitfall



Siddiqui MT. *et al.* (2022). Suspicious for High-Grade Urothelial Cacinoma (SHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

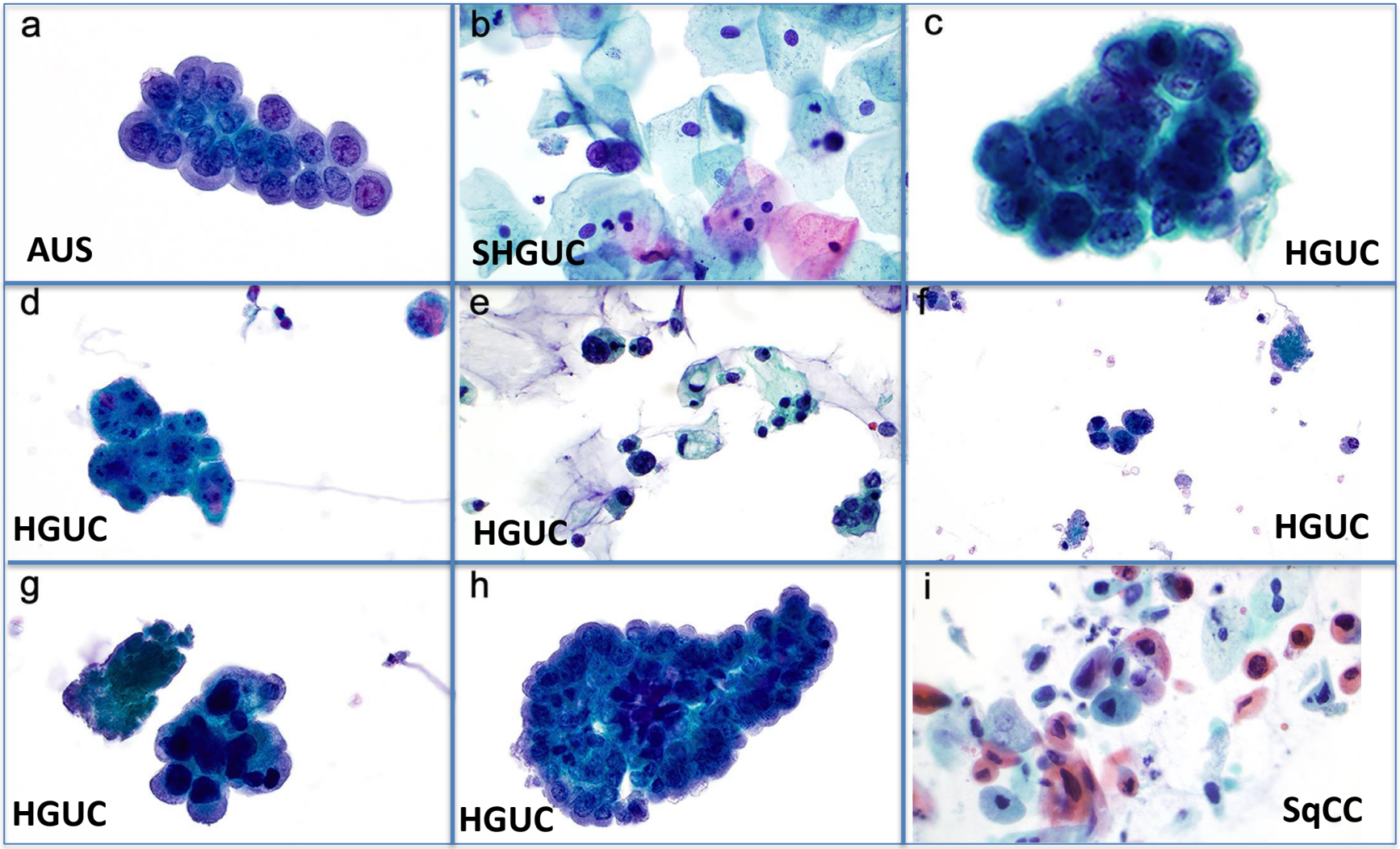
High-Grade Urothelial Carcinoma: HGUC with *hypochromatic nuclei*

(A) High magnification of heterogeneous specimen with both hyper- and hypochromasia
(B) Hypochromatic HGUC with an adjacent neutrophil
(C) Additional example of Hypochromatic HGUC
(D) Hypochromatic HGUC



McIntire PJ, Aragao A, Burns BL, Pambuccian SE, Wojcik EM, Barkan GA. Digital image analysis of high-grade urothelial carcinoma in urine cytology confirms chromasia heterogeneity and reveals a subset with hypochromatic nuclei and another with extremely dark or “India ink” nuclei. *Cancer Cytopathol*. 2022

AUC – SHGUC – HGUC



Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. J Clin Transl Pathol. 2023;3(2):59-74.

High-Grade Urothelial Carcinoma: HGUC

Important histologic variants of HGUC in urine cytology

- A total of 14 histologic variants of HGUC were recognized in the 2022 World Health Organization (WHO) classification of tumors of the urinary system

