

# An International Telecytologic Quiz on Urinary Cytology Reveals Educational Deficits and Absence of a Commonly Used Classification System

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## Abstract

*Urinary cytology is limited by high interobserver variability in the evaluation of cells with little atypia. We set up an online quiz on urinary cytology and tested the performance of 246 international participants. The quiz consisted of still images of 42 urinary specimens with equivocal morphologic features and 10 control cases with an unequivocal cytologic diagnosis. The nature of the cells on the 292 quiz images had been verified by multitarget fluorescence in situ hybridization in addition to the information obtained by cystoscopy, clinical follow-up, and/or histologic examination.*

*The original quiz cases and the percentage of answers given by the participants can be viewed at: <http://kathrin.unibas.ch/urinzyto/>. High-grade cancers were diagnosed correctly in 76.0% and low-grade cancers in only 33.9%. Remarkably, 54.5% of all participants misclassified decoy cells as malignant. This study shows that large-scale international online quizzes may be used to find educational deficits in cytopathology.*

Urinary cytology is used routinely for the diagnosis and management of patients with urothelial carcinoma and its precursors. The diagnostic yield of urinary cytology in daily practice depends on the grade of the primary lesion and the type of specimen examined. Although diagnostic accuracy is very high for high-grade carcinoma and carcinoma in situ, cells of low-grade urothelial neoplasms often lack recognizable features, resulting in a low detection rate.<sup>1-5</sup> The frequently encountered diagnosis of nonconclusive atypia is another important problem of urinary cytology because it leaves patients and physicians in uncertainty and may result in unnecessary procedures.<sup>6</sup> In addition, there is a disturbingly high rate of false-positive results in cytologic samples of patients receiving intravesical therapy with cytotoxic agents or bacille Calmette-Guérin.<sup>7</sup>

Recently, substantial research efforts have been put into the development of noninvasive adjunctive tests that could improve the sensitivity and specificity of urinary cytology for low-grade tumors or clarify equivocal cytologic findings.<sup>1</sup> Among these, multitarget fluorescence in situ hybridization (FISH) has been shown to significantly improve the sensitivity for detection of urothelial carcinoma at a retained high specificity.<sup>8-14</sup>

The high interobserver variability in the evaluation of atypical urinary cytologic specimens as experienced in daily routine and the lack of a widely used consensus classification system for urinary cytology limit the value of urinary cytology. To quantify this problem, we tested the diagnostic performance of a large number of participants in urinary cytology in an international online quiz. The quiz consisted of 42 urinary specimens with equivocal cytologic features and 10 cases with an unequivocal cytologic diagnosis used as positive and negative control

cases. It is important to note that we verified the nature of the shown cells by FISH in addition to the information obtained by cystoscopy, follow-up, and/or histologic examination. To set the stage for a consensus classification system of urinary cytology, we also asked the participants to indicate their preferred classification as used in their daily practices.

## Materials and Methods

### Quiz Cases

The cytology specimens were from the Institute for Pathology, University Hospital Basel, Basel, Switzerland. The 52 quiz cases were obtained from July 2002 through November 2004 and included 40 bladder washings, 6 voided urine specimens, 4 renal pelvic washings, and 2 ureteral washings. The final diagnoses included benign/reactive changes (31), polyomavirus infection with decoy cells (2), moderate urothelial dysplasia (1), papillary neoplasm of low malignant potential (2), low-grade papillary carcinoma (9), and high-grade papillary carcinoma/carcinoma in situ (7). Samples were assigned to 3 unequivocal categories: (1) negative, benign; (2) reactive changes; and (3) severe atypia, positive, and two equivocal categories: (1) mild atypia, cannot exclude low-grade neoplasia; and (2) moderate atypia, "suspicious."

The quiz included 5 benign and 5 malignant control cases with an unequivocal cytologic diagnosis. The 5 positive control cases were all from high-grade bladder cancer or carcinoma in situ. In the remaining 42 cases, at least 2 of 3 experienced cytopathologists (P.D., G.F., and L.B.) considered the cytomorphologic findings as equivocal.

