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ThinPrep® imaging system-assisted vs manual screening of urinary cytology slides in the detection of the "suspicious for high-grade urothelial carcinoma" category

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Abstract

Background: The ThinPrep® Imaging System (TIS) is a Food and Drug Administration-approved review system for cervical cytopathology, where it has been shown to increase performance over manually reviewed slides. Application of the TIS to urinary cytology has only been reported in a single study, in 2013.

Methods: We aimed to compare the agreement of two cytotechnologists' and a pathologist's manual screening (dots) with the fields of view (FOVs) selected by the TIS. We also aimed to track cases in which the TIS could identify missed abnormals and reduce the false-negative fraction. Electronically marked TIS fields (EMTFs) suspicious for high-grade urothelial carcinoma (SHGUC) were controlled by follow-up cystoscopy and histology, where available.

Results: A total of 826 consecutive specimens were studied. Of those, 94 (11.4%) were unreadable by the TIS. There were 710 possible comparisons, of which 380 (53.5%) received no dot after manual screening. Of the 330 remaining slides, 149 (45.1%) had at least one dot matching with the TIS FOVs. After TIS reading, EMTFs were noted in 13 of 636 (2.0%) negative cytology cases. Surveillance showed that 3/13 (23.1%, 0.4% of the 710 possible comparisons) of those cases matched with high grade urothelial carcinoma (HGUC), whereas 6/13 (46.1%, 0.8% of the 710 possible comparisons) had negative follow-up at 24 months, and 4/13 (30.8%) were lost for follow-up.

Conclusion: The TIS increases the detection rate of SHGUC cells, potentially leading to a slight decrease in the false-negative fraction, but at the expense of a slight but larger increase in the number of false-positive cases. These findings stress the importance of a careful approach to the evaluation of the FOVs.

KEYWORDS
atypical urothelial cells, bladder, high-grade urothelial carcinoma, Paris system, Thinprep® imaging system, urinary cytology

1 | INTRODUCTION

The introduction of automated liquid-based cytology (LBC) systems to cervical cytopathology in the mid 1990s made the further development of computer-assisted screening a logical next step, since, basically, false-negative cases are caused either by human failure to identify rare abnormal cells or by misinterpretation of cellular atypias that are present in the sample. To counter this problem, automated Papanicolaou (Pap) test screening devices have been developed along two principles: (a) autonomous systems that do the job without the intervention of cytotechnologists, and (b) interactive location-guided screening systems that aid the cytotechnologist in reviewing a slide.[1–3] Imaging technologies have been widely used throughout the USA for primary screening in gynaecological cytology since the 2000s. No system is currently approved for use in non-gynaecological cytology.

The PAPNET® System (Neuromedical Systems Inc.) and the AutoPap 300 QC System (NeoPath, Inc.), both approved by the Food and Drug Administration (FDA), were the first devices intended for use in the quality control of manually screened cervical smears. Research in morpho-analysis of individual cells, aided by continuous technological progress, favoured the development of location-guided screening devices that present fields of view (FOVs) for a practitioner to use to make a decision. Nowadays, this principle is applied in the ThinPrep® Imaging System (TIS, Hologic Corporation), the FocalPoint GS Imaging System and the FocalPoint Slide Profiler (TriPath, BD Diagnostics), which were approved by the FDA in June 2003, March 2008 and August 2010, respectively. Since the TIS received FDA approval, it has become the most widely used imaging system in the USA for cervical cancer screening. In routine use, the TIS selects 22 FOVs for a cytotechnologist to review. In many published series, the TIS has been shown to increase the detection rate of high-grade squamous intraepithelial lesions (HSILs) and low-grade lesions (LSILs) compared to manually reviewed ThinPrep Pap test slides.[4–7] Additionally, TIS-assisted reading has been shown to improve cervical cancer screening productivity and therefore address workforce issues.[8]

Interestingly, the current version of the TIS and its dedicated staining protocol is based in part on nuclear DNA cytometry.[9] It uses a Feulgen-like stain which is stoichiometric for DNA; Feulgen staining remains the gold standard for precise DNA determination.[10] The stain, although different in its mode of action, is visually similar to the Papanicolaou stain.[11,12] However, it allows measurement of the integrated optical density (IOD) of the nucleus, which is essential to the imaging of the slide: the greater the DNA quantity, the greater the quantity of stain in each point of the nucleus.[12] The stain therefore has the ability to identify aneuploid cells, even if it does not take into account a known internal standard from the same sample for diploid value, as recommended.[13] Clinical application of DNA cytometry has not gained wide acceptance, but in the 2000s, DNA flow and static cytometry were often used to evaluate urinary cytology specimens in light of their improved sensitivity compared with voided urinary cytology.[14–18]