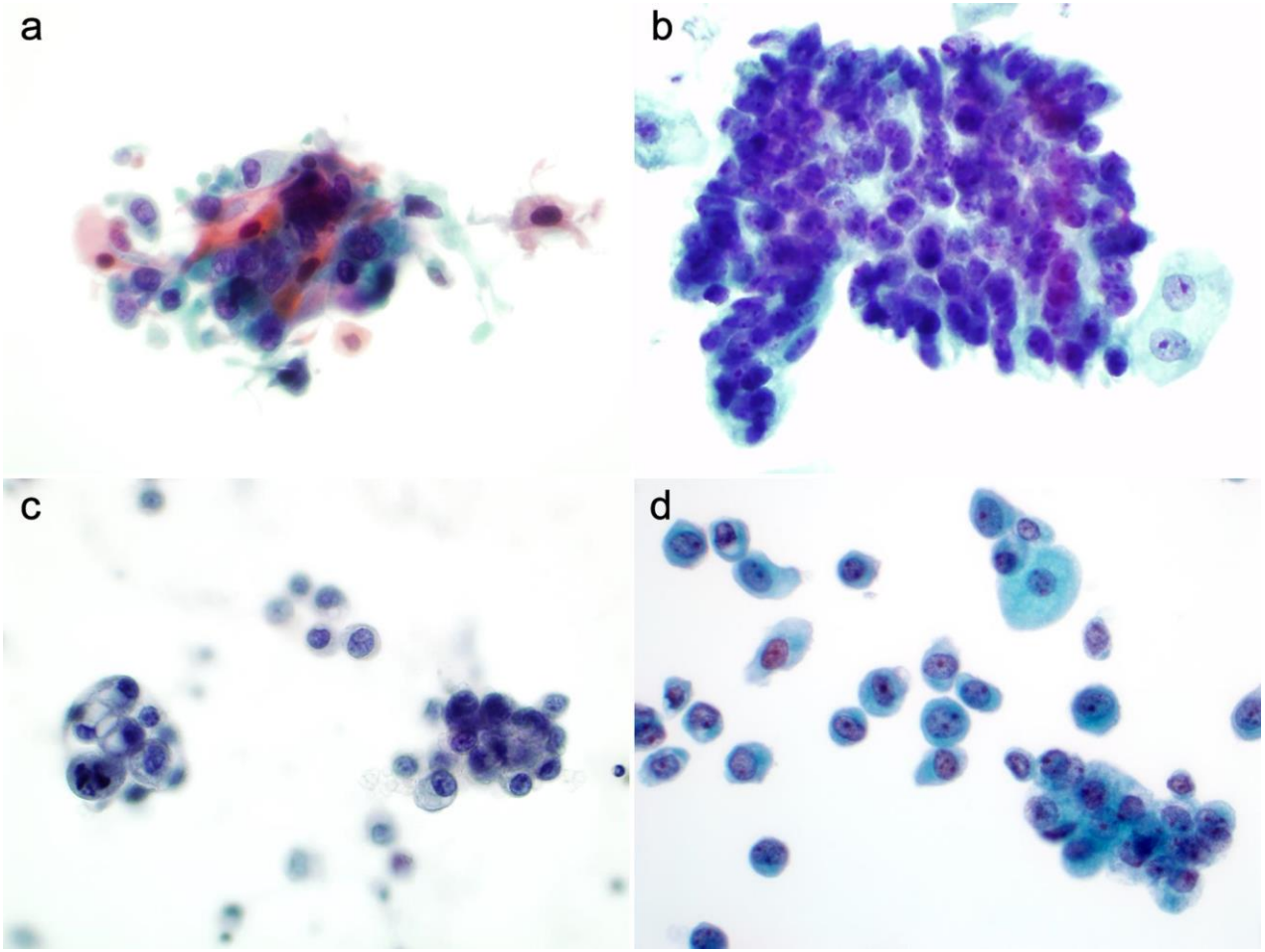
- Can be extremely challenging to diagnose some HGUC variants by urine cytology.
  - Classic features of HGUC may be absent
  - Rare cases
  - Often associated with classic HGUC

Siddiqui MT. *et al.* (2022). Suspicious for High-Grade Urothelial Cacinoma (SHGUC). In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

HGUC Histologic Variants

HGUC w/squamous diff

HGUC w/ glandular diff



Micropapillary HGUC

Plasmacytoid HGUC

Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. J Clin Transl Pathol. 2023;3(2):59-74. doi: 10.14218/JCTP.2022.00035.

Upper Tract Urothelial Carcinoma: UTUC

Background

- UTUC accounts for 5-10% of all UC
- Voided urine (VU) or washings from upper urinary tract (UUT) is part of work up for UTUC
- Instrumented/selective UUT specimens are superior to VU to detect UTUC

VandenBussche CJ. *et al.* (2022). Cytopathology of the Upper Urinary Tract. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

