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The DOI for this manuscript is doi: 10.5858/arpa.2018-0541-OA

The final published version of this manuscript will replace the Early Online Release version at the above DOI once it is available.

Complete Digital Pathology for Routine Histopathology Diagnosis in a Multicenter Hospital Network

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• ***Context.***—**Complete digital pathology and whole slide imaging for routine histopathology diagnosis is currently in use in few laboratories worldwide. Granada University Hospitals, Spain, which comprises 4 hospitals, adopted full digital pathology for primary histopathology diagnosis in 2016.**

Objective.—**To describe the methodology adopted and the resulting experience at Granada University Hospitals in transitioning to full digital diagnosis.**

Design.—**All histopathology glass slides generated for routine diagnosis were digitized at ×40 using the Philips IntelliSite Pathology Solution, which includes an ultrafast scanner and an image management system. All hematoxylin-eosin–stained preparations and immunohistochemistry and histochemistry slides were digitized. The existing sample-tracking software and image management system were integrated to allow data interchange through the Health Level 7 protocol.**

Results.—**Circa 160 000 specimens have been signed out using digital pathology for primary diagnosis. This comprises more than 800 000 digitized glass slides. The scanning error rate during the implementation phase was below 1.5%, and subsequent workflow optimization rendered this rate negligible. Since implementation, Granada University Hospitals pathologists have signed out 21% more cases per year on average.**

Conclusions.—**Digital pathology is an adequate medium for primary histopathology diagnosis. Successful digitization relies on existing sample tracking and integration of the information technology infrastructure. Rapid and reliable scanning at ×40 equivalent was key to the transition to a fully digital workflow. Digital pathology resulted in efficiency gains in the preanalytical and analytical phases, and created the basis for computational pathology: the use of computer-assisted tools to aid diagnosis.**

(*Arch Pathol Lab Med.* doi: 10.5858/arpa.2018-0541-OA)

Digital pathology is rapidly evolving, driven by developing technology, decreasing costs, and regulatory changes. The basis of digital pathology lies in obtaining a digital replica of the histologic slide, called a whole slide image (WSI). Ultimately, digital pathology aims to promote diagnostic precision by providing digital tools for accurate histologic assessment, to facilitate collaborations and remote consultations.[1,2] However, one of the benefits of digital pathology is that it represents a step on the road to computational pathology, whereby the diagnostic process is aided by artificial intelligence tools[3] and big data are created. Other benefits of adopting a digital workflow include the decrease of mismatch errors between patient and slide information and more efficient archiving and retrieval of slides,[2] as well as added benefits for educational and research purposes.[1] Furthermore, digital pathology can facilitate workload management by tracking, triaging, and assigning cases to specific pathologists.[4]

Granada University Hospitals (GUH), which is part of the publicly funded health service, is located in the province of Granada, in Andalusia, southern Spain (Figure 1, A). It comprises 2 teaching hospitals located in the city of Granada, which share a single central histopathology laboratory, and 2 peripheral district general hospitals, each with its own laboratory. Our intent was to implement digital pathology in our hospitals, to fully digitize all prospective histopathology cases, and to perform all routine diagnosis on a digital basis, thus creating a fully digital multisite network. The present paper aims to describe our approach and experiences in this process.

METHODS

Pathology Laboratories at GUH

The hospital service provision in the Granada province consists of 2 central teaching hospitals located in the city of Granada and 2 peripheral hospitals serving the towns of Motril and Baza, respectively some 75 and 100 km from Granada city (Figure 1, B). The Campus de la Salud Hospital, a newly purpose-built teaching hospital, was completed in 2015 and replaces an older teaching hospital. The sample processing for the metropolitan area is centralized at Campus de la Salud Hospital, which has a dedicated molecular biology laboratory with next-generation sequencing. Virgen de las Nieves Hospital, the second teaching hospital in the

Accepted for publication March 20, 2019.

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Figure 1. *A, Location of Granada in southern Spain. B, The pathology laboratories at Granada University Hospitals comprise 4 different sites. Map data copyright 2018 Google. Abbreviation: VNH, Virgen de las Nieves Hospital.*

metropolitan area, has a small laboratory for processing intraoperative frozen sections and fine-needle aspiration cytology samples, and all histology specimens are sent to Campus de la Salud Hospital. In addition, each of the peripheral hospitals has its own fully functioning histopathology laboratory.