Apart from an abstract for the USCAP 101st Annual Meeting in 2012[19] and an original research article in 2013,[20,21] the application of TIS to urinary cytology has not been reported. Both texts reported a good correlation between conventional screening and the TIS, with an average reduction in screening time of 25%.[19,20]

The present study aims to compare the agreement of two cytotechnologists' and a pathologist's manual screening (dots) with the the FOVs selected by the TIS. We also aimed to track cases in which the TIS could identify missed abnormals and reduce the false-negative fraction, thus potentially providing improved patient care. Conversely, we aimed to verify whether improved abnormal cell detection could lead to overinterpretation of negative or equivocal cases (mainly atypical urothelial cells [AUC]) into "suspicious for high-grade urothelial carcinoma" (SHGUC) cells and, therefore, increase the false-positive fraction.

2 | PATIENTS AND METHODS

A total of 826 voided urine samples were collected over a 5-month period from 826 consecutive patients referred for cystoscopy at the two urology departments of the Centre Hospitalier Lyon Sud (Prof. A. Ruffion) and Hôpital Edouard Herriot (Prof. M. Colombel), Lyon, France. The study protocol received a priori approval by the review committee of the Hospices Civils de Lyon, and it followed the principles outlined in the Declaration of Helsinki. There were 169 female patients and 657 male patients (mean age, 68.88 ± 14 years). Patients underwent consultation for symptoms or were followed after complete transurethral resection (TUR), Bacillus Calmette-Guérin (BCG) immunotherapy or surgery for lesions involving the bladder or the upper urinary tract (UUT). We recorded prolonged follow-up data, including cyto-histological, cystoscopy and clinical findings (mean follow-up period: 2.5 years). TUR was performed for every case of papillary bladder lesion, whereas mucosal abnormalities suspicious for carcinoma in situ were sampled by biopsies. Some patients also underwent surgery for UUT tumours.

2.1 | Urinary cytology and histopathology

Voided urine specimens were fixed with 50% ethanol (Merck). The samples were sent to the laboratory within 12 hours, with clinical and cystoscopy data. After centrifugation (600 *g* for 10 minutes), the cell pellet was suspended in a 45 ml CytoLyt solution. After 30 minutes at room temperature, cells were centrifuged and resuspended in a PreservCyt solution before being treated with the ThinPrep 5000 processor loaded with non-gyn blue filters (Hologic Corp.). Slides were then stained with the ThinPrep Stain™ (proprietary stain) in accordance with the applicable TIS slide staining protocol. However, as in the study by Van Hemel et al,[20] because the TIS nuclear staining standardised for cervical specimens was too dark, the staining time was reduced from 6 to 4 minutes. Staining was performed using a Tech-Inter TST30

processor (Tech-Inter ZA). Finally, the slides were embedded in a permanent mounting medium under coverslips.

The cytological results were all classified according to the Paris System for Reporting Urinary Cytology (TPS) published in 2015 and revised in 2022.[22] According to TPS, normal, inflammatory, reactive, and degenerative conditions of the urothelial component were considered negative for high-grade urothelial carcinoma (NHGUC), as described by previous studies and actualised in TPS.[22,23] AUC were clearly separated from SHGUC cases. NHGUC and AUC cases were grouped together as negative results. Low-grade urothelial neoplasia (LGUN) cases were included in the NHGUC category, in accordance with TPS 2022.[22] Only specimens with obvious high-grade cancer cells and those in the SHGUC category were considered positive.

The grading and staging systems used for biopsies, TUR and surgical specimens were those of the 2016 World Health Organisation (WHO)[24] and the International Union Against Cancer TNM classifications. Histopathological data were separated into three groups: one positive for high-grade urothelial lesions (pTIS, papillary, and invasive), one gathering negative results (eg, cystitis), and another consistent with papillary urothelial neoplasm of low malignant potential (PUNLMP) and low-grade papillary carcinoma (pTa-1). As for TPS, the 2016 WHO classification, following the 2004 WHO/International Society of Urological Pathology consensus clearly defines a group of lesions (HGUC) with a high risk of progression that may be candidates for adjuvant therapy.