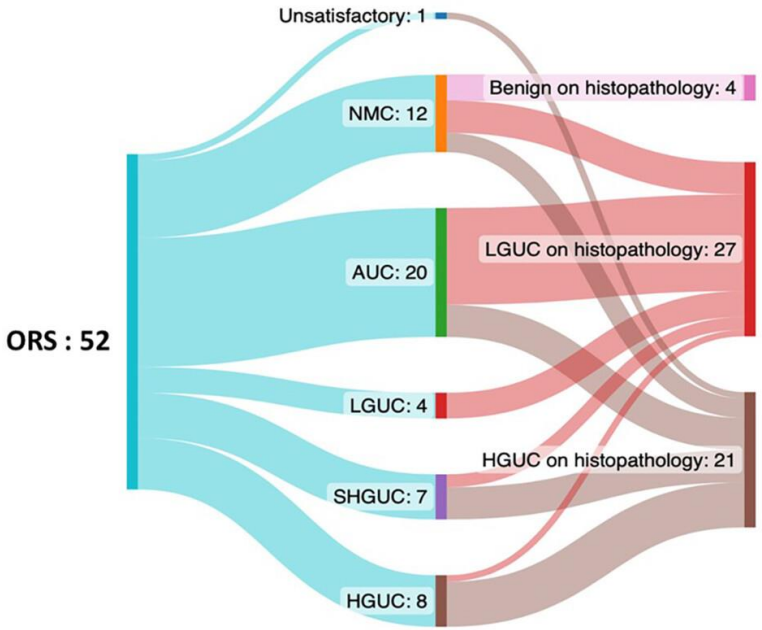
Upper Tract Urothelial Carcinoma: UTUC

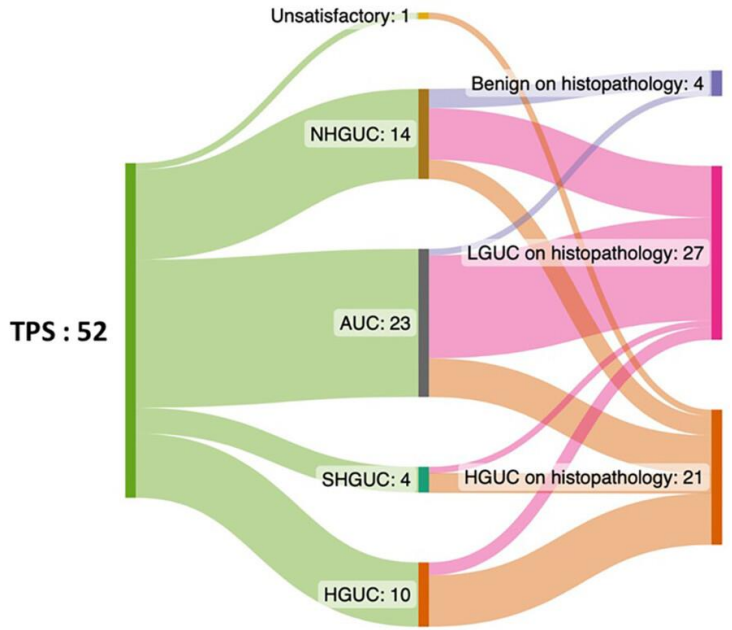
Definition of UTUC

- UC rising in the renal pelvis or ureter
- The focus of TPS remains on the detection of upper tract high-grade urothelial carcinoma (UTHGUC)

VandenBussche CJ. *et al.* (2022). Cytopathology of the Upper Urinary Tract. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Cytologic evaluation of UUT specimens:
An institutional RS study using TPS 2.0 with histopathologic follow up

