Daily Biopsy Diagnosis in Surgical Pathology

Concordance Between Light Microscopy and Whole-Slide Imaging in Real-Life Conditions

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ABSTRACT

Objectives: *The current challenge for the various digital whole-slide imaging (WSI) systems is to be definitively validated for diagnostic purposes. We designed a concordance study between glass slide and digital slide diagnosis in real-life conditions, coupled with an ergonomic study.*

Methods: *Three senior pathologists evaluated, first in glass slides and then in digital slides, 119 biopsy cases, including 749 slides, with 332 H&E saffron stains and 417 additional techniques, mainly immunohistochemistry.*

Results: *All digital slides, including specially stained slides, were interpretable. Concordance between glass slides and digital slides was observed in 87.4% of cases. Minor discordances were observed in 12 (10.1%) cases and major discordances, with therapeutic impact, in three (2.5%), including one related to WSI. The satisfaction of participants was high and increased with time.*

Conclusions: *Our study confirms the feasibility and accuracy of WSI diagnosis, even for cases having multiple samples and requiring special staining techniques, such as immunohistochemistry and in situ hybridization.*

Digital whole-slide high-resolution imaging is a rapidly expanding technology forming the core of digital pathology.[1-3] Its principle is to scan conventional histologic glass slides at resolutions up to ×40 to produce digital images that can be examined on a computer screen through adequately designed viewers. The technology of digital whole-slide images (WSIs) has several advantages over conventional microscopy. It enhances portability, improves the sharing and retrieval of archival images, and is well adapted to the use of computer-aided diagnostic tools. WSI has been successfully used in various fields related to pathology such as education, training, research, quality assurance, teleconsultation, and image analysis. The challenge is now to definitively validate its use for diagnostic purposes and to implement this technology in the laboratory workflow.[4,5] An important step in this direction has been achieved with the recent agreement given to the use of one specific digital pathology system in routine pathologic diagnosis.[6] However, additional studies remain necessary to validate digital imaging technology with other systems in real-life conditions. For a new technology or a new instrumentation, validation refers to a process aiming to demonstrate that the new method performs as expected for its intended use and environment prior to its application for patient care. With regard to WSI, validation must determine whether a pathologist can use this technology to achieve an accurate diagnosis with the same or even a better level of ease than with a

conventional microscope, without interfering artifacts or technological risks for patient safety.

We therefore aimed to evaluate the diagnostic use of WSI technology in real-life conditions, following the guidelines proposed by the College of American Pathologists.[7] The primary objective of our study was to evaluate intraobserver concordance between diagnoses made from either glass or digital slides. Our secondary objectives were (1) to identify the main causes explaining the potential discrepancies between glass and digital slides and to propose curative actions and (2) to evaluate the satisfaction of pathologists about the workflow proposed. The latter point is particularly important. Viewer ergonomics is directly involved in image interpretation and diagnosis quality, whereas the various tools and software designed for digital pathology must ensure the safety of diagnosis.[8]

For these purposes, we designed a study coupling a diagnostic concordance study and an ergonomic study. In conceiving the protocol, we paid particular attention to reproduce the real-life conditions of routine pathologic diagnosis. The study set was made of cases initially signed out from glass slides by the participants. The conditions in which digital slides were examined were as similar as possible to real-life conditions of routine diagnosis. The design of our study is therefore well adapted to evaluate the capacity for a digital pathology system to provide pathologists with images suitable for diagnostic purposes and to evaluate their adhesion to this new modality of tissue examination, analysis, and interpretation.

Materials and Methods

Description of the Environment

The medical staff of the Department of Pathology at the Gustave Roussy Cancer Campus is composed of 17 senior pathologists and a variable number of residents and trainees. Senior pathologists are referent for one of the 14 organ boards of the institution and usually contribute to the activity of one or two more other boards; two senior pathologists are specialized in cytopathology. The activity associated with each tumor board is not organ specific and includes all the samples taken during patient management. This explains the composition of our study sets, made of a large spectrum of lesions, neoplastic and nonneoplastic, from a variety of anatomical sites.

Overall Study Design

The study was coordinated by a principal investigator (I.V.), in charge of the selection of cases, digitalization of slides, and collection of results. Three senior pathologists (J.B., M.-C.M., and P.D.) participated in the study. They were referents for three different organ boards, respectively: hematopathology (A), breast pathology (B), and gastrointestinal pathology (C). They first received training to the digital pathology system before working with their own study set.