2.2 | Conventional and ThinPrep Imaging System screening protocol

The Centre de Pathologie Est is a tertiary care university hospital laboratory with a cytopathology unit that receives mainly non-gynaecological samples (about 10 000 per year). The cytopathology unit mostly uses the Hologic Thinprep 2000 and 5000 processors, cytocentrifugation, cell blocks, May-Grünwald-Giemsa and Papanicolaou stains combined, immunocytochemistry and molecular biology techniques. Due to a limited volume of samples received yearly, it is not equipped with the TIS, which was loaned by Hologic France for use in this study. As a consequence, the routine screening relies on conventional microscopic examination.

As recommended by Koss (2006),[25] we use ink dots to facilitate the examination and review of slides on multiple occasions or by several readers, including during continuous medical education, and not only to mark the more severe abnormalities. It is therefore possible that cases ultimately considered as NHGUC are marked with two or more dots. Conversely, in cases loaded with tumour cells, we usually do not add dots, thus avoiding (1) the selection of only a fraction of cells, and (2) overloading the slide with unnecessary marks.

Before conventional screening, all urinary cytology slides were scanned by the TIS. Rejected cases were re-screened two or three additional times by the TIS, if necessary, before being stored for further analysis and review.

Slides were then screened with 10× and 40× objectives by two experienced cytotechnologists, having achieved the International Academy of Cytology (IAC) comprehensive cytotechnology examination (KH and CN). The goal being to compare the respective performance of man and machine, the cytotechnologists did not refer to the TIS FOV review in their manual screening. Time spent analysing a given specimen was not recorded. In a second round of screening, the pathologist (EP) analysed the cases on his own microscope, added dots if necessary, and edited the diagnostic report according to TPS after having considered all available data. He then reviewed each of the FOVs at 10× and 40× magnification using the TIS review scope. FOVs matching with dots previously added by the readers were recorded for comparison.

Additionally, FOVs showing potential SHGUC cells at 400× magnification not previously identified by the readers were electronically marked (electronically-marked TIS fields, EMTFs). EMTFs were counted, recorded and subsequently compared with the follow-up information. All data were computerised in an Excel 2016 database.

2.3 | Prolonged follow-up data

All patients with cystoscopic abnormalities had histological controls after consultation, with a 0- to 6-month delay. All patients, whatever their cystoscopy findings, were then followed for 24 additional months (effective duration: 28-32 months). Cystoscopy and urinary cytology were performed according to the recommendations for follow-up of the European Association of Urology (http://www.uroweb.org). Progression was defined as recurrence at a higher stage or grade (TNM pTa-1 with a transition from G1/G2 to a higher grade, progression from pTa-1 to pT2 or higher, extension to the UUT, histologically documented metastases, or death from urothelial cancer). We identified clinical and follow-up data from the DIAMIC laboratory database (Infologic-Santé) and from the Easily Information System developed by the Hospices Civils de Lyon.

3 | RESULTS

The total number of slides consecutively processed was 826 (Figure 1). All were screened by two IAC-certified cytotechnologists (CN and KH) and reviewed by a pathologist (EP), all of whom are referred to here as "the readers". Of the 826 cases, we identified 37 (4.5%) unsatisfactory slides, containing no cell in 9 cases, fewer than 20 urothelial cells in 19 cases, and 9 cases in which the slide was loaded with a heavy bacterial, bloody or inflammatory background. Among those 37 unsatisfactory slides, 15 (45%) had error codes generated by the TIS. Accordingly, 22 cases were considered unsatisfactory by the readers, whereas the TIS selected 22 FOVs for review.

For comparison, the TIS image processor controller identified 162 (19.6%) slide events or system errors, 94 of which (11.4% of the