Benign diagnoses were confirmed by benign histologic findings, repeated unsuspecting urinary cytologic findings, normal cystoscopy or retrograde pyelography, an uneventful clinical course with follow-up ranging from 6 to 16 months (mean  $\pm$  SD, 10.8  $\pm$  4.0 months), and/or a clinical diagnosis that could explain the atypical cytologic features. A final diagnosis of carcinoma in situ or cancer was based on histologic and cystoscopic findings or unequivocal cytologic findings in subsequent specimens. Histologic follow-up was available for 20 of 42 equivocal cases and 7 of 10 unequivocal control cases.

All atypical cells from carcinoma cases showed chromosomal aberrations detectable by FISH except those in 3 cases of noninvasive papillary carcinomas that proved to be FISH-negative by cytology and histology (true-negatives). FISH results were normal in all reactive and benign lesions.

### Fluorescence In Situ Hybridization

All cell groups shown in the quiz had been analyzed by multitarget, multicolor FISH with the commercially available multitarget FISH probe LA Vysion (Abbott/Vysis, Downers

Grove, IL). FISH was performed as previously described.<sup>13</sup> Briefly, we used the multitarget FISH probe UroVysion (Abbott/Vysis), which includes probes for the centromeres of chromosomes 3, 7, and 17, and for the gene locus 9p21 labeled with different fluorescent dyes (blue, red, green, and gold). Whereas normal cells contain 2 copies of each DNA target, tumor cells may show a variable pattern of losses or gains of signals. Before hybridization, the Papanicolaou-stained atypical cell groups were photographed (AxioCam Color, Type 412-312, Carl Zeiss, Oberkochen, Germany), and the exact locations on the specimens were saved by using an automated stage (Type 00-24-473-0000, Carl Zeiss) on a Zeiss Axioplan 2 epifluorescence microscope (Zeiss, Jena, Germany) and relocalization software (Mark&Find Module, Carl Zeiss Vision, Halbermoos, Germany). After relocalization, the hybridized atypical cells were scored selectively at a magnification of  $\times$ 630 with a Zeiss Axioplan 2 fluorescence microscope (Zeiss). At least 25 target cells per lesion were analyzed.

The criteria for a positive FISH result were as follows: 4 of 25 screened cells or more with 2 or more gains of chromosome 3, 7, or 17 or loss of one or both copies of 9p21 (heterozygous or homozygous deletion) in 12 cells or more. The presence of rare tetrasomic cells without other chromosomal aberrations was considered normal.<sup>14</sup>

### Quiz

The online multiple choice questionnaire and an online registration form were constructed by FlexiForm (<http://flexiform.unibas.ch>). This questionnaire tool had been programmed at the information technology department of the University of Basel. In a first step, an invitation e-mail was sent to (cyto)pathologists worldwide. Online registration was possible during the following 6 weeks. All enrolled participants received an automatically generated e-mail with personalized URL access to the quiz. The quiz was subdivided into 5 sections with 5 cases each and an introductory section with questions about basic personal data (country, type of hospital, subspecialty training, and experience). The answers to each section could be saved separately. This enabled participants to interrupt the online test after any section and to use their personalized URL to complete the quiz at a later time.

Each of the 52 quiz cases comprised 4 to 7 images (total, 292), information on specimen type, and relevant clinical findings. Cystoscopic findings were not indicated to prevent bias. For each quiz case, participants had to choose from 1 of the following 5 answer categories: (1) negative, benign; (2) reactive changes; (3) mild atypia, cannot exclude low-grade neoplasia; (4) moderate atypia, suspicious; and (5) severe atypia, positive. The answer categories corresponded to the classification system that the majority of registered participants used in their own laboratories (Table 1). The cases were arranged in random order. Participants were not informed

about the existence of control and equivocal categories or about the number of benign and malignant cases.

Participants had 2 months to submit answers. After the deadline, the image gallery was no longer accessible online. Participants who had completed the quiz received an e-mail with an attached list of correct answers for comparison with their own answers and confirmation of quiz participation with 5 credit points (equivalent to 5 hours of continuing medical education activity) assigned by the Swiss Society of Cytology.

Submitted answers were exported into an Excel (Microsoft, Redmond, WA) file and were evaluated statistically anonymously by the computing center of the University of Basel.

### Determination of Correct Answers

The final quiz diagnoses were based on all available information (cytology, FISH, biopsy, cystoscopic findings, and clinical follow-up). In cytologic preparations of the urinary tract, there is a continuum of morphologic findings that may be classified correctly as normal, reactive changes, or mild atypia. In 15 cases with morphologically overlapping features, we therefore accepted more than 1 answer category as correct (<http://kathrin.unibas.ch/urinzyto/loesung/solution-final.html>).