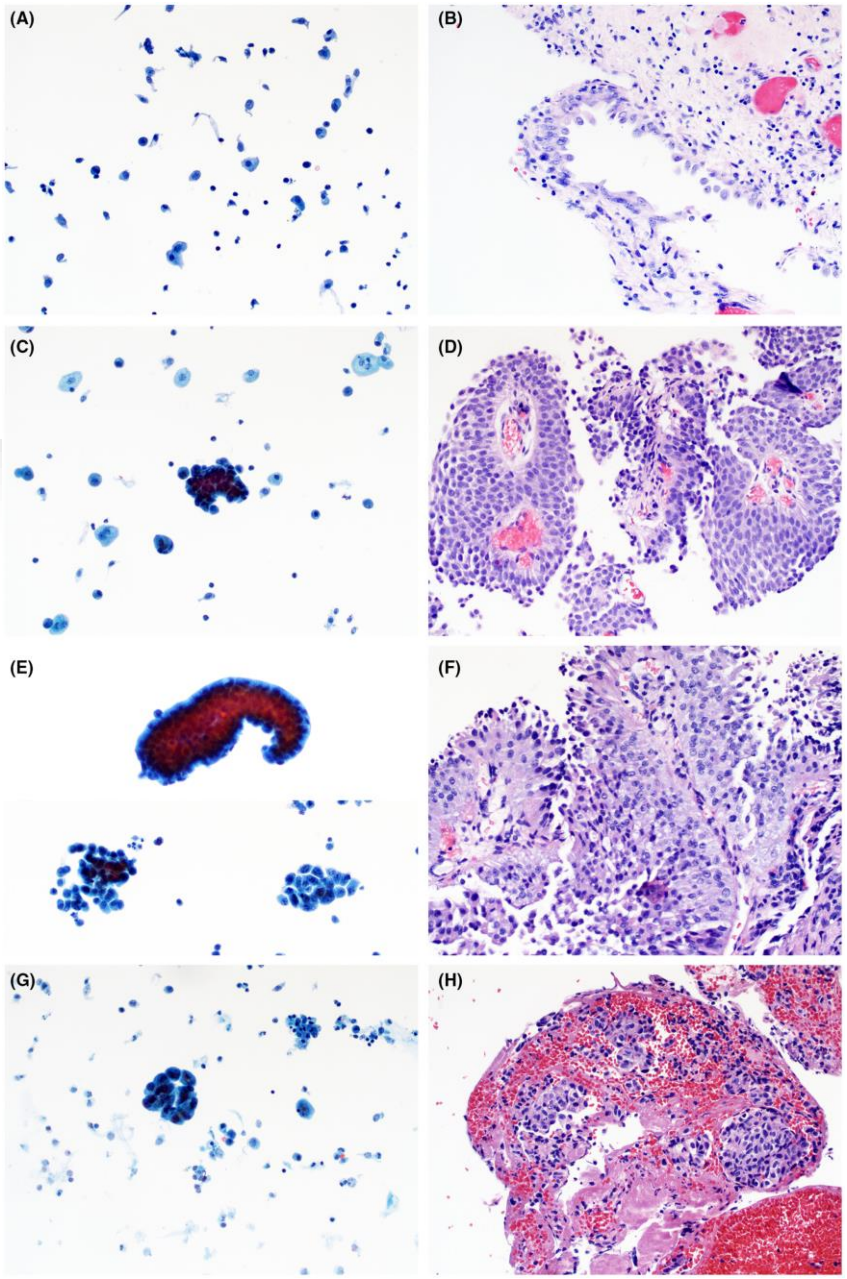




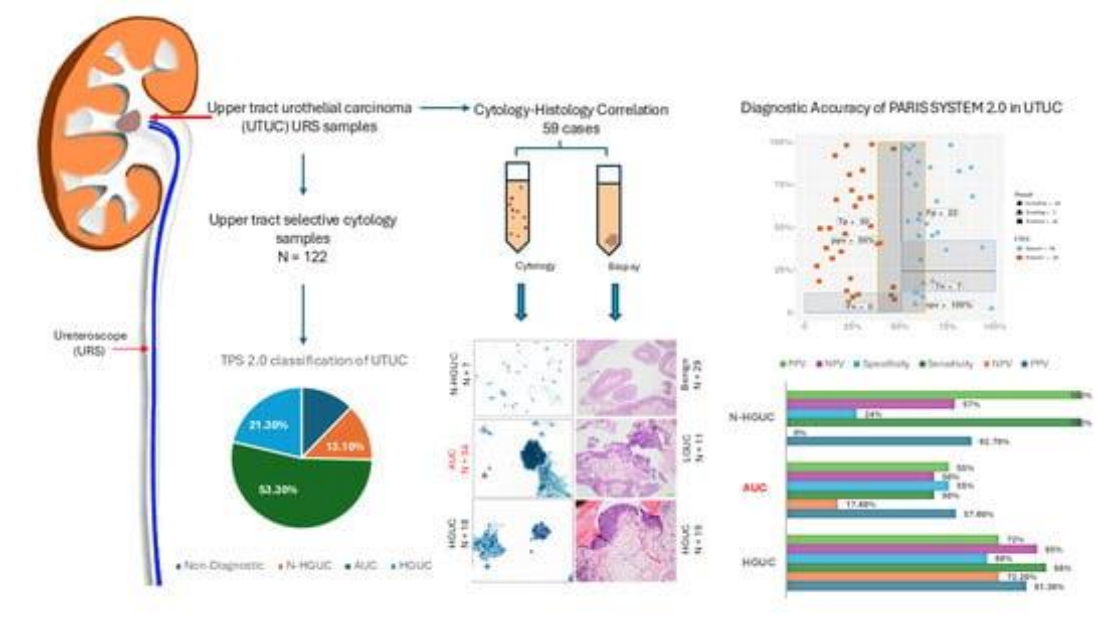
Khajir G, Sun T, Wang H, Sprenkle PC, Adeniran AJ, Cai G, Levi AW. Cytologic evaluation of upper urinary tract specimens: An institutional retrospective study using The Paris System for Reporting Urine Cytology second edition with histopathologic follow-up. Cytopathology. 2024

Cytologic evaluation of UUT specimens:
An institutional RS study using TPS 2.0

- Negative for malignant cells in urine cytology (A), and the corresponding benign surgical biopsy specimen (B)
- Atypical urothelial cells in urine cytology (C), and the corresponding atypical papillary proliferation on a surgical biopsy specimen (D)
- Low-grade urothelial carcinoma (LGUC) in urine cytology (E) and the histological correlate showing LGUC (F)
- High-grade urothelial carcinoma (HGUC) in urine cytology (G), and the histological correlate demonstrating HGUC (H)



Khajir G, Sun T, Wang H, Sprenkle PC, Adeniran AJ, Cai G, Levi AW. Cytologic evaluation of upper urinary tract specimens: An institutional retrospective study using The Paris System for Reporting Urine Cytology second edition with histopathologic follow-up. Cytopathology. 2024



Mansour, M.A.; Ozretić, L.; El Sheikh, S. The Diagnostic Accuracy of the Paris System for Reporting Upper Urinary Tract Cytology: The Atypical Urothelial Cell Conundrum. *Cancers* **2025**, *17*, 1097.

Upper Urinary Tract

Studies on TPS 2.0 for UTUC are fewer and evolving

TPS 2.0 shows high sensitivity and specificity for HGUC, effectively ruling it out in non-HGUC cases

It struggles with high AUC rates due to frequent cytological atypia in the upper tract, leading to low sensitivity and PPV

Strict criteria and refined guidelines may reduce AUC rates

Future ancillary molecular tests could enhance upper tract urothelial cytology accuracy

Non-urothelial malignancies (NUM)

Background

- Non-urothelial malignancies are rare in urine (<5%)
- Majority of NUM are epithelial origin (90%)
  - SqCC, ADCa, SmCC
- Non-epithelial malignancies
  - Sarcoma, Melanoma, Lymphoma

Primary vs. Secondary Malignancy

- Clinical history and a
- Ancillary studies

Elsheikh TM. *et al.* (2022). Non-Urothelial Malignancies and Other Miscellaneous Lesions. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Non-urothelial malignancies (NUM)

Primary Malignancy

- SqCC second most common malignant neoplasm of UT
  - S. haemstibium vs. recurrent infection, indwelling catheter
- Atypical squamous cells (ASC)
  - Metaplasia, dysplasia, HPV
  - Bladder, urethra, Gyn tract*

Secondary Malignancy

- Most are direct extension vs. metastasis
  - Colorectal, prostate, Gyn; breast, gastric, lung, RCC
- Can mimic primary urothelial and NUM
  - Clinical history and IHC

Elsheikh TM. *et al.* (2022). Non-Urothelial Malignancies and Other Miscellaneous Lesions. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