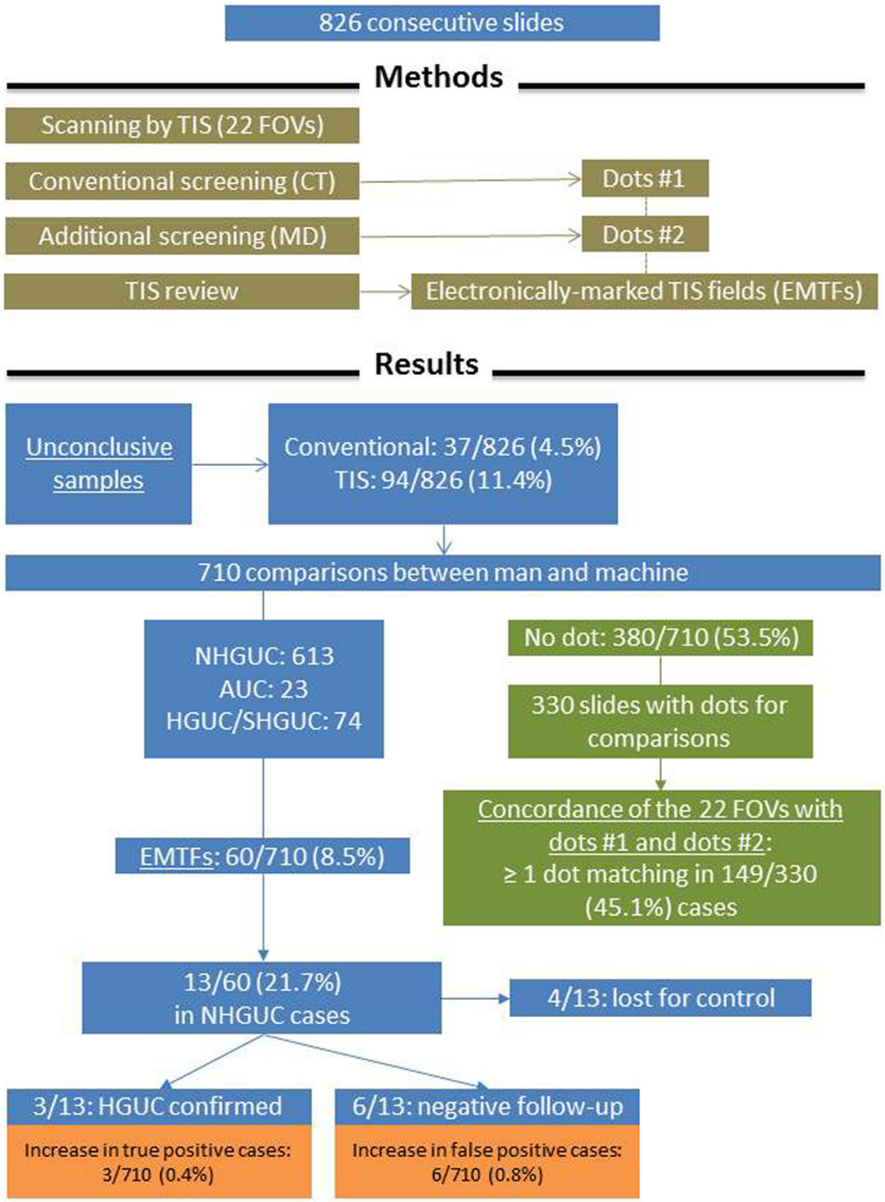

FIGURE 1 Flow chart summarising the methods and results of the study

whole series) were non-recoverable after remounting and reprocessing attempts. Among the reasons for rejection, 55 of 94 (58.5%) concerned a "biological event where the sample may contain abundant clumpy inflammation or bacteria", according to the manufacturer's datasheet (MDS). Practically, the slides may have shown bubbles under the coverslip, a heavy inflammatory background and/or necrosis, corpora amylacea of prostatic origin, an incorrectly placed coverslip, or mounting medium lying on the coverslip (Figure 2). In 16 of 94 cases (17%) the internal processor controller was "unable to process" the slides for unknown reasons, including problems with "slide preparation and quality" according to the MDS. Other errors accounted for the remaining 23 cases (24.5%). TIS alone and human screening alone being unconclusive in 94 and 22 cases, respectively, there remained 710 slides for comparison between man and machine.

The present study attempted to compare manual screening with the performance of the TIS. To reach this goal, we studied the correspondence between dots placed by the readers and the 22 FOVs selected by the TIS (Table 1). Of the 710 available slides, 380 (53.5%) received no dot after manual screening.

Accordingly, there remained 330 valid comparisons between manual screening and TIS. Of the 330 specimens, 149 (45.1%) had at least one dot matching with the TIS FOVs. Including the unmarked slides (n = 380), concordance between manual screening and the TIS was obtained in 529 of 710 (74.5%) cases. The Cohen Kappa coefficient was not considered, since the high proportion of cases without dots did not allow an inter-rater agreement calculation.