The total population in the Granada area approaches 1 million inhabitants. In total, the histopathology laboratories are staffed by 23 pathologists (many of whom have teaching appointments at the University of Granada and only consulting or part-time clinical commitments), 8 trainee pathologists, 32 histotechnicians, and additional clerical and support staff. The case workload for GUH is summarized in Table 1.

Information Technology Infrastructure

The publicly funded regional Andalusian health care service has a central patient database and electronic medical records system called Diraya. The laboratory information system (LIS) and sample-tracking software in use at GUH are Vitropath and VTS, respectively (Vitro SA). Vitropath offers a comprehensive preanalytical and postanalytical solution and is mainly used by pathologists for reporting and requesting ancillary tests. It is integrated with Diraya, which supports electronic histopathology requests. VTS, mainly operated by laboratory histotechnicians, tracks the sample state during the process of slide preparation and distribution and documents its progress. All the assets generated

Table 1. Caseload at Granada University Hospitals at the Time of Implementation of Digital Pathology (2016)				
Site	Beds	Cytology Samples	Histopathology Samples	Postmortem Samples
Virgen de las Nieves Hospital (Granada city)	1000	48 652	43 202	101
Campus de la Salud Hospital (Granada city)	600			
Motril General Hospital	200	8326	9549	Centralized at Campus de la Salud Hospital
Baza General Hospital	120	3789	3890	Centralized at Campus de la Salud Hospital
Total	**1920**	**60 767**	**56 641**	

in the workflow are tagged with a quick response (QR) bidimensional code, which reduces the chances of mislabeling errors and permits easy identification. This information technology (IT) infrastructure is present in all GUH histopathology laboratories, which share the same patient information. In addition, there is a postanalytical tracking system to manage and archive these assets.

Imaging Technology

Granada University Hospitals uses the Philips IntelliSite Pathology Solution, which provides high-quality automated digital WSI creation, viewing, and management. It is permitted for primary diagnostic use in the United States by the US Food and Drug Administration,[5] and is licensed for in vitro diagnosis in the European Union, Canada, Japan, Singapore, Korea, and the Middle East. A key element in this system is the ultrafast scanner (UFS), a continuous throughput scanner with the capacity for 300 slides that requires minimal user intervention, hence facilitating overnight operation, and scans only at ×40 equivalent. This scanner is self-calibrating, and incorporates a continuous autofocus mechanism. It provides a resolution of 0.25 μm per pixel, using a ×40 Olympus Plan Apo objective with a numerical aperture of 0.75 to achieve a magnification of ×400. There are 2 UFSs at Campus de la Salud Hospital, plus 1 additional UFS at both Baza General Hospital and Motril General Hospital. Immediately after scanning, the digital images are available in the image management system (IMS), which has an array of digital tools for image evaluation and creates virtual slide trays for each case. These virtual trays are elaborated upon using the information supplied by the LIS, and they emulate the physical trays that a pathologist would use in conventional light microscopy.

The pathologists have access to these images through a workstation comprising a HP Z440 PC with an Intel Xeon CPU E5-1620 v3 at 3.50-GHz processor, 16 GB RAM, and an NVIDIA Quadro K4200 graphic card. Each workstation is equipped with 2 monitors. A 24-in (61-cm) Barco MDRC-2224 BL LED monitor with a resolution of 1920 × 1200 is used for image viewing, and has a system called MediCal QAWeb that ensures automatic calibration and image quality. In addition, each workstation has a 24-in (61-cm) Philips 246V5L LED monitor with a resolution of 1920 × 1080 pixels, used for reporting in the LIS, consulting patient records, and so on.

IT Integration

A crucial step toward 100% caseload digitization is the integration between the IMS and the existing clinical IT infrastructure. In this way, the digitized WSI is identified by its QR code and matched with the corresponding patient and sample details automatically, thanks to the information fed onto IMS by the LIS. At GUH, the pathologists can consult their daily caseload work lists either in the LIS or in the IMS, which displays the virtual slide trays created; the cases are then reported in the LIS.

The integration between LIS and IMS took a phased approach, being initially unidirectional, whereby the LIS offered the IMS the necessary specimen data to properly identify the slides scanned. These included bar code information, specimen site, staining techniques, number of glass slides produced per case, and the assigned pathologist. Contextual icons were created on the LIS screen that would call up that particular case image on the IMS. At a later stage, bidirectional communication was implemented to improve sample tracking and status updates, so new information pertaining to slide status is continuously exchanged and updated in both systems. The integration process took approximately 1 month.