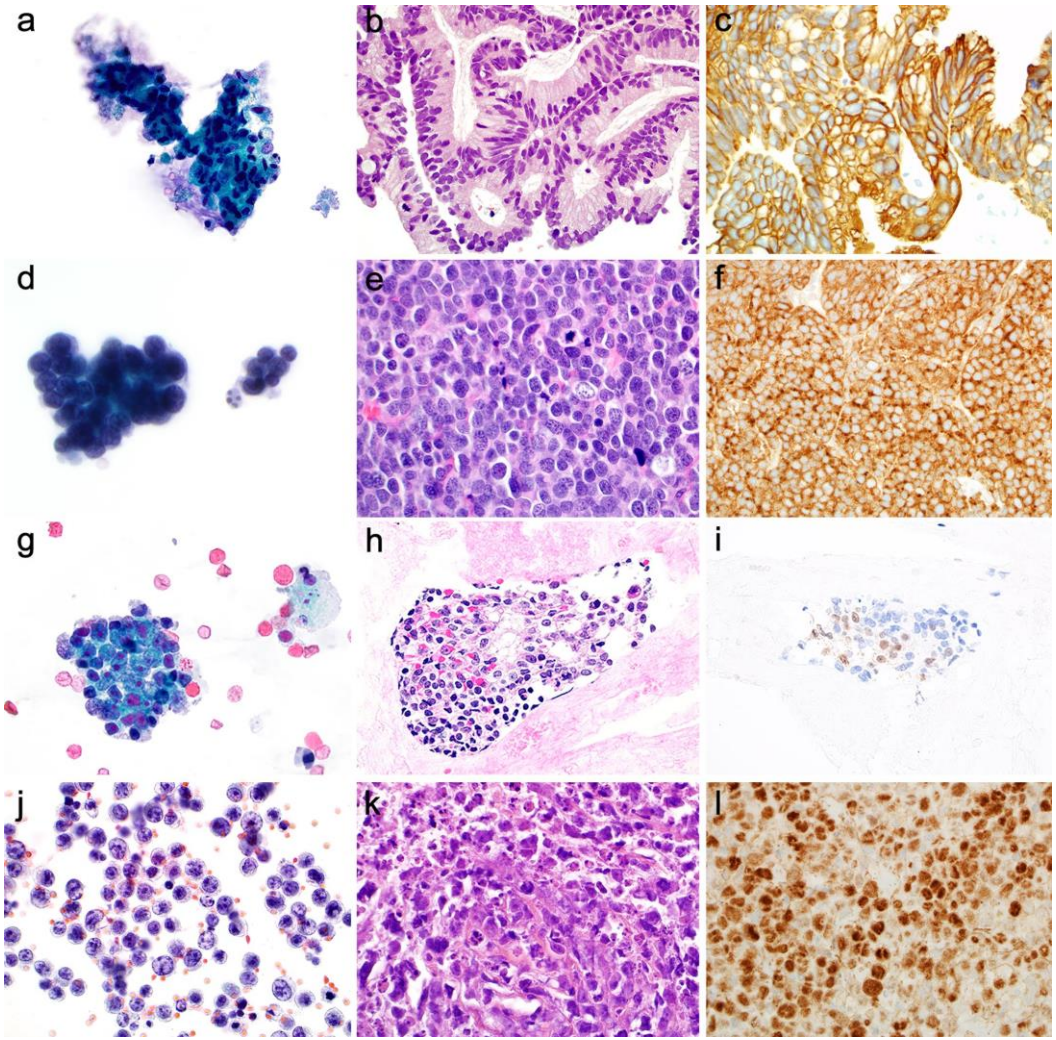
NUM: Secondary Malignancies

a-c) AdCa, CK7/20+

d-f) SmCC, Synap+

g-i) AdCa, NKX3.1+

j-l) DLBL, PAX5+



Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. J Clin Transl Pathol. 2023;3(2):59-74. doi: 10.14218/JCTP.2022.00035.

Ancillary studies in urinary cytology

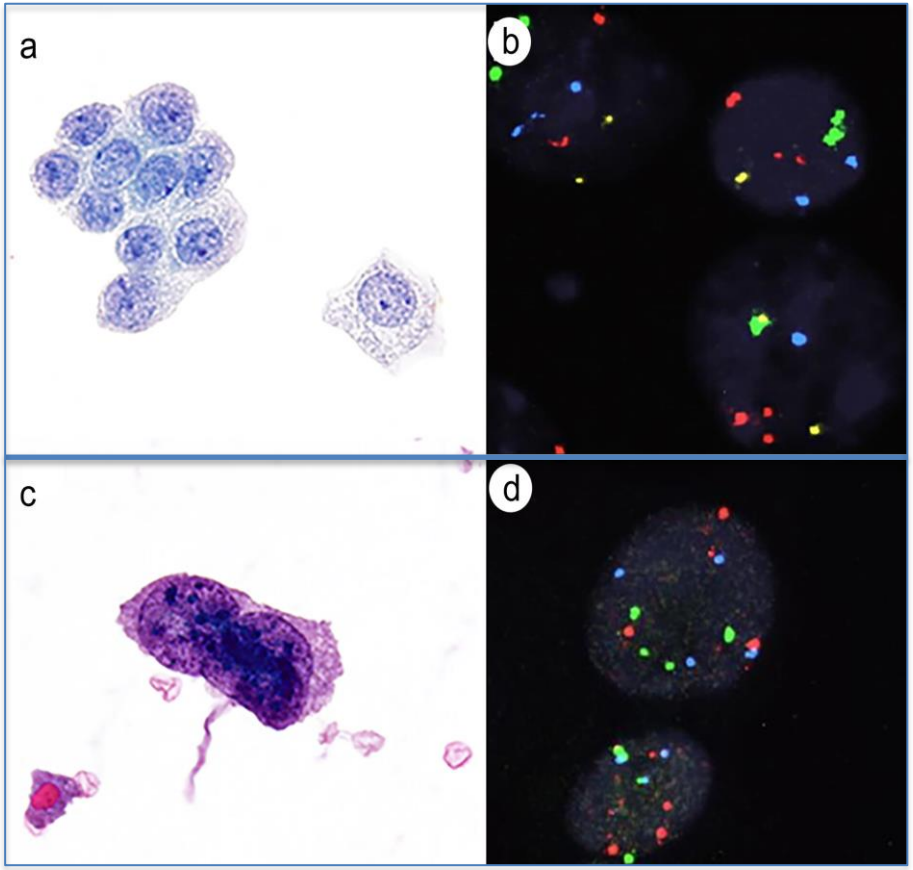
FDA-approved liquid-based tests

- UroVysion® fluorescence *in situ* hybridization (U-FISH)
- BTA™ - lower sensitivity (~65%) and specificity (~74%)
- NMP22™ - high false positive rate in benign urothelial cases

Bubendorf L. *et al.* (2022). Ancillary Studies in Urinary Cytology. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

UroVysion® fluorescence *in situ* hybridization (U-FISH)

- Four single-stranded DNA probes
- Three chromosome enumeration probes (CEPs) targeting the pericentromeric regions of chromosomes 3, 7, and 17
- locus-specific identifier (LSI) probe that targets 9p21
- Sensitivity of 89–100%
- Specificity of 60–100%
- Utility in AUC (FPs*)
- Automated imaging systems



Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. J Clin Transl Pathol. 2023;3(2):59-74. doi: 10.14218/JCTP.2022.00035.