We also aimed at tracking those cases in which the TIS could identify missed abnormals and reduce the false-negative fraction, thus potentially providing improved patient care. Conversely, it was also necessary to verify whether increased abnormal cell detection by the TIS would lead to over-representation of the SHGUC category and therefore increase the false-positive fraction. To achieve

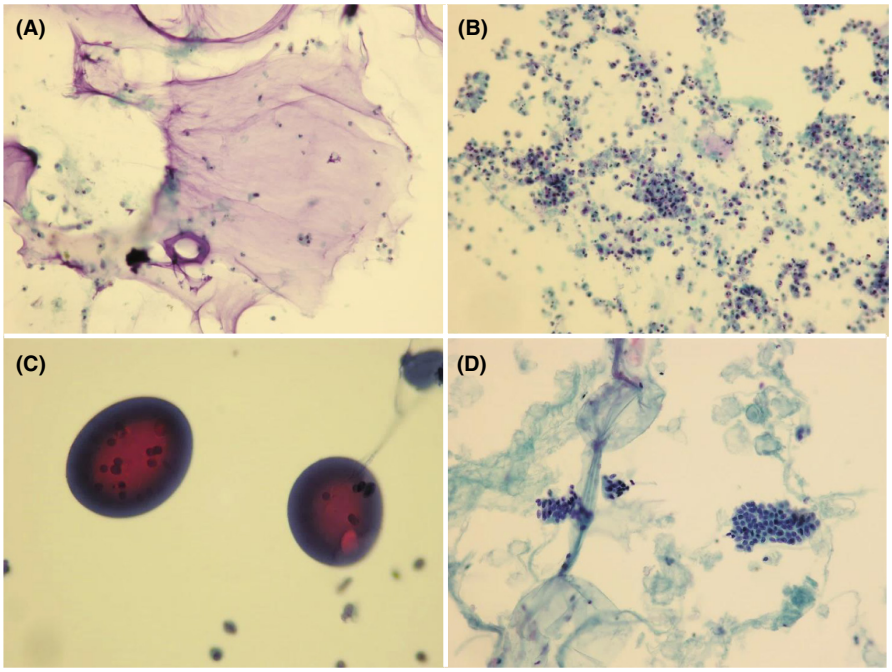

FIGURE 2 Specific and non-specific causes of rejection of urinary cytology slides by the ThinPrep Imaging System (TIS). (A) Cytology after cystectomy and ileocystoplasty. Dirty background with mucus (200×). (B) Cytology after cystectomy and ileocystoplasty. Huge inflammatory background (200×). (C) Numerous corpora amylacea of prostatic origin (400×). (D) Many pieces of debris between benign tissue fragments (200×)

TABLE 1 Correspondence between dots placed by the readers and the 22 fields of view (FOVs) selected by the ThinPrep Imaging System (TIS)

	Matching TIS FOVs					
	0	1	2	3	4	Total
Manual screening (number of dots)						
0	380	-	-	-	-	380
1	70	11	-	-	-	81
2	36	15	1	-	-	52
≥3	75	76	33	11	2	197
Total	561	102	34	11	2	710

Note: The orange shade indicates the high proportion of slides with no dots. The green shade indicates correspondence between dots and FOVs in cases where both are > 1.

this goal we verified, whenever possible, clinical surveillance and histology reports in cases where suspicious cells (ie, SHGUC cells) were marked electronically.

Among the 710 slides available for comparison between man and machine, there were 74 (10.1%) HGUC and SHGUC, 23 (3.1%) AUC, and 613 (86.3%) NHGUC diagnoses according to TPS (2015).[22]

After TIS reading, EMTFs (potentially SHGUC cells, depending on the pathologist's interpretation) were recorded in 13 of 636 (2.0%) NHGUC and AUC cases (some examples are shown in Figure 3). Clinical surveillance, including histology controls, showed that 3/13 (23%) of those cases matched with high-grade urothelial lesions, 6/13 (38.5%) had negative follow-up at 19 or 24 months and 4/13 (38.5%) were lost for follow-up (Figure 1, Table 2).

4 | DISCUSSION

As pointed out by Van Hemel et al[20] (2013) the introduction of standardisation through liquid-based cytology made the further development of automated screening a logical next step. Location-guided screening devices like the TIS and the FocalPoint GS Imaging System are now widely used in gynaecological cytology.