The communication between the LIS and the IMS is done by means of Health Level 7 messaging protocol. It is essential that both the LIS and the image viewing software vendors be involved in the integration process, and that their software be open and flexible to permit the necessary data interchange.

Test Phase: Toward a Fully Digital Workflow

Once a level of integration between the software elements that allowed communication from LIS to IMS was achieved, we conducted a test phase comprising the last 11 758 archived glass slides, including hematoxylin-eosin, histochemistry, and immunohistochemistry slides, that originated from clinical routine practice from the Granada central hospital (Table 2). The purpose of this test phase was twofold: we wanted to know, first, what the average scanning time was per slide, and second, how many slides could be scanned per working day. In these real-life tests, the average glass slide measured 289 mm^2 and took an average of 114 seconds to scan, or 31 slides per hour. This is from the moment the slide was introduced in the scanner to the moment the WSI was available for viewing.

These tests showed that one scanner could theoretically handle the slide volume routinely generated in the central Granada laboratory (about 700 slides per day). This was largely possible because of the scanner's fully automated continuous workflow operation, which makes possible unsupervised overnight scanning. However, a decision to install 2 UFSs at the central Granada laboratory was made, in order to ensure that a backup was in place and to have spare capacity to allow scanning of nonroutine samples, such as archived and research slides, when required. In addition, 1 additional UFS was installed at each of the peripheral

Table 2. Results of the Test Phase[a]				
Batch No.	Slide Volume	Stains	Average Slide Scanning Time, s	Average Scanned Area, mm^2
1	5469	HE, HC, IHC	121	302
2	2630	HE	141	353
3	1547	IHC	112	280
4	1323	HE, HC, IHC	89	233
5	789	HE, HC, IHC	108	278
Mean			114	290

Abbreviations: HC, histochemistry; HE, hematoxylin-eosin; IHC, immunohistochemistry.

[a] A total of 11 758 slides were scanned in 5 batches. The average slide measured 20 × 14.5 mm^2 and took 114 seconds to scan (equivalent to 31 slides per hour). The scanner digitized only at ×40 equivalent.