Ancillary studies in urinary cytology

Ancillary tests based on next-generation sequencing (NGS)

- Various mutations can be present in UC
- Mutations, epigenetic alterations, and copy number changes can be detected by NGS, simultaneously
- Commercially available NGS tests
  - uCAPP-Seq, AssureMDx, and UroSeek
  - Sensitivity of 83–93%, and a Specificity of 86–99%.

Bubendorf L. *et al.* (2022). Ancillary Studies in Urinary Cytology. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Clinical Management

Summary of Changes in 2.0

- AUA guideline changes for evaluation of microscopic hematuria
- AUA guideline changes for surveillance of non-muscle invasive bladder cancer
- Use of reflex biomarker assays for AUC
- Role of enhanced endoscopic techniques “blue light” cystoscopy

Quek ML. *et al.* (2022). Ancillary Studies in Urinary Cytology. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Clinical Management: NHGUC

- New guidelines do not recommend cytology for initial evaluation of microscopic hematuria
- Patient-centered approach to diagnostic testing for microhematuria based on risk of UC
- Urine cytology/urinary biomarkers not recommended for patients with a h/o low-risk cancer
- Urine cytology is essential in the surveillance of patients for recurrences following therapy

Quek ML. *et al.* (2022). Ancillary Studies in Urinary Cytology. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Clinical Management: LGUC

- AUA/EAU recommend risk-adapted surveillance protocol for non-muscle-invasive bladder cancer
- Routine surveillance cystoscopies performed at regular intervals
- Stratification into low-, intermediate-, and high-risk groups for decision to use adjuvant intravesical chemotherapy or BCG therapy

Quek ML. *et al.* (2022). Ancillary Studies in Urinary Cytology. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Clinical Management: AUC

- Workup based on the patient's risk assessment
- Patients with hematuria/persistent irritative voiding symptoms:
  - upper tract imaging
  - cystoscopy
- Reflex UroVysion FISH testing for AUC diagnoses
  - positive FISH assay → managed as SHGUC
  - negative FISH test → follow up

Quek ML. *et al.* (2022). Ancillary Studies in Urinary Cytology. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Clinical Management: SHGUC/HGUC

SHGUC/HGUC

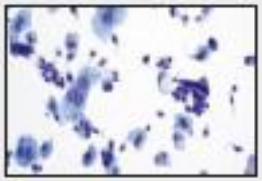
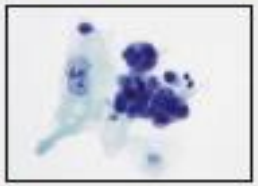
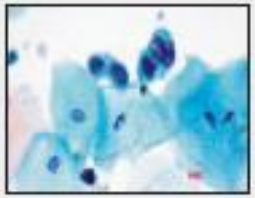
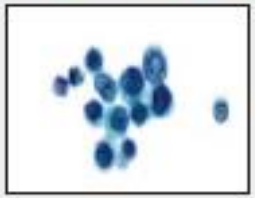
- Active investigation by cystourethroscopy
  - fluorescence “blue light” cystoscopy, narrowband imaging
  - bladder biopsy
- Prostatic urethra evaluation
- Upper tract evaluation with imaging studies
  - CT/MR urography
  - U/S with retrograde pyelography

Quek ML. *et al.* (2022). Ancillary Studies in Urinary Cytology. In: Wojcik, E.M., Kurtycz, D.F., Rosenthal, D.L. (eds) The Paris System for Reporting Urinary Cytology.

Summary of Changes: TPS 1.0 to 2.0

- Updated clinical management to current AUA guidelines
- Expanded discussion of HGUC morphologic subtypes
- New chapter on UUT
- Established ROHM for each diagnostic category

Essential data for each diagnostic category

Diagnostic category	Diagnostic criteria	Example	Frequency	ROHM
Unsatisfactory	Voided urine–volume (>30ml) Instrumented urine-cellularity		0 - 5%	0 - 16%
Negative for High Grade Urothelial Carcinoma (NHGUC)	Benign urothelial, glandular, squamous cells, benign tissue fragments, changes due to instrumentation, lithiasis, polyoma virus, therapy. Low Grade Urothelial Neoplasm (LGUN)		70 - 90%	8 - 24%
Atypical Urothelial Cells (AUC)	Required – increased N/C ratio ($\geq$ 0.5) and one of: Hyperchromasia, Irregular clumpy chromatin or Irregular nuclear contours		5 - 15%	24 - 53%
Suspicious for High Grade Urothelial Carcinoma (SHGUC)	Required – Few cells (< 5-10) with high N/C ratio (> 0.7) and hyperchromasia, and/or Irregular clumpy chromatin, Irregular nuclear contours		0.5 - 3%	59 - 94%
Positive for High Grade Urothelial Carcinoma (HGUC)	Required – Many cells (> 10) with high N/C ratio (> 0.7) and hyperchromasia, Irregular clumpy chromatin, Irregular nuclear contours		0.1 - 3%	76 - 100%

ROHM –Risk of High Grade Malignancy

Wojcik EM, Kurtycz DF, Rosenthal DL. The Paris System for Reporting Urinary Cytology, 2nd ed. Cham: Springer Nature Switzerland AG; 2022

Estimated risk of high-grade malignancy (ROHM) for each category of TPS 2.0

TPS category	Risk of high-grade malignancy
ND	0–16%
NHGUC	8–24%
LGUN	0–44%
AUC	24–53%
SHGUB	59–94%
HGUC/malignant	76–100%

Chen F, Lin X. The Paris System for Reporting Urinary Cytology: An Updated Review. *J Clin Transl Pathol*. 2023;3(2):59-74.