The advantages of TIS for cervical screening have been well described in published series: tested in different clinical settings, it has proven to be as efficient, if not better, at detecting cervical squamous intraepithelial lesions than manual screening.[1,5,8,12,26,27] Advantages were also noted in glandular lesions in some studies.[28]

Other known benefits of using TIS to read cervical specimens are the decreased screening time and increased productivity, though these factors were not always studied in detail.[29–31] Accordingly, the turnaround time—which is the time period from when a specimen is accessioned in the laboratory to the time at which the report is signed out—may be shortened, in order to improve the functionality of the overall service.[32,33]

Such improvements would prove useful when applied to non-gynaecological cytology and particularly to urinary cytology, because of its increasing volume in most laboratories. As stressed by Van Hemel et al[20] (2013) urinary cytology now represents a major workload in general cytology departments, owing to a decrease in gynaecological cytology following the guidelines edited by the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology in 2012.[34] At the University of Chicago, a trend towards reduction was noted by Antic, who reported a subsequent 25% increase in the number of urine samples submitted since 2008.[21] In Europe, guidelines for quality assurance in cervical cancer screening that recommend human papillomavirus (HPV) primary screening alone have had

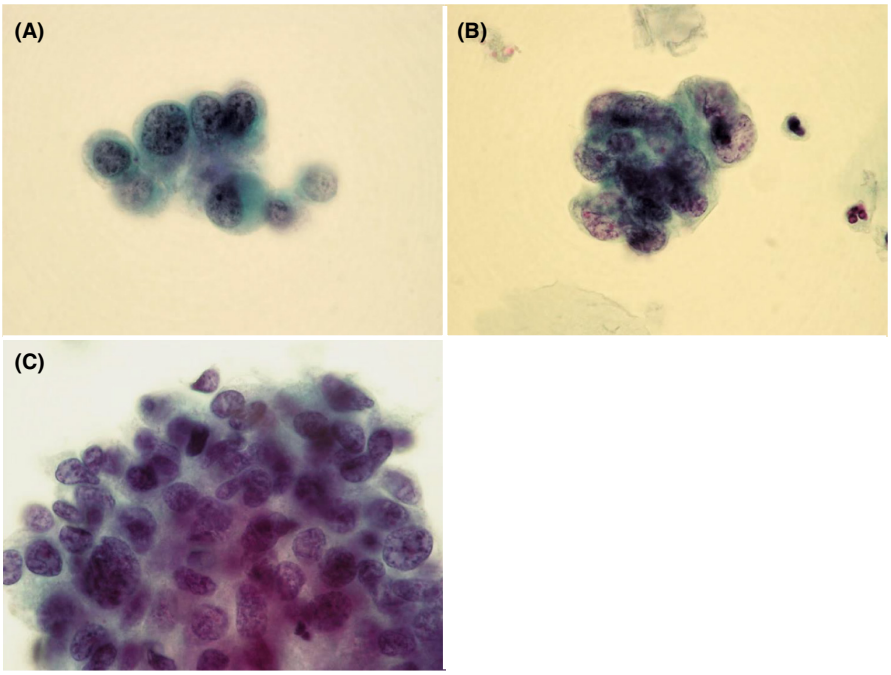

FIGURE 3 Urinary samples with electronically-marked ThinPrep Imaging System fields (EMTFs) suggesting high-grade urothelial carcinoma (HGUC). Comparison with the clinical outcome. (A) Patient treated for pTa HGUC, presenting with recurrence at cystoscopy. Urinary cytology showed low-grade urothelial neoplasia (LGUN). Bladder transurethral resection (TUR) was negative, showing cystitis. Clinical follow-up over a 2-year period was negative (Papanicolaou [Pap], 1000×). (B) Patient previously treated for pTa HGUC, presenting with inflammatory bladder at cystoscopy. Urinary cytology was suspicious for HGUC. Clinical follow-up over a 2-year period was negative or showed only atypical urothelial cells (Pap, 1000×). (C) Patient previously treated for pTa low-grade urothelial carcinoma, presenting with a lesion of the upper tract. Urinary cytology was consistent with LGUN. Bladder TUR 4 months later showed pTa HGUC (Pap, 1000×)

TABLE 2 Correspondence of urinary cytology with the final diagnosis according to the Paris System for Reporting Urinary Cytology (TPS) categories