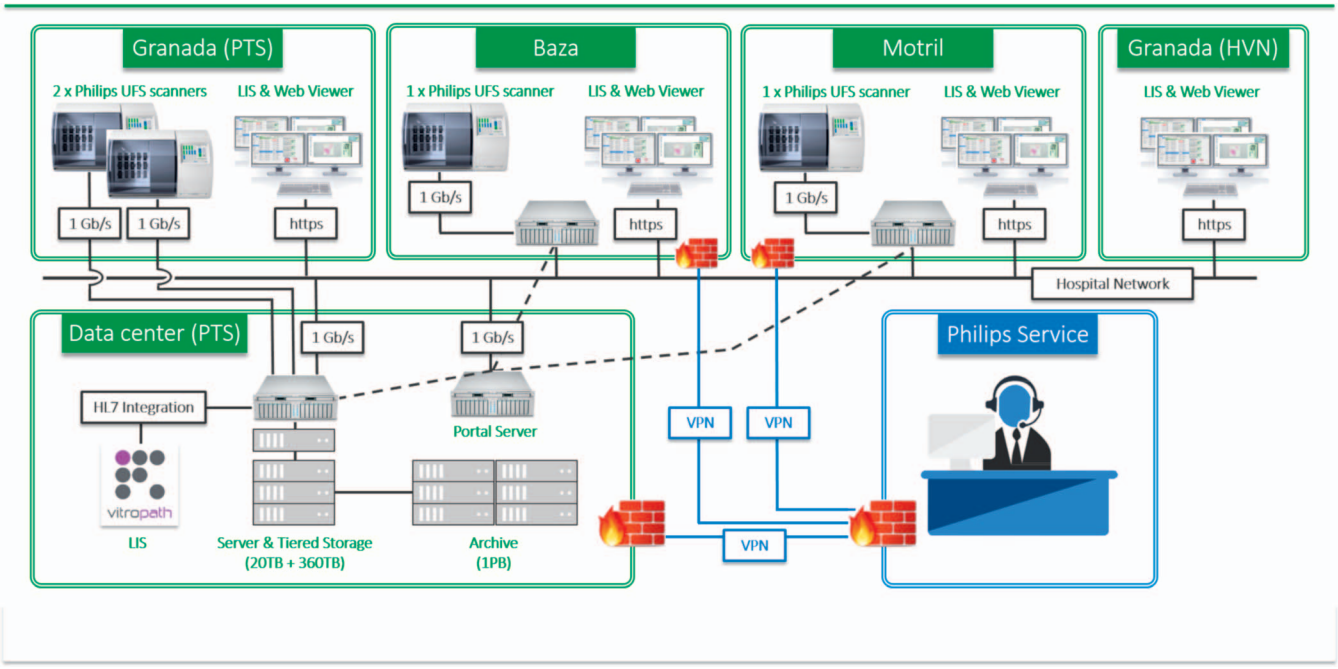

Figure 2. *Schematic representation of the system architecture at Granada University Hospitals. Thanks to the portal architecture, all digitized images are available throughout the entire network. Abbreviations: HVN, Virgen de las Nieves Hospital; PTS, Campus de la Salud Hospital.*

laboratories at Motril and Baza, so all their slides could also be digitized.

The scanners were linked via a dedicated 1 GB/s network connection. Three application servers were installed, 1 at Campus de la Salud hospital at Granada and 1 server for each of the hospitals at Motril and Baza. These servers were connected to a portal server to create a multisite network. The portal integrates the case and image data from the 3 application servers into a single integrated work list for all users (Figure 2).

Following this initial phase, our pathologists were asked to conduct a validation procedure (see below) to ensure their diagnostic accuracy using digital images was comparable to that using the microscope. After this, we proceeded to scan all the slides generated for routine clinical practice, which permitted the use of digital WSI for primary diagnosis. Once all glass slides generated were available in digital format, the cases were no longer routinely delivered to the assigned pathologists in analog format. However, pathologists had access to the physical glass slides on demand. This resulted in the suppression of the analog workflow.

In all, the transition from analog to digital pathology took a total of 6 months, from April to September 2016, which encompassed the installation of the required hardware and software, the integration of the IT elements, the vendor training sessions, and a test phase as described.

RESULTS

Since the implementation of digital pathology, circa 160 000 histopathology specimens have been diagnosed using digital pathology as means of primary diagnosis in the province of Granada. This comprises around 800 000 digitized glass slides, including routine hematoxylin-eosin stains, histochemistry, and immunohistochemistry samples. In our setting, the majority of biopsy specimens comprise a single slide per specimen. The average case comprises approximately 5 or 6 slides.

The most common error encountered during the test phase (0.76% of all slides) involved slides skipped because the QR code was not recognized, usually because of poor slide label quality or because it had been rendered unreadable by pigment spatters on the label during the staining process. In these cases, the nonrecognized slides are digitized, but no ID is allocated to them, and thus they cannot be automatically assigned to the case they belong to. They go to a dedicated system folder called "action required." These slides require the scanning histotechnician to open the action required folder and manually assign their ID. Therefore, and thanks to the integration between the workflow-tracking system and the digital pathology system, all scanned slides are accounted for, thus limiting the chance of slides becoming lost in the workflow.

The second most common error during the test phase (0.70%) occurred when the prongs of the robotic arm and the stage mechanism malfunctioned and the digitizing slide could not be released properly. This occurred when the slide label was misaligned and stuck to the prongs, or when there was excess mounting media in a slide. On 2 occasions, the mounting media interfered with the optical system, which required a full cleanup.

Out-of-focus issues occur infrequently, owing to the scanner's continuous autofocus system, and in the majority of cases the out-of-focus areas are rarely critical for diagnosis. Usually, these areas correspond to stromal regions or lesion areas that add little additional information to a lesion that has otherwise been correctly digitized in its majority. Therefore, rescan rates for this reason are below 0.1%.

The role of scanning technician was created; it fulfills many purposes, including checking the quality of all the slides prior to being scanned, loading the scanner, and checking the scanning results. The first step involves checking that the glass slides are suitable for scanning, ensuring that there is no excess mounting media in the slides, that the coverslips and labels are well aligned, and that the labels and QR codes are legible. This is done relatively quickly, because our average daily slide output can

be accommodated in 30 to 35 universal racks, which are then inserted in the scanners. Loading the scanners takes a short few minutes. From this moment, the scanning process begins automatically, requiring no human intervention. In case of an incident (ie, no slide bar code detected), the scanner digitizes that slide and sends its image to the action required folder, continuing with the next slide as usual; however, it creates a visual alert to the scanning technician, who then manually assigns the right identity to those unrecognized slides. The fact that the scanning process continues despite these incidents permits unsupervised overnight scanning. In all, our total scanning time takes approximately 24 hours, divided among the 4 scanners available at GUH.