Summary of Changes: TPS 1.0 to 2.0

- Incorporation of The Cancer Genome Atlas molecular characterization into the pathogenesis of LGUC and HGUC
- Integration of LGUN into NHGUC category
- Updated performance data for each diagnostic category

TPS 2.0+

- [A real-world study of the clinical application of the **Paris system** for **reporting urinary cytology** in cancer hospital]. Zhao H, et al. Zhonghua Zhong Liu Za Zhi. 2024. PMID: 39034806 Chinese.
- A Comparative Study of the **Paris System** and Common **Reporting System** for Urine **Cytology** With Cyto-Histology Correlation: A Study of 829 Urine **Cytology** Specimens. Khairwa A, et al. Diagn Cytopathol. 2025. PMID: 39412371
- A review of the performance of **urinary cytology** with a focus on atypia, upper **tract** and updates on novel ancillary testing. Chukwudebe O, et al. J Am Soc Cytopathol. 2025. PMID: 39505676 Review.
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TPS-applied studies with rates of **AUC**

Author/Year	Country	Atypia rate (%)	Study approach	Sample size
Saharti et al 2022[69]	Saudi Arabia	32	Retrospective TPS1	316_s
Phruttinarakorn et al 2022[71]	Thailand	13.9	Retrospective TPS1	2178_s
Hermans et al 2022[72]	Germany	20.6	Retrospective TPS1	$197_p/389_s$
Moulavasilis et al 2022[73]	Greece	9.6_p	Retrospective TPS1	$146_p/438_s$
Christofidis et al 2023[74]	Greece	23.3_a, 21.7_b	Retrospective TPS2	$129_a/276_b$
Poyry et al 2023[75]	Finland	5.5	Prospective TPS1	3741_s
Lobo et al 2023[76]	Portugal	5.6	Retrospective TPS1	1180_s
Rakhshan et al 2022[77]	Iran	11.4	Retrospective TPS1	$741_p/2612_s$
Miyai et al 2023[52]	Japan	$10.3_{p,}$ 13.9_s	Retrospective TPS2	$137_p/223_s$
Celik and Kavas. 2023[80]	Turkey	14.1	Retrospective TPS1	205_s
Jain et al 2023[81]	India	22	Prospective TPS1	150_s

Chukwudebe O, Lynch E, Vira M, Vaickus L, Khan A, Shaheen Cocker R. A review of the performance of urinary cytology with a focus on atypia, upper tract and updates on novel ancillary testing. J Am Soc Cytopathol. **2025** Jan-Feb;14(1):23-35.

Diagnostic performance of TPS 2.0, TPS 1.0 and FTRS for the detection of **HGUC**

Diagnostic parameters	**TPS 2.0 and TPS 1.0**	**FTRS**	**TPS 2.0 (UUTC cases only)**
Sensitivity (95% CI)	**70.91%** (61.83–78.58)	**59.09%** (49.75–67.82)	**62.5%** (30.57–86.32)
Specificity (95% CI)	**90.77%** (84.56–94.64)	**81.54%** (74–87.27)	**100%** (51.01–100)
PPV (95% CI)	**86.67%** (78.13–92.21)	**73.03%** (62.48–76.92)	**100%** (56.55–100)
NPV (95% CI)	**78.67%** (71.44–84.46)	**70.2%** (62.48–76.92)	**57.14%** (25.05–84.18)
Diagnostic Accuracy (95% CI)	**81.67%** (76.29–86.05)	**71.25%** (65.22–76.61)	**75%** (46.77–91.11)

Jangir, H., Narwal, A., Adhikari, S.S., Batra, A., Nayak, B., Seth, A. and Kaushal, S. (2025), Evaluation of Diagnostic Accuracy of the Paris System (TPS 2.0) in Urine Cytology Specimens: An Institutional Experience From a Large Cohort of a Tertiary Care Centre. Cytopathology, 10.1111/cyt.13458, 36, 2, (140-149), **2024.**