Both training and study sets were constructed in the same way. To avoid any allocation bias, cases included in the study were consecutive biopsy cases signed out by the three pathologists during their routine duty, over a 4-month period (July 2015 for the training set, July-October 2015 for the study set). Each case could include one or several tissue samples (obtained through endoscopic or radiologic procedures). For each tissue sample, at least one glass slide was prepared and stained with H&E saffron (HES); this staining is routinely performed in our laboratory, as often done in France, and has the advantage over the conventional H&E stain to highlight connective, fibrous, and stromal tissues. Additional stains and immunohistochemical techniques were performed as required for diagnostic purposes; all techniques were performed according to the standard procedures of the department.

After the initial diagnostic step, whole-tissue sections of the cases included in the study were scanned with a NanoZoomer HT C9600 (Hamamatsu Photonics KK, Hamamatsu, Japan) digital scanner, using a ×40 objective. Scanned slides were uploaded on the CaloPix database (Tribvn Healthcare, Chatillon, France). They were viewed on a DICOM, diagnostic-grade, color-calibrated monitor (24-inch, 4-megapixel Eonis MDRC-2224 flat screen; Barco, Duluth, GA) equipped with a joystick (Xbox 360; Microsoft, Redmond, WA). All cases included in the study set were anonymized and assigned with a study case number, which was used to identify all the slides available in each case. In addition, for each case, the number of slides, their nature, and all the information available to the pathologist at the diagnostic step (such as the clinical data available in the Gustave Roussy medical database and any additional comment or information related to the case) were recorded in a specific anonymized patient file identified by the study case number.

After a washout period of at least 1 month, pathologists were given access to the digital slides associated with the corresponding anonymized patient file to ensure that all the relevant information for the interpretation of the case was provided and was identical to the information available at the diagnostic step. When performing the analysis of digital slides, pathologists were blinded to the initial diagnosis made on glass slides.

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Training Set

The aim of the training set was to make pathologists familiar with the technology and the software used in the study to avoid any learning curve bias during the analysis of the study set. The training set was made of 17 cases signed out by the three pathologists during their routine duty in their respective organ board. The 17 cases included a total of 34 different tissue samples (range, 1-6 per case; median, 2); 59 slides were prepared and digitalized (range, 1-7 per case; median, 1). Washout period was 4.2 to 4.4 months. Through the training set, pathologists got accustomed to the viewer, study workflow, access to patient files, and use of the Xbox joystick.

Study Set

The main objective of the study set was to compare the initial diagnosis made on conventional glass slides and the second diagnosis made on the corresponding WSI. According to the literature,[7] the expected concordance rate between diagnoses was about 83%. We first evaluated the number of cases required to accurately estimate the concordance rate in our study. We calculated that, with a sample size of 120 cases, the size of the 95% confidence interval (CI) of the concordance rate would be equal to or less than ±7.5% for a concordance rate of at least 83%. A lower bound of the CI higher than 90% would be considered acceptable for a daily use of the technology.

In total, 120 consecutive biopsy cases were extracted from the cases signed out by each participant over a 4-month period (July-October 2015). Forty cases were submitted to each pathologist. One case had to be discarded because of an anonymization default. A total of 119 cases were finally retained in the study set.

Pathologists were asked to provide a description of the lesions found in each sample and to propose a final diagnosis for each case. The diagnosis provided at the sample level was mainly descriptive. The diagnosis provided at the case level was integrative and corresponded to the final diagnosis made after examination of all samples and evaluation of the available clinical data. The conclusions were provided as a four-character code, extracted from the ADICAP scoring system (http://www.adicap.asso.fr) familiar to all French pathologists and used on a daily basis in all French laboratories. This code is a unique and precise descriptor of the type of lesion identified by the pathologist and/or of the final diagnosis proposed. The ADICAP codes were collected for each sample and, after examination of all samples, for each case. All data were collected in a specific database developed using the MACRO system (InferMed, London, UK).