### Data Analysis

Contingency table analysis was used to study frequency comparisons of nominal categorized variables.

## Results

### Participants

The quiz was completed by 246 of 399 individuals who had registered for participation. The 138 female and 108 male participants were from Switzerland (64), Germany (63), Italy (41), the United States (25), Austria (10), the Netherlands (6),

and Turkey (5). The remaining 32 were from 17 other countries. The participants included 99 surgical pathologists with experience in cytopathology, 58 cytotechnologists/cytotechnicians, 47 certified cytopathologists, 16 surgical pathologists without experience in cytopathology, 3 residents in training for cytopathology, 9 residents in training for surgical pathology, and 14 biologists. They practiced at teaching hospitals/universities (112), community hospitals (91), and private laboratories (43). A majority was experienced in cytopathology and had practiced for 6 to 15 years (30.1%) or more than 15 years (42.3%), 16.2% had up to 5 years of experience, and only 11.4% were novices with less than 1 year of experience in cytopathology or still in training. The average  $\pm$  SD number of urinary cytology specimens examined per week was estimated at  $20.7 \pm 39.5$  (range, 0-500 specimens).

For statistical analysis, experts ( $n = 119$ ) were defined as participants with more than 5 years of experience in cytology seeing more than 9 urinary cytology specimens per week on average (mean, 32.6 specimens per week; 60.5% with more than 15 years of experience). The remaining participants ( $n = 127$ ) with less experience were regarded as nonexperts (mean, 7.4 specimens per week; 74.8% with less than 15 years of experience) **Table 2**.

### Classification Systems

We asked the participants on registration whether they would support the introduction of the term atypical urothelial cells of undetermined significance (AUCUS). The meaning and use of AUCUS would be analogous to the category of atypical squamous cells of undetermined significance (ASCUS) as used in gynecologic cytology. Of the 399 persons who had registered for the quiz, 223 (55.9%) advocated the introduction of such a designation for equivocal urinary cytologic specimens.

Furthermore, we proposed 7 classification systems for urinary cytology and asked participants which of these corresponded or came closest to the system they used in their daily practice (Table 1). None of the suggested systems

**Table 1**  
Survey of Preferred Classification Systems Among Eight Given Classification Systems on Registration of 399 Participants

Classification System	Participants (%)
Negative, "suspicious," positive	9.0
Negative, inflamed, suspicious, malignant <sup>15</sup>	10.8
Negative; atypical, favor reactive; suspicious for high-grade urothelial carcinoma; positive <sup>16</sup>	10.8
Negative, suspicious for low-grade neoplasm, suspicious for high-grade neoplasm, positive <sup>2</sup>	8.3
Negative, mild atypia, moderate atypia, severe atypia	3.8
Negative, infectious agents, nonspecific inflammatory changes, atypical urothelial cells with comment describing differential diagnostic possibilities, low-grade urothelial carcinoma, high-grade urothelial carcinoma <sup>17</sup>	20.7
Negative, benign; reactive changes; mild atypia, cannot exclude low-grade neoplasia; moderate atypia, suspicious; severe atypia, positive*	27.8
I don't practice urinary cytopathology routinely.	8.8

\* These are the answer categories used in the quiz. They correspond to the classification system used at the Institute for Pathology, University Hospital Basel.

**Table 2**  
**Distribution of Answers Stratified by Diagnostic Categories and Experience of the 246 Participants\***

Diagnostic Category	No. of Cases	Percentage of Answers in Each Category for Experts (Nonexperts)				
		Negative, Benign	Reactive Changes	Mild Atypia, Cannot Exclude Low-Grade Neoplasia	Moderate Atypia, "Suspicious"	Severe Atypia, Positive
Control cases						
Benign	5	21.5 (22.2)	32.3 (32.6)	27.7 (30.1)	15.1 (12.8)	3.4 (2.3)
Malignant	5	0.0 (0.0)	3.9 (4.6)	2.2 (2.3)	15.3 (17.1)	78.6 (76.0)
Benign cases <sup>†</sup>	31	11.1 (11.4)	32.1 (32.6)	25.6 (26.5)	20.2 (19.7)	11.0 (9.8)
Low-grade carcinomas, dysplasia	11	10.5 (9.5)	29.9 (29.1)	31.4 (36.2)	20.0 (18.7)	8.2 (6.5)
High-grade carcinomas, in situ carcinomas	8	1.2 (1.1)	13.8 (18.1)	7.2 (7.7)	21.3 (21.7)	56.5 (51.5)
Decoy cells, benign	2	6.7 (4.3)	42.0 (33.5)	5.0 (8.3)	14.3 (16.5)	31.9 (37.4)