Upon completion of the scanning process, the scanning technician conducts the quality control of the scanned images, inspecting approximately 25% to 30% of all slides. This is done in the IMS, using a viewing workstation for this purpose. This quality control involves checking that the scanner has performed self-calibration successfully, that the scanned areas includes all tissue in the glass slide, that the images are free from stitching or other image artifacts, and that the color, contrast, and focus are appropriate. Rescan rates for these reasons are less than 0.1%, and on the occasions when a rescan is required, it may be initiated by the scanning technician or at the relevant pathologist's request. The scanner takes a snapshot of each slide prior to scanning, and this snapshot is made available in the viewer. Therefore, pathologists perform a final quality check, ensuring in their workstation's viewer that all the tissue regions have been successfully scanned, because the viewer allows pathologists to compare this snapshot of the glass slide with the digitized WSI counterpart, hence revealing any possible discrepancies. A rescan is decided at the discretion of the histotechnician or the pathologist, and is done when it is felt that the problem area compromises the appropriate assessment of that slide. This is similar to when an analog pathologist accepts wrinkles, tears, or air bubbles in a conventional slide without demanding recuts, because it is felt that what is seen is sufficient. In all, thanks to the changes introduced in the slide preparation workflow (see Discussion), the overall error ratio is below 0.1%, and consequently the total of all the tasks performed by the scanning technician usually requires approximately 0.5 full-time equivalent (FTE).

The adoption of a fully digital workflow has resulted in the practical suppression of the analog workflows corresponding to the slide sorting and case assembly and distribution processes. Because cases are automatically assembled and made available by the digital pathology system, the laboratory staff traditionally in charge of these tasks can now be dedicated to other duties. Before digital pathology was implemented, a total of 3 FTE histotechnicians were dedicated to these processes. Now, thanks to digitization, these are managed by 0.5 FTEs. After digitization, the slides are sorted before being filed, but, because the digital images are already available to the pathologists, this sorting is not urgent and therefore is not as labor-intensive as that of an analog workflow. In general, the histotechnicians at GUH do not feel that the filing process in a digital workflow is much more demanding than that in an analog workflow.

The multisite architecture ensures that all digitized images are available to anyone, anywhere within the network. Thus, images digitized at the Campus de la Salud Hospital can be assessed at the peripheral sites and vice versa. In addition, a sizable memory storage solution is required. In our practice, a typical WSI requires, on average, approximately 1 GB. At GUH, a multitier storage solution is in place. Tier 1 is a 20-TB online storage capacity for immediate fast access consumed by image data sent from the scanners to the servers. Within 12 hours the WSIs are transferred from tier 1 to tier 2, which has a capacity of 360 TB and stores all the WSIs from approximately the last 12 months. Whole slide images in tiers 1 and 2 are immediately available for viewing, and represent the working-memory element of the system. Whole slide images older than 12 months are transferred to tier 3, which is a high-capacity nearline tape storage with capacity for 1 petabyte, or approximately 3 years' worth of WSIs at our current production rate. Despite the availability of digital replicas, all glass slides are archived and kept indefinitely. Because the glass slides are preserved and can be rescanned, these memory tiers are not backed up, which would effectively double the digital storage costs.

To ensure diagnostic accuracy, it was recommended that the pathologists at GUH follow a validation process based on the guidelines provided by the College of American Pathologists.[6] In our setting, the majority of the cases used for validation purposes comprised formalin-fixed, paraffin-embedded tissue. Although frozen sections were not included in the initial validation phase, some users also validated for these specimens (notably a dermatopathologist interested in digitizing Mohs surgery samples). The cases had been diagnosed primarily on the microscope, scanned during the test phase, and reviewed subsequently. To avoid selection bias, each pathologist was to randomly select 60 complete cases from his or her recent caseload, at least 2 weeks after the primary diagnosis was signed. When those cases comprised fewer than 20 examples containing immunohistochemistry or special stains, additional cases were included to ensure those techniques were adequately represented. These cases were then scanned using any of the scanners available and diagnosed digitally. That diagnosis was then contrasted with the original primary diagnosis made on the microscope, and the result recorded. The main criterion to assess accuracy was absence of discrepancy likely to result in different clinical outcome or management.