Concordance Study

To evaluate the overall concordance rate between the two examinations, we compared the ADICAP codes provided by each pathologist after interpretation of, respectively, glass and digital slides. The comparison was performed at two levels: for each sample and for each case. The result of the comparison was expressed on a 4-point scale: full concordance, concordance, minor discordance, and major discordance.

Full concordance was defined by the exact matching between the ADICAP codes provided for glass and digital slides from the same case. All other cases were individually reviewed by the three participating pathologists in a joint meeting. The diagnosis was declared "concordant" when the difference between ADICAP codes was not medically significant (as in the case of slightly different codes expressing only variants of the same lesion). All other cases were classified as "discordant"; the causes of the discrepancy were analyzed and the possible medical consequences evaluated. Discordances were considered minor in the absence of therapeutic or clinical impact. Other discordances were classified as major.

WSIs of discordant cases were reviewed and discussed by all pathologists to achieve a final diagnosis; if necessary, it was agreed between participants that an external review could be performed by another expert pathologist.

Ergonomic Study

In parallel to the concordance study, we performed an evaluation of the digital pathology system ergonomics. Eleven functionalities, in three categories, were evaluated.

Five functions were related to CaloPix database used in the study (interface look and feel, find, open and close patient's files, and open the related slide tray), since the display of database information, such as patient identification and clinical information, is a crucial point for daily use. Five items aimed at evaluating the viewer ergonomics (open a slide, open several slides, move into a slide, zoom into a slide, and locate the area examined into a topographic view of the whole slide). One item evaluated the ergonomics of the navigation into slides through a joystick.

For each of these functionalities, the three participating pathologists were asked to give a mark between 0 and 3 (from not satisfied to very satisfied). To monitor its evolution over time, satisfaction was evaluated at the end of two periods: the first 10 cases per pathologist and the following ones. Ninety-two questionnaires were available for analysis.

Results

Characteristics of the Study Set

In total, 119 cases included in the study Table 1 were from 76 male and 43 female patients, with a mean age of 59.6 years (range, 20-88 years). The 119 cases were made up of 237 samples (mean, two samples per case; range, 1-11). A total of 749 slides were examined; the mean number of slides per case was 6.3 (range, 1-39); the mean number of slides per sample was 3.1. In total, 332 (44.3%) slides were stained with HES, 22 (2.9%) slides were stained with special techniques (including periodic acid–Schiff, Alcian blue, Giemsa, Grocott, and Ziehl), 390 (52.1%) slides were from immunohistochemical techniques (with 84 different antibodies), and five (0.7%) slides were from in situ hybridization techniques (Epstein-Barr encoding region, human papillomavirus type 16). The distribution of cases and samples and the washout period between the examination of glass slide and digital slide for each participant are given in Table 1. The site of origin of the 237 samples included in the study is given in Table 2. The most frequent sites of origin were the breast and the digestive tract. The initial diagnoses, made from glass slides during patient care, are given in Table 3. Benign or malignant tumors were diagnosed in 67.9% of samples. Nonneoplastic lesions were present in 18.1% of samples.

Diagnostic Concordance Between Glass and Digital Slides

All digital slides were found to be interpretable, including those corresponding to special stains and immunohistochemical or in situ hybridization techniques. We analyzed the diagnostic concordance between glass and digital slides at two levels: the description provided for each sample and the final diagnosis given for each case. It was important to verify how changes in sample descriptions influence the final diagnosis provided for the corresponding case.

Table 1
Characteristics of the Study Set

Characteristic	Total	Pathologist A	Pathologist B	Pathologist C
No. of cases	119	40	39	40
No. of samples	237	51	122	64
No. of slides	749	160	371	218
HES	332	55	197	80
Others	417	105	174	138
Washout delay, mean (range), mo	5.6 (1.6-7.4)	6.4 (5.7-7.0)	4.3 (1.6-5.0)	6.0 (5.1-7.4)
Minor discordances at case level, No.	12	4	4	4
Major discordances at case level, No.	3	2	1	0

HES, H&E saffron.

Concordance at the Sample Level

A full concordance between diagnoses or descriptions provided from either glass or digital slides was observed in 179 (75.5%) samples.

Differences between ADICAP codes were observed in 58 (24.5%) samples. After review, descriptions were declared concordant in 28 samples, since the differences observed were due to a variation in the ADICAP code unrelated to a change in the pathologic interpretation. The most frequent cause was the use of two slightly different codes to describe variants of the same lesion or the same diagnosis. Diagnoses were classified as definitely discordant in 30 (12.7%) of 237 samples. The discordance was classified as minor in 24 samples and as major in six samples.