	Final diagnosis, including prolonged follow-up data					
Cytology results	**HGUC**	**HGUC not confirmed**	**Negative findings**	**LGUN**	**lost for follow-up**	**Total (%)**
NHGUC	37[a] (6.0)	-	476[b] (77.7)	20 (3.3)	80[c] (13.0)	613 (86.3)
AUC	3[d] (13.0)	-	13[e] (56.5)	-	7 (30.4)	23 (3.2)
SHGUC	10 (47.6)	8 (38.1)	-	-	3 (14.3)	21 (2.9)
HGUC	38 (71.7)	10 (18.9)	-	-	5 (9.4)	53 (7.5)
Total	88 (12.4)	18 (2.5)	489 (68.9)	20 (2.8)	95 (13.4)	710 (100.0)

Note: Clinical findings in the 13 cases with EMTFs in AUC/NHGUC/LGUN results.

Abbreviations: AUC, atypical urothelial cells; EMTFs, electronically-marked TIS fields; HGUC, high-grade urothelial carcinoma; LGUN, low-grade urothelial neoplasm; NHGUC, negative for high-grade urothelial carcinoma; PUNLMP, papillary urothelial neoplasm of low malignant potential; SHGUC, suspicious for high-grade urothelial carcinoma.

[a]One case concerned a patient treated for a bladder PUNLMP presenting with negative cystoscopy. One EMTF was selected. Bladder TUR performed 12 months later showed a pT1a HGUC. Another case concerned a patient followed after resection of a pTa, LGUN of the upper tract. Two EMTFs were selected. Ureteral biopsies 1 month later showed PUNLMP, but bladder transurethral resection (TUR) 7 months later showed a pTa HGUC.

[b]Including 83 cases with negative histology (bladder TUR and/or biopsies) and 372 cases with negative cystoscopy and urinary cytology at annual surveillance. Three cases with EMTFs were selected. One case concerned a patient followed after pT1 HGUC, presenting with positive cystoscopy. One EMTF was selected. Bladder TUR was negative, and follow-up was unremarkable at 24 months. Another case concerned a patient followed after pTa, LGUN with negative cystoscopy. Three EMTFs were selected. Follow-up was unremarkable up to 24 months after the diagnosis.

[c]Including four cases with EMTFs.

[d]One case concerned a patient followed after pTa, HGUC treated by TUR and Bacillus Calmette-Guérin (BCG) immunotherapy. Three EMTFs were selected. Histology 1 month later showed a CIS.

[e]One case concerned a patient followed after pT1, HGUC treated by TUR and BCG immunotherapy. One EMTF was selected. Hexvix-aided biopsies were negative 4 months after. Clinical surveillance was negative up to 19 months.

the same impact. HPV-positive women with abnormal cytology are now referred to colposcopy, and retesting is organised after 1 year in HPV-positive women with negative cytology.[35] In Europe, implementation of the new standards has resulted in a sharp decline in the volume of gynaecological cytology. Accordingly, the non-gynaecological fraction, and particularly urinary cytology, has increased.

Concerning the performance comparisons, Bongiovanni et al[36] (2009) showed that the diagnostic concordance was not related to the number of dots per slide. In the present study, we tested the concordance between man and machine by comparing dots and the TIS FOVs: including the unmarked slides (mainly NHGUC cases), concordance between manual screening and the TIS was obtained for 74.5% of cases, and 45.2% of dotted cases had at least one dot matching with the FOVs. In the Ferraro et al series, concordant diagnoses were obtained in 78% (67 of 86 cases).[19] Such values indicate that man and machine share a common zone of confidence, despite the fact that each has its own logic.

Knowing that the main utility of urinary cytology is to track high-grade urothelial neoplasia, we aimed at verifying whether the TIS could identify missed abnormals and improve the pathologist's diagnostic capabilities. We also attempted to identify possible over-interpretation bias of negative or equivocal cases into the SHGUC category. According to TPS, the SHGUC category includes cases with severe urothelial atypia that fall quantitatively short of a definitive HGUC diagnosis. The major (required) criteria are the presence of non-superficial and non-degenerated urothelial cells with an N/C ratio greater than 0.7 and severe nuclear hyperchromasia. The minor criteria (one of which is required) include irregular nuclear membranes and dark, irregular, coarse chromatin.