Summary of Changes: TPS 1.0 to 2.0

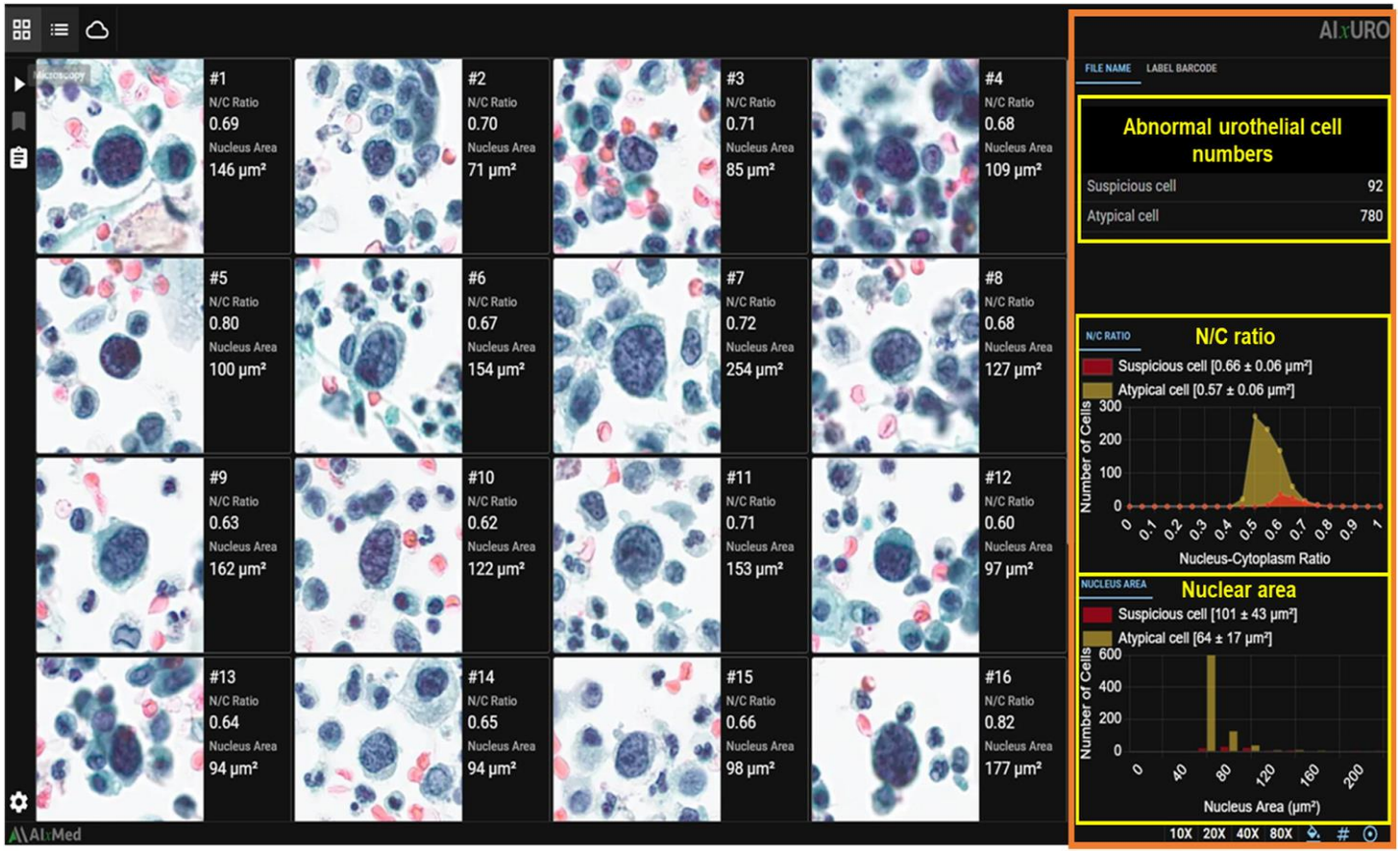
Revised criteria for AUC, SHGUC, HGUC

→ N:C

→ Number of diagnostic cells

AI redefines N:C thresholds for TPS categories?

- 106 urine cytology slides diagnosed as
- AUS (15.1%)
  SHGUC (23.6%)
  HGUC (61.3%)
- Biopsy-confirmed HGUC or CIS
- Digitized and analyzed by AIxURO
- The model quantified suspicious and atypical cells, N/C ratios, and nuclear areas



Conclusion: Lower N/C ratio cutoff (0.66) for SHGUC/HGUC may be more appropriate than the TPS threshold (>0.7)

Yang WL, Crothers BA, Liu TJ, Hsu SW, Yeh CH, Liu YS, Shao G, Lin MY, Tsao TY, Tung MC, Chu PY, Hang JF. Does artificial intelligence redefine nuclear-to-cytoplasmic ratio threshold for diagnosing high-grade urothelial carcinoma? Cancer Cytopathol. **2025** May;133(5):e70017. doi: 10.1002/cncy.70017. PMID: 40317981; PMCID: PMC12049170.

Conclusions

- Strategies to reduce AUS categorization include:
  - Recurring review of AUS rates
  - Departmental review of AUS cases
  - Implementation of focused education to improve the application of the TPS criteria
  - Recognition of benign pitfalls
  - Accurate N: C ratio estimation
  - Additional criteria as adjuncts to TPS (nuclear area)
  - Role for image analysis and AI; objective criteria
  - Reflex to ancillary testing; FISH, NGS (FPs and cost)

Conclusions

TPS 2.0 has set the bar high for standardized reporting systems

Provides a high PPV and achieves its aim of decreasing the AUS category with an increased ROHM and increased specificity of HGUC

AUS rates exceeding the TPS recommended threshold of 15% still exist

Conclusions

TPS has evolved from 1.0 to 2.0, refining diagnostic criteria and reinforcing focus on HGUC

TPS remains the universally acceptable standard of urinary cytology reporting

Continuous research and adaptation are crucial for improving urine cytology efficacy

Conclusions

Future studies are needed

Further define the utilization of image analysis/AI and molecular testing in urine cytology

Refine AI, and the molecular basis of **HGUC** and biomarkers for **AUS**

Stay tuned for **TPS 2.0+ and beyond**

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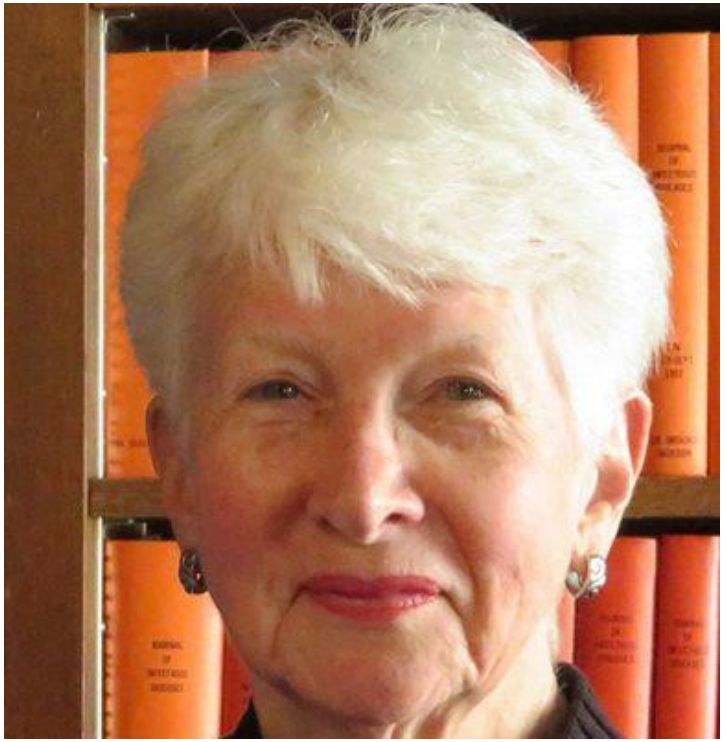
November 2022 ASC/ICC Baltimore, MD

Dedication

- Dorothy L. Rosenthal, M.D., Professor Emerita of Pathology and former Director of the Division of Cytopathology in the Johns Hopkins Department of Pathology
- Served as Director of Cytopathology and Director of the Cytopathology Fellowship program at the Johns Hopkins Hospital from 1995 to 2003



- Yale University School of Medicine
- New Haven, Connecticut

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Thank you
謝謝

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