At the sample level, diagnostic concordance (full concordance + concordance) between the two successive examinations was 87.3% (207/237).

Concordance at the Case Level

Final diagnoses provided from, respectively, glass and digital slides were fully concordant or concordant in 104 (87.3%) cases; 21 (17.6%) of these cases contained at least one sample for which the ADICAP code was different at the two successive examinations.

Minor discordances were observed in 12 (10.1%) cases. In five cases of nonneoplastic lesions, the diagnosis was changed from absence of lesion to mild abnormalities such as incipient fibrosis or mild inflammation (n = 3) or the contrary (n = 2). Three cases were benign epithelial tumors: two adenomas of the colon and one intraepithelial neoplasia of the uterine cervix;

Table 2
Origin of the Samples (n = 237) Included in the Study

Site	No. (%) of Samples
Breast	122 (51.5)
Digestive tract	35 (14.8)
Head and neck	33 (13.9)
Lymphoid organs	15 (6.3)
Bone marrow	14 (5.9)
Liver	6 (2.6)
Female genital organs	5 (2.1)
Thorax	4 (1.7)
Skin	2 (0.8)
Bone	1 (0.4)

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Table 3
Initial Diagnoses for Samples Made Through the Examination of Glass Slides (n = 237)

Diagnosis	No. (%)
Benign or malignant tumors	161 (67.9)
Benign epithelial tumors	13 (5.5)
Carcinomas	119 (50.2)
Sarcomas	4 (1.7)
Lymphomas	22 (9.3)
Mesotheliomas	1 (0.4)
Others	2 (0.8)
Nontumoral lesions	43 (18.1)
Inflammatory lesions	16 (6.7)
Others	27 (11.4)
Normal tissue	21 (8.9)
Noninformative samples	12 (5.1)

the lesions were correctly identified but graded differently. In all three cases, the grade of dysplasia provided by the pathologist was higher in digital slides compared with the original glass slides. The four remaining cases were correctly identified as carcinomas, but they were classified in different subtypes at the two successive examinations.

There were three major discordances, all with therapeutic impact. In one case (MD1), a neoplastic lesion of the breast, identified from the glass slide as an intraductal apocrine carcinoma, was interpreted as fibrocystic change with apocrine metaplasia in the digital slide; an external reviewer confirmed that the correct diagnosis was the one made from the glass slide. In the second case (MD2), the initial diagnosis of follicular lymphoma, correctly made from the glass slide, was missed in the digital slide. In the last case (MD3), a squamous cell neoplasia of the tonsil, correctly diagnosed as invasive carcinoma in the initial glass slide, was incorrectly interpreted as noninvasive, grade 3 intraepithelial neoplasia in the digital slide. No external review was necessary to assess the final diagnosis in MD2 and MD3.

In all discordant cases, the final diagnosis eventually retained was the diagnosis provided through the examination of glass slides. No change in diagnosis was performed after examination of digital slides.

Analysis of the Causes of Major Discordances

In two cases (MD1 and MD2), the major discordance between glass slide and digital slide diagnoses was due to variations in the interpretation of the pathologist and not to technical issues. However, for MD1, the pathologist complained of a lack of clinical and radiologic information in the anonymized file, and for MD2, the pathologist pointed out that the diagnostic error was likely favored by a lack of concentration attributed to the work on a computer screen rather than on a conventional microscope. In the remaining case (MD3), the discordance was attributed to a technical issue related to the control of the illumination parameters in the viewer. The software used in our study made it possible to modify the gamma balance to improve the visualization of cellular details. In the discordant case, the gamma balance was inappropriately settled by the system because of the thickness of the section and the high cellular density of the tissue. This prevented a correct identification of the invasive component of the tumor in the digital slide. In the meantime, a new version of the viewer was released; it now includes a function mimicking the light button of a microscope to briefly increase the brightness of an image, to improve the evaluation of darkly stained cells. This change was hence considered a significant improvement in terms of risk reduction.