Logically, the follow-up of cases diagnosed as SHGUC should reveal a higher rate of HGUC compared with that of AUC.[22,37] Accordingly, we studied immediate cyto-histological comparisons as well as prolonged follow-up data in cases with EMTFs.

It must be noted that with the TIS, SHGUC fields not previously retained by the pathologist were identified—by the same pathologist—in 13 (1.8%) cases (details in Table 2). According to available follow-up data, false-negative diagnoses might have been avoided in three cases (accounting for 0.4% of NHGUC cases). Conversely, six cases might have led to false-positive diagnoses (accounting for 0.8% of NHGUC cases). In spite of the low risk of potential false-positive reporting, such discrepancies raise the question of a possible "focusing effect" (focus bias) induced by the selection of FOVs. Intrinsically, the TIS selects (highlights) 22 FOVs for a reader to review. As stressed by Legrenzi et al[38] (1993) and by Cherubini et al[39] (2003), a focusing effect can occur when "before making a choice, individuals gather information about alternatives explicitly stated in the problem context and do not pay attention to other possibilities". Accordingly, though the reader must review the entire slide if any abnormalities are identified, he might be influenced by the FOVs that he would not necessarily have chosen if he had screened manually (potential risk of overinterpretation).

As reported by Dawson (2004) "A critical component of the TIS is the ThinPrep Pap Stain… developed to be 'near stoichiometric' to DNA content."[12] However, although the TIS uses DNA cytometry in addition to morphometric features, it does not provide usable information on the DNA profile of the FOVs. As a consequence, the pathologist's interpretation of the FOVs only relies on morphological features. However, it is known that DNA cytometry applied to urinary cytology allows a higher sensitivity in the detection of malignant cells than the Papanicolaou stain.[14,40–43] DNA cytometry, which is described as the "critical component of the TIS" could be used to display histograms which could aid the pathologist in reaching the correct diagnosis, provided a diploid internal cell population (eg, polymorphonuclear leukocytes) is taken as a reference.[42] We therefore suggest that, for an updated version devoted to non-gynaecological cytology, DNA cytometry should be better integrated into the process leading to FOV selection.

There is, however, an increasing interest in automation in non-gynaecological cytopathology which goes beyond the DNA issue. Vaickus et al[44] (2019) presented a deep-learning, morphometric model that aims at automating TPS with an algorithm similar to the FocalPoint GS Imaging System. In France, systems like the CytoProcessor™ (Datexim, Caen) or the VisioCyt® (VitaDX International, Rennes) tests[45] use virtual microscopy tools to detect, analyse, and classify cells in cervical and urinary cytology slides, respectively. There is no doubt that we are now in an era in which new tools are being built for the screening and analysis of LBC-processed non-gynaecological specimens (eg, urine) that will improve the pathologists' performance.[3]

Limitations of our study include a low number of specimens and high percentage of unreadable slides. In the study by Van Hemel et al[20] (2013), the main disadvantage of using TIS was the relatively high percentage (7.4%) of slides that could not be scanned. In cervical specimens, the rate of unreadable slides usually varies between 0.87% and 3.7%,[1,12] as a consequence of poor cellularity, excessive blood, or technical problems (eg, presence of bubbles under the coverslip). When using TIS, most of the technical pitfalls can be reduced by adequate handling of the material, such as lysis of bloody samples or cautiousness in the mounting of slides. However, the rate of unsatisfactory slides may reach higher values: in our series, in spite of reprocessing attempts, 11.4% of slides remained unreadable. After remounting and several reprocessing attempts, 75% of those cases remained unreadable.

In conclusion, our results do not show a real benefit of automation vs manual screening in the detection of the SHGUC category. However, applying the current version of the TIS to urinary cytology may provide some assistance, provided (1) particular attention is paid to the mounting of slides, and (2) reporting is based on a reasoned analysis of the FOVs, due to the risk of overinterpretation.

AUTHOR CONTRIBUTIONS

EP: Conceptualisation, data formatting, methodology, analysis and writing. JJP: Conceptualisation, data analysis, investigation, and methodology. CN: Screening, investigation, and methodology. KH:

Screening, investigation, and resources. MC: Patient data, methodology. AR: Patient data, methodology.

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None.

CONFLICT OF INTEREST

Eric Piaton is member of the Paris System for Reporting Urinary Cytology working group. Jean-Jacques Prat has acted as Cytology Application Specialist for Hologic France. He is now retired.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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