\* Experts were defined as participants with more than 5 years of experience in cytology seeing 10 or more urinary cytology specimens per week. These criteria were met by 119 participants. The remaining 127 with less experience were regarded as nonexperts. There was no statistically significant difference between the results of experts and those of nonexperts.

<sup>†</sup> The 2 cases with decoy cells are not included.

clearly predominated, and 22 additional classification systems were specified by participants, including the Bergkvist (2 mentions), WHO (2 mentions), European Organization for Research and Treatment of Cancer (1 mention), and Papanicolaou (1 mention) systems, the Düsseldorf Classes<sup>18</sup> (1 mention), and other less well-defined or unpublished systems (17 mentions). The classification system used in our laboratory (Institute for Pathology, University Hospital Basel) received the highest percentage of votes (27.8%). Our preferred classification system remained at its top position even after subtraction of the 10 votes from our staff.

We consider the following morphologic features to define the 5 categories of this classification system (Table 1): (1) negative: unremarkable urothelial cells; (2) reactive changes: heterogeneous population of activated urothelial cells; typically a high proportion of large and multinucleated umbrella cells with variably sized, round, and often large nuclei; cytoplasm abundant and often finely vacuolated; (3) mild atypia, cannot exclude low-grade neoplasia: key feature, relative homogeneity with rather uniform cells that do not show apparent nuclear abnormalities such as coarse and dark chromatin, thickened nuclear membrane, or irregular nuclear outline; however, nuclear/cytoplasmic (N/C) ratio can be slightly increased and nuclear grooves occasionally present; (4) moderate atypia, suspicious: increased N/C ratio, dark and irregular chromatin, and subtle yet clearly recognizable irregularities of the nuclear membrane; nuclear grooves may be present; and (5) severe atypia, positive: strikingly atypical, polymorphic, hyperchromatic and enlarged nuclei with coarse chromatin; high N/C ratio.

### Staining Technique Used by Participants

Participants were asked which staining they preferred for urinary cytology: Papanicolaou, May-Grünwald-Giemsa, H&E, or others. A majority, 84.6%, routinely applies

Papanicolaou staining. Among the 24 participants who indicated that they prefer H&E staining, 17 were from Germany (27% of the German participants). May-Grünwald-Giemsa is used by 5 Austrians, 5 Germans, and 4 Italians representing 50%, 8%, and 10% of the participants of these countries, respectively. A combination of Papanicolaou and May-Grünwald-Giemsa, Giemsa, Feulgen, or H&E is applied in 7 laboratories.

### Quiz Results

The original quiz cases and the percentage of answers given by the participants can be viewed at <http://kathrin.unibas.ch/urinzyto/loesung/solution-final.html>. The percentage of correct answers among the total of 12,792 answers given for the 52 cases ranged from 8.5% to 93.1%. When the results were analyzed by diagnostic categories (Table 2), the best concordance was found for high-grade malignant tumors, whereas the correct distinction of reactive lesions and low-grade tumors turned out to be most difficult. It is interesting that the percentage of false-positive answers (suspicious or positive) in the 5 negative control cases was significantly higher than the percentage of false-negative answers (negative, reactive, or mild atypia) in the 5 positive control cases, respectively (18.5% vs 6.1% for experts and 15.1% vs 6.9% for nonexperts;  $P < .05$  for both). Most participants rated the image quality as excellent (49.6%) or good (42.3%), a minority of 7.7% as moderate, and only 1 participant indicated poor quality.

### Results for Selected Cases

#### Case 6

Almost half of the participants (48.4%) misdiagnosed this invasive high-grade papillary urothelial carcinoma as a reactive lesion **Image 1**.