Intraobserver Concordance

All three pathologists involved in the study were responsible for minor discordances (Table 1). Two experienced major discordances (Table 1). Intraobserver diagnosis concordance (full concordance + concordance) between the two successive examinations was 87.4% (104/119; 95% CI, 80.1%-92.8%). When major discordances only are excluded, intraobserver concordance between glass slides and WSI was 97.5% (116/119; 95% CI, 92.8%-99.5%). The lower CI bound was higher than 90%: this was our condition for a possible use of WSI in daily practice.

Ergonomic Evaluation

We first evaluated the functions of the database and the viewer. Users were very satisfied or satisfied with nine of the 11 functionalities. Only two functionalities were evaluated as not fully satisfactory: slide synchronization and joystick navigation. The comparison of the questionnaires filled in the course of the study showed a trend toward increased satisfaction with the digital pathology system. However, the number of questionnaires exploitable was not large enough to allow a statistical analysis of the results.

Discussion

Our study confirms the feasibility and accuracy of the pathologic diagnoses made from digital slides in real-life conditions and supports the possible use of WSI technology in daily biopsy diagnosis. It also shows the rapid

adhesion of pathologists to this new technology and the feasibility of its inclusion in the laboratory workflow.

Our study was designed according to the recommendations of the College of American Pathologists for the validation of digital pathology systems.[7] It involved several senior pathologists from the same department, previously trained to the use of the digital pathology system to avoid any learning curve bias.[9] The validation set was based on a large number of consecutive cases extracted from the routine activity of each pathologist, representative of his or her daily recruitment. A large proportion of cases were neoplastic diseases, as might be expected in our institution, but inflammatory and other nonneoplastic lesions were also included. In this way, our study differs from most previous works, which focused on restricted specialty or subspecialty "niches."[10-21] As recommended,[7] a washout period was organized between the initial diagnosis and the analysis of digital slides. In our study, this period was particularly long, ranging from 1.6 to 7.4 months, to avoid any bias due to case remanence, which might persist for much more than the 2-week interval recommended by the College of American Pathologists, as shown before.[22]

In our study, we paid particular attention to reproduce real-life conditions of diagnosis for the analysis of digital slides. Pathologists were provided with a set of digital slides reproducing the complete set of slides available for the conventional diagnosis, including not only HES stains but also special stains, immunohistochemical techniques, and in situ hybridization studies. In addition, for the analysis of digital slides, the whole clinical documentation available at initial diagnosis was made accessible to the pathologists through an anonymized patient file. Our study therefore makes it possible to test the capacity for the pathologists not only to provide a description and/or a diagnosis for one individual digital slide but also to give an integrated diagnosis for a complete case, including several tissue samples, a large number of slides, and special techniques. To express the pathologic diagnosis, we decided to use, as in real life, the structured French ADICAP coding system to facilitate the comparison between glass and digital slide diagnoses. However, in our experience, this method proved to have some pitfalls, mainly due to the use of different diagnostic codes for variants of the same lesion. An additional review was therefore necessary to verify the consistency of the codes provided by the participating pathologists and to avoid any bias due to the use of the coding system.

One original point of our study is that we included not only conventional HES-stained slides, the only ones tested in most previous studies, but also special stains, immunohistochemical techniques (with no less than 84 different primary antibodies), and even in situ hybridization studies. While these techniques are often essential to the final diagnosis, the feasibility and accuracy of their interpretation from WSI have been rarely evaluated.[23,24] In our study, all digital slides were found interpretable by the participants, including those corresponding to special stains and immunohistochemical techniques. We therefore greatly expand the message of previous studies in showing that WSI can be used for the analysis and interpretation of immunohistochemistry in a diagnostic setting and is not restricted to the acquisition of images for automated quantitative analysis.

In our study, the intraobserver concordance was 87.3% for the individual diagnosis of each sample and 87.4% for the integrated diagnosis of full cases. If only major discordances, with possible clinical impact, are excluded, intraobserver concordance amounted up to 97.5%. This fulfills our requirements for considering an implementation in daily diagnosis. Our figures compare well with previous results. In a recent comprehensive review,[25] the diagnostic concordance was reported to be 90% or greater in 18 of the 30 studies analyzed and greater than 95% in 10. It is important to underline that these results are not significantly different from those obtained for intraobserver concordance between two successive lectures using conventional microscopy.[26,27] These concurrent results strongly support the feasibility of daily diagnostic pathology through WSI. Previous studies have also shown that WSI can also be used with success in other indications, such as consultation for difficult cases[22] or frozen-section diagnosis.[28,29] This suggests that WSI could be an alternative to conventional light microscopy in most fields of diagnostic pathology.