The average intraobserver variability rate between the optical and digital diagnoses observed during the validation process was below 1%, and consisted of minor interpretative discordances involving benign entities, likely to be of little clinical significance. In no instances were major diagnostic discrepancies noted, or misinterpretations that could have the potential to affect clinical outcome or management. Some pathologists commented on the slightly different appearance of certain structures, such as nuclear features in papillary thyroid carcinoma or neuroendocrine chromatin. However, these differences were not perceived as problematic. There were no recorded instances in which all of the tissue in the physical glass slide had not been digitized in the WSI.

Cytology, polarized light, and immunofluorescence slides are currently assessed using conventional microscopy. At GUH, only regular-size slides (75 × 25 mm) are in use, and no other formats are produced. Although outside of intended use, some frozen section slides are diagnosed digitally, particularly those pertaining to Mohs surgery. However, all frozen section slides and their accompanying cytology smears are routinely digitized for archiving purposes, once diagnosed under the microscope, mainly to

Table 3. Yearly Caseload Variation at Granada University Hospitals (2015–2018, Numbers Rounded)[a]								
Year	No. of Pathologists	Histology Samples	Caseload Change From Previous Year, %	Histology Cases per Pathologist	Histology Cases per Pathologist % Change (Compared With 2015)	Total RVU	RVU per Pathologist	RVU per Pathologist % Change (Compared With 2015)
2015	24	53 500		2229		1 375 544	57 314	
2016	22	56 500	6	2568	15	1 450 225	65 919	15
2017	23	61 500	9	2674	20	1 581 231	68 749	20
2018	23	64 500	5	2804	26	1 687 039	73 350	28

Abbreviation: RVU, relative value unit.

[a] Only histology cases are depicted. The caseload has increased yearly between 6% and 9%. That, together with variations in the number of pathologists, has resulted in an increase in the percentage of cases per pathologist of between 15% and 26% each year compared with 2015, the year prior to full digitization. The RVUs show similar increases.

facilitate comparison between the frozen and the paraffin-embedded sections.

Since the adoption of digital pathology, the training of residents at GUH is based in its majority in digital images of histopathology specimens. However, residents are advised to refer to glass slides in certain cases to ensure familiarity with both diagnostic mediums. Because all cytology and most frozen sections specimens are diagnosed on conventional microscopy, residents are suitably exposed to the use of both the microscope and the digital system.

Compared with 2015, the year prior to digital pathology implementation, GUH has experienced variations in the number of yearly caseloads, as well in pathologist availability. Table 3 shows the caseload variation at GUH, and compares it with the number of available pathologists. The amount of relative value units, a measure of complexity associated to each sample, is also shown. Since 2015, GUH has experienced an increase in caseload of between 5% and 9% per year. After the full implementation of digital pathology, 2 pathologists retired, and only 1 of them was replaced the following year. The number of histology cases per pathologist experienced an increase of 17% in 2016, of 20% in 2017, and of 26% in 2018 compared with 2015, the year prior to going fully digital. These data reveal that, because of diminishing pathologist numbers and caseload increases, the pathologists at GUH have signed out, on average, 21% more cases each year since the implementation of full digital pathology for primary diagnosis, signaling improved efficiency.

DISCUSSION

Digital pathology has been used for primary diagnosis for all histopathology specimens at GUH since its full implementation in September 2016. The creation of a full digital multisite network, where all slides are available to any user from any location, has brought about several advantages, the most salient of which is the ability to assign caseloads according to specialty interest among our pathologists, and not by geographical site. Also, pathologists based at the peripheral hospitals of Motril and Baza can request immediate consultations from the specialists located at the central Campus de la Salud Hospital. Sharing cases with colleagues and requesting "curbside consultations" is straightforward, even between distant sites. On-call pathologists covering another site can report their routine cases from within the hospital network, and transport of physical glass slides is no longer required.

Histologic images can be easily identified, tagged, and displayed during multidisciplinary team meetings, and frozen sections obtained during Mohs surgery can be diagnosed live from the operating room, with a dermatopathologist (J.A.F.) visiting the surgical theatre and interacting face to face with the surgical team (Figure 3). The digital tools available permit easy and precise assessment of lesion dimensions and of lesion distance to surgical margins and the overlay of several slides, which is particularly helpful when comparing hematoxylin-eosin slides with their corresponding immunohistochemistry. Mitotic counting is aided by annotation tools and the use of a customizable digital grid. In addition to this, the fact that all the slides pertaining to a case are displayed in an orderly manner also facilitates navigating through a particular case, especially when a case comprises several slides with multiple ancillary techniques.