### Case 33

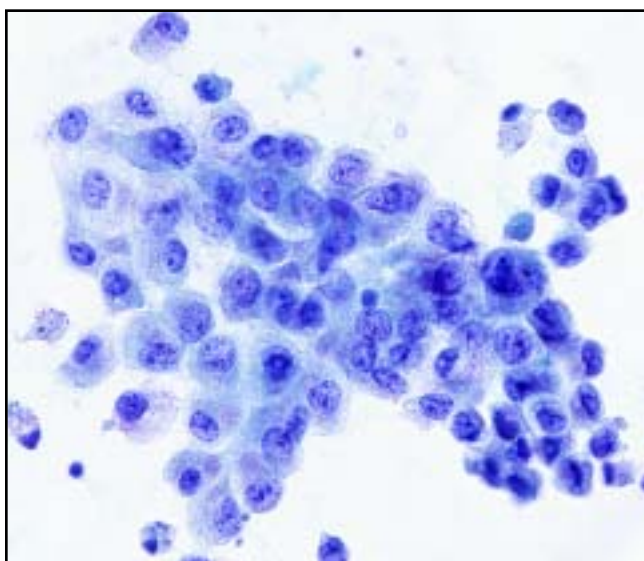
This voided urine sample of a 63-year-old kidney transplant recipient contained numerous decoy cells (354/10 high-power fields), and the allograft biopsy confirmed polyomavirus-associated nephropathy. Almost all cells of this case shown in the quiz images were decoy cells with readily identifiable cytopathic effects **Image 2**. Nevertheless, 117 of 246 participants misclassified the case as “severe atypia, positive” and another 17 as “moderate atypia, suspicious.” Thus 54.5% of the participants made a false-positive diagnosis because they probably were unfamiliar with the morphologic features of polyomavirus-infected urothelial cells (decoy cells). The performance of the participants in this case was equally poor in all participant subgroups, independent of laboratory type (private, community hospital, or university hospital) and profession (cytologist, cytotechnician, or surgical pathologist). Only participants with more than 15 years of experience achieved a significantly better result compared with participants with less than 1 year or no experience (48.1% vs 75.0% wrong answers;  $P = .003$ ).

### Case 41

In this bladder washing from a 55-year-old woman with chronic microhematuria, the occurrence of basal cells **Image 3** misled a majority of participants to make a diagnosis of mild (26.0%), moderate (25.6%), or severe atypia (27.6%) instead of negative, benign (8.9%).

### Case 50

This follow-up cystoscopy after treatment for a noninvasive, low-grade papillary urothelial carcinoma (pTa) contained



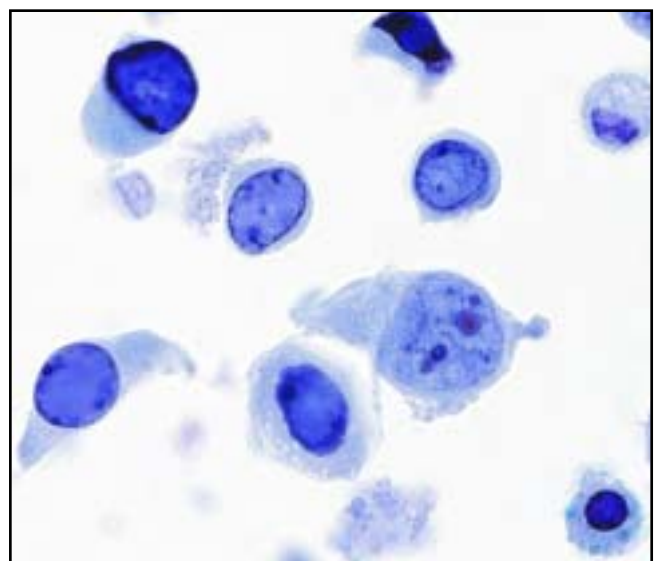
**Image 1** (Case 6) Cellular atypia in this invasive high-grade papillary urothelial carcinoma was misdiagnosed as reactive by 48.4% of the quiz participants.

tumor cells with moderate atypia **Image 4** that were identified correctly by only 8.5% of the participants. In this rare example of a cytologically and histologically FISH-negative tumor, the incorrect diagnosis of benign or reactive changes given by 64.4% of the participants could not have been prevented by FISH.