In this context, it is very important to analyze the causes of the discrepancies observed between the first lecture using conventional microscopy and the second lecture using digital imaging. Twelve (10.1%) cases of minor discordances, without significant clinical impact, were observed in our study; all participating pathologists were involved. Only three cases of major discrepancies, which would have been able to modify the management and/or the treatment of the patient, were encountered. We paid particular attention to identify their causes, particularly the possible role of the digital imaging technology. After careful review, it appears that only one of these major discrepancies was related to the digital pathology system, especially to illumination settings inappropriate for the visualization of nuclear details in histologic sections showing some technical defaults (excessive thickness, imperfect staining). Comparable difficulties with the evaluation of exquisite cellular details have been previously reported.[14,30-33] In our study, a curative action could be performed immediately to fix the issue, whereas in initial studies, a significant number of the

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discrepancies observed between conventional microscopy and WSI could be explained by technical issues in the digital pathology system, including poor image quality and/or logistic issues.[8,34] This was no longer the case in more recent works.[25,30,35] This clearly shows the rapid improvement of the technology. However, it remains important to underline that the diffusion and implementation of digital pathology systems in the daily laboratory workflow will require a further effort in the standardization and quality control of histologic preparations to avoid technical pitfalls and ensure a smooth processing of digital slides.[8,36]

An essential requirement for the implementation of digital pathology systems in the laboratory workflow is the adhesion of the pathologists to this new modality of work. We paid particular attention to this point in our study. Several approaches were used. The first method was to set up an ergonomic study and to measure user satisfaction. In our experience, satisfaction was high and increased with regular use of the system, as previously observed.[37,38] A second approach was to compare the performances of the three pathologists participating in the study. All three were responsible for minor discordances, and two were responsible for major discordances. This indicates that all three encountered comparable problems with the analysis and interpretation of digital slides. Three points are of interest. The first one is that, in our study, no final diagnosis was changed after digital slide examination. Moreover, in all discordant cases, the final diagnosis retained after review was the diagnosis made from glass slides. The same general trend was observed in all previous studies, even if, in rare cases, the diagnosis was modified after examination of digital slides.[12] This indicates that, as could be expected, pathologists are obviously more familiar with the pitfalls susceptible to be encountered in the examination of glass slides than in that of digital slides. A second interesting point is that some difficulties were noted by all three pathologists. One was the trend to upgrade dysplastic lesions in digital slides compared with glass slides. This might have an impact on patient management and follow-up, especially if surveillance biopsy specimens are to be analyzed with different modalities at different time points. This point has to be confirmed in further studies, and its reasons have to be explored. So far, only hypotheses can be proposed. One is that digital imaging encourages an analytical approach rather than a bird's-eye view of the slide[13,31]; this might increase the weight given to cellular alterations in the elaboration of the final diagnosis. A further point of attention has been noted by one participant, who experienced some difficulty in maintaining a prolonged concentration when examining slides with the digital pathology modality. Looking at a computer screen was perceived as working in an open environment, whereas looking through the objectives of conventional microscopes was perceived as working in a close, protected environment. This further illustrates the variety of individual reactions that have to be taken into account in preparing the implementation of a digital pathology system in a daily workflow.[13,37]

In conclusion, our study confirms the feasibility and accuracy of digital imaging as a modality of diagnosis in real-life conditions and demonstrates its suitability not only for the analysis of conventionally stained slides but also for the interpretation of special techniques, including routine immunohistochemistry and in situ hybridization. We also observed a rapid adhesion of the participants to the system used in the study. However, in accordance with recent proposals,[5] a number of important conditions must be kept in mind to achieve the implementation of this technology in the laboratory workflow, including (a) standardization and quality control in the preparation of histologic specimens to ensure a smooth processing of digital slides, (b) organization of an adapted working environment, and (c) availability of an ergonomic, adaptable, and reactive digital pathology system able to obtain the adhesion of pathologists to this new working modality but also able to fix rapidly the technical issues raised by users.

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