The existence of a digital archive enables the immediate availability of previous slides, which is helpful, for instance, when comparing the findings in resection specimens with those of the initial incisional biopsy. The memory organization in tiers allows all the WSIs from approximately the last 12 months to be immediately available for viewing. Whole slide images older than this are archived on tape. The retrieval of the slides from the tape archive takes a few minutes, instead of the hours it took previously to request, find, and retrieve the slides in a traditional analog archive. Therefore, and largely because of these advantages, acceptance by our pathologists, a commonly mentioned barrier to adoption,[2] has been fairly immediate and complete. Within 2 weeks from going live, all of the pathologists at GUH were using digital pathology for primary diagnosis and the analog workflows were suspended.

The College of American Pathologists has published guidelines[6] for validating a WSI system intended for clinical use. These guidelines recommend the comparison of at least 60 routine cases per application, and the assessment of intraobserver concordance between WSI and optical slides at least 2 weeks apart. A large multicenter blinded randomized noninferiority study,[7] involving 2000 cases and 16 000 reads, concluded that WSI was not inferior to microscopy for primary diagnosis including hematoxylin-eosin, immunohistochemistry, and special histochemistry stains, and that this conclusion was valid across a wide array of organ system and specimen types. This study was pivotal in warranting Philips IntelliSite Pathology Solution's permit for marketing its use for primary diagnosis by the US Food

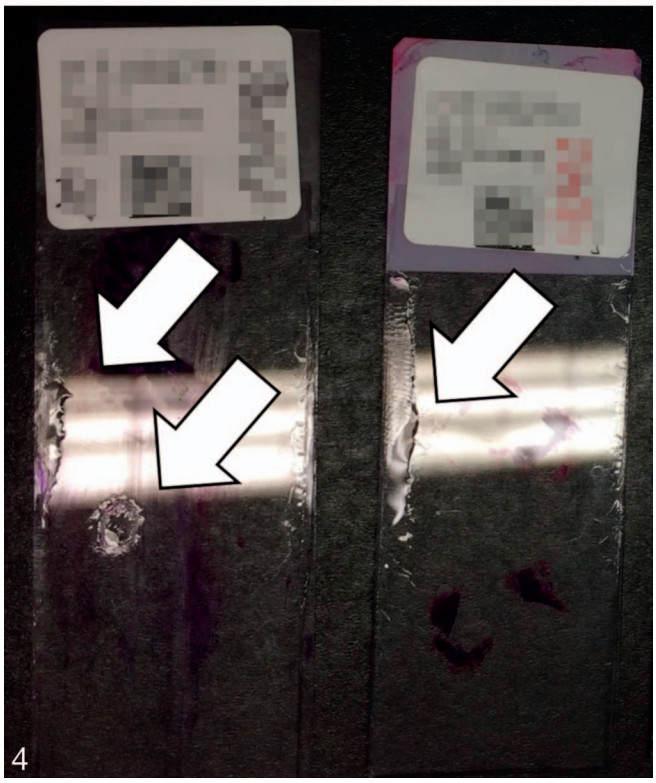

Figure 3. *The surgical margins obtained during Mohs surgery are routinely assessed live in the operating room by one of our dermatopathologists (J.A.F.).*

Figure 4. *Excessive mounting media can interfere with the mechanical functioning of the scanner.*

and Drug Administration. In our experience, the high-quality images that scanning at ×40 equivalent provides have been essential in the rapid transition to a digital workflow at GUH. Owing to the low discrepancy rates observed during our validation process, the majority of our pathologists felt confident and safe reporting cases using WSI, which reflects its appropriateness as a diagnostic medium.[7] However, some users may welcome the aid of training sets in the transition to digital pathology, to ensure pathologists gain the sufficient experience and confidence in their newly acquired digital skills. This may be particularly relevant for certain aspects, such as training to identify neuroendocrine chromatin, or nuclear features of papillary thyroid carcinoma.

A key element in the rapid implementation of digital pathology for primary diagnosis was the availability of sample tracking prior to effecting a full digital workflow. This becomes the foundation upon which digital pathology

Figure 5. *A typical pathologist workstation at Granada University Hospitals. The microscope is no longer required for routine histopathology diagnosis.*

is built, and requires open and flexible IT systems that permit patient and specimen information transfer among the different elements. Not having at least some degree of sample tracking, or having a system that does not permit bidirectional transfer of sample information, would hinder going fully digital.