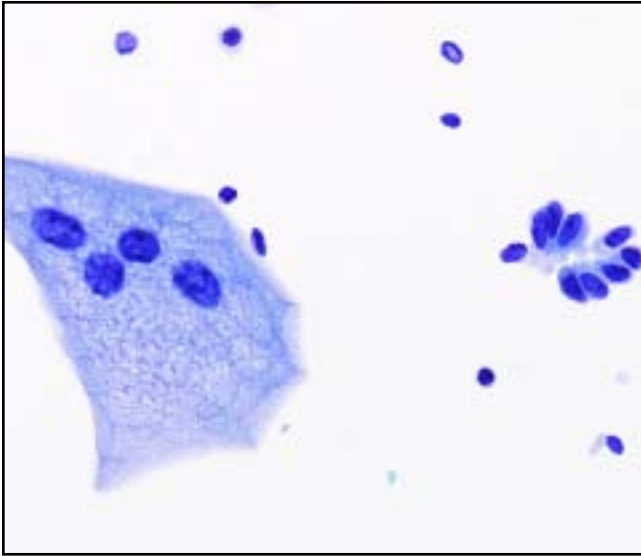
## Discussion

In this large-scale, Web-based online quiz, we found considerable interobserver variability in the interpretation of urinary cytology based on a selected series of 292 images from 52 mostly difficult cases. The rate of misjudgments was expectedly high in the selected group of difficult cases with equivocal cytologic features. In addition, the high rate of up to 18.5% false-positive answers as opposed to the 6.1% false-negative answers in the control cases suggests that overinterpretation of reactive changes is a particular concern in urinary cytology. Notably, the percentage of correct answers was largely independent of the experience of the participants. Therefore, the lower performance cannot be attributed to the fact that many noncytologists participated in this study. On the contrary, this reflects the limitations of cytomorphologic diagnosis in certain low-grade diagnostic categories that cannot be overcome by increased experience of the diagnostician.

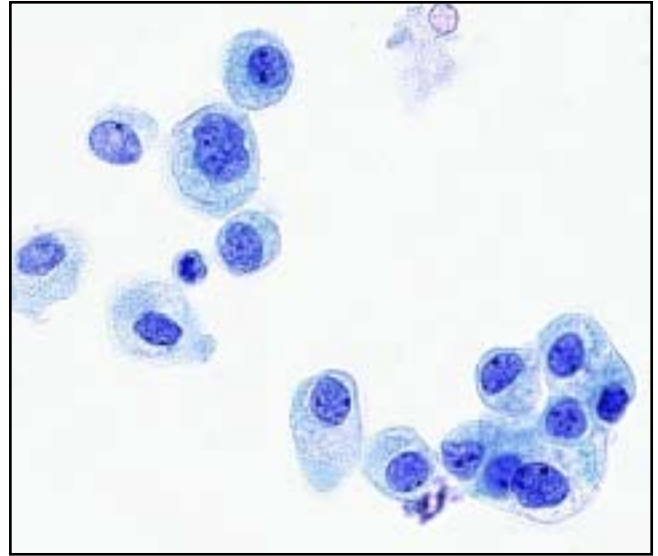
Making a diagnosis by viewing static images is not equivalent to making a diagnosis on a real slide. Accordingly, the concordance between a telecytologic diagnosis and a diagnosis made from the corresponding glass slide has been shown to be imperfect and somewhat lower than the levels reported



**Image 2** (Case 33) Decoy cells with clearly visible ground-glass nuclear inclusion bodies.



**Image 3** (Case 41) Basal cells (cell group on the right) in this bladder washing from a patient with chronic microhematuria misled almost 80% of the participants to make a diagnosis of mild, moderate, or even severe atypia.



**Image 4** (Case 50) Despite the presence of moderately atypical cells, this cytologically and histologically fluorescence in situ hybridization–negative noninvasive low-grade papillary urothelial carcinoma was diagnosed as a benign or reactive lesion by 64% of the participants.

for surgical telepathology.<sup>19</sup> Inappropriate selection of fields producing sampling bias and insufficient image quality are among the major problems associated with telecytologic diagnoses.

The adverse influence of these 2 factors was minimized in our online test. On the one hand, the image quality of the quiz cases was rated as good or excellent by a majority of the participants (92%) and is not likely to have influenced performance. On the other hand, by using technology of automated relocation, we knew exactly whether the cell groups depicted on the static quiz images were positive or negative by FISH and, therefore, most likely represented true tumor cells or benign cells, respectively. With the exception of 3 FISH-negative and biopsy-confirmed low-grade urothelial tumors, all malignant quiz cases had a positive FISH result and all benign or reactive cases were FISH-negative. Thus, we could ascertain with unprecedented precision that quiz diagnoses were based on representative cell groups that were not diluted by reactive bystander cells.

The major strength of urinary cytology lies in the diagnosis and monitoring of high-grade tumors such as carcinoma in situ and occult invasive cancers that are not identifiable on cystoscopic examination. The results of our online test, when stratified by diagnostic groups (Table 2), were remarkably similar to the results of other published studies on conventional cytologic preparations<sup>2,16,20,21</sup> in that high-grade cancers were diagnosed correctly by more than 75% of the quiz participants. Conversely, the distribution of answers for low-grade papillary tumors was similar to those for reactive or

benign lesions (Table 2). This reflects the well-known difficulties in differentiating these 2 diagnostic categories from one another by cytomorphologic features alone.<sup>1,2,16,21,22</sup>

Compared with other studies on conventional cytologic preparations, the overall performance of our quiz participants was lower. On the one hand, this difference may be explained by the quiz format. On the other hand, we included a high percentage of equivocal cytologic cases (81%) in our quiz. In daily diagnostics, the frequency of equivocal cytologic samples may vary between laboratories but probably does not exceed 20%. Because the quiz consisted of a nonrandom selection of equivocal and unequivocal cases, general conclusions on the interobserver variability in daily routine urinary cytology cannot be drawn from the results of our study.

In addition to FISH, many noninvasive adjunctive tests have been developed for the detection of low-grade urothelial carcinomas and may supplement classic urinary cytology for solving these diagnostically problematic cases in the future.<sup>1</sup> It is important to note that cytology-based supplementary methods not only can improve diagnostic precision but also may have an educational effect on the cytopathologist by allowing more precise distinction of tumor cells from reactively altered bystander cells. In our experience, the targeted FISH analysis of atypical urothelial cells on the Papanicolaou-stained slides sensitizes the reader to subtle cytomorphologic changes that otherwise may be overlooked.

We found the inability of a majority of quiz participants to recognize decoy cells. Remarkably, this inability was evident

irrespective of profession, experience, or type of institution. Because there is an increasing number of renal transplant recipients who are screened regularly for polyomavirus-associated nephropathy,<sup>23</sup> any professional engaged in urinary cytology should be familiar with the characteristic appearance of decoy cells. We prepared 5 virtual slides containing decoy cells as an educational tool to increase awareness and improve recognition of decoy cells. These slides are freely accessible on the Internet (<http://vmic.unibas.ch/patho/seminar/2005-09-03/index.html>).

There is no universally accepted nomenclature in urinary cytology, although several classification systems have been described.<sup>2,15-17,20,24,25</sup> The introduction of a uniformly applied classification system would be helpful in consultation<sup>3</sup> and allow better comparison of study results. Among 7 classification systems proposed to the participants in our study, none was chosen by a majority. The approval for each system was generally low, ranging from 3.8% to 27.8%, and 22 indicated an additional system. This high variability illustrates the need for a widely accepted international consensus classification system in urinary cytology.

The diagnostic category of ASCUS in cervical cytology successfully stratifies patients at risk for a significant underlying lesion and helps in patient management.<sup>26</sup> More than half of the 399 who responded to our survey (55.9%) would support introduction of the term AUCUS with a meaning and usage similar to ASCUS in gynecologic cytology but applicable to atypical urinary cytology.<sup>27</sup> Further studies are needed to determine the prevalence and clinical significance of AUCUS. This survey also illustrates that online questionnaires may be used not only for educational purposes but also for the harmonization of nomenclatures by asking for preferences.

The ability of Web-based tutorials to improve the diagnostic skills of practicing pathologists was demonstrated in an international study on Gleason grading.<sup>28</sup> Similarly, an online tutorial is available to practice the Bethesda classification in gynecologic cytology (<http://www.cytopathology.org/NIH/review.php>).

This type of easily accessible online education with the possibility of earning continuing education credit meets a need of the target group. Of the 399 individuals who enrolled, 61.7% completed the whole quiz consisting of 69 questions with 292 images. It is important to note that 95.1% of participants responded that they would appreciate similar cytopathology courses on the Internet on a regular basis. This high percentage of positive answers was comparable to the responses to a previous quiz on lung cytology (97%, unpublished data, May 2004) and reflects the high acceptance of online continuing medical education.

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