Although the rates of scanning errors have been low, the adoption of digital pathology at large scale has required some changes in habits aimed at minimizing these errors. These changes mainly involve the quality of the glass slides being prepared for digitization, and thus histotechnicians need to be conscious of the importance of these factors. Glass slides need to be clean and free of artifacts that may unnecessarily increase scanning time. Also, the histologic preparations need to have carefully placed coverslips that are well aligned and free of excess mounting media, which could interfere with the mechanical elements of the scanning system (Figure 4). These errors have been minimized since the adoption of film coverslippers (Sakura). In addition, the labeling should be fully readable and free of any pigment splatters that could hinder label identification. This issue has been addressed with the introduction of glass printers, which imprint the slide ID and QR codes on the glass slide itself and are thus less prone to artifacts, significantly reducing the number of errors encountered. The implementation of these workflow changes has brought the error rate from approximately 1.5% down to 0.1%.

Although some authors advocate a "hybrid" mode of diagnosis during the transition period,[8] we adopted full digital diagnosis shortly after total implementation. This had the advantage of rendering redundant some of the analog workflows, like slide sorting and case assembly and distribution, which were suppressed and resulted in histotechnician time savings, from 3 FTEs to less than 1. The time required to scan the glass slides is compensated for by the time savings in these processes, which the digital pathology system does automatically. This also compensates for the additional attention that is required to ensure that slide quality is sufficient to minimize scanning errors. In general, our experience is similar to that reported elsewhere,[9] and results in better laboratory efficiency in the preanalytical phase.

Pathologists felt attracted to diagnosis using only digital pathology from the start, given that this provides a tidier workspace without the clutter normally associated with piling glass slides and request forms (Figure 5). The availability of digital tools for marking, measuring, and mitotic counting; the orderly disposition and immediate

availability of glass slides, including those archived; the better perceived quality of low-power images; and the added ease of preparing for multidisciplinary team meetings and conducting teaching sessions made our pathologists willing to transition to digital diagnosis. This, together with the rational case allocation permitted by the creation of a fully digital multisite network, has resulted in a more productive working environment.

The adoption of digital pathology has resulted in improved efficiency, also perceptible in the analytical phase. Owing to the decline in the number of pathologists due to unreplaced retirement vacancies, and increasing yearly caseloads, there has been an increment in the number of cases signed out per pathologist each year following digital implementation at GUH. The yearly numbers of cases per pathologist depicted in Table 3 show that, in contrast to 2015, the year prior to digitization, pathologists signed out on average 21% more cases after adopting digital pathology.

Leaving aside the intangible benefits derived from the ease of working with digital tools in an ergonomic, largely glassless environment, the investment that is required to implement digital pathology can be justified only if the cost incurred is outweighed by the benefits obtained. A cost-benefit model[2] proposes that improvements in productivity of at least 10% to 15% are required to amortize the investment after 1 to 2 years. Following this model, the fact that pathologists at GUH were able to absorb a 21% increase in cases per pathologist suggests that amortization occurred before that time. In any case, the savings incurred by doing more work with fewer pathologists in the more than 2 years since the implementation of digital pathology largely justify the investment. The increase in caseload between 2015 and 2018 of circa 11 000 new cases would have required a total of 29 pathologists (at the 2015 rate of 2229 cases per pathologist, prior to full digitization), instead of the existing 23. To this number, we must add 2.5 FTEs saved in histotechnician time as discussed above.

In addition to the advantages in efficiency and workflow optimization that digital pathology brings about, the availability of digitized WSI creates the opportunity of using computer-assisted diagnostic technology,[10] including artificial intelligence tools, to assist pathology diagnosis.[3] Deep-learning algorithms applied to image analysis will have the potential to help pathologists to further optimize their workflow by means of screening slides to search for malignancy, generating preliminary reports, or objectively quantifying marker expression. In addition, morphologic patterns that may have diagnostic or prognostic significance, such as nuclear features,[9] tumoral cell density, and lymphocytic infiltration will be better assessed by means of computational tools. Also, these tools facilitate the integration between genomic platforms and histologic images[11] and their application to clinical practice. Therefore, in addition to the mentioned advantages, digital pathology also represents a necessary step toward a higher goal: attaining computational pathology.

The authors acknowledge Stuart Shand, BSc, MBA, from Philips Digital and Computational Pathology Solutions for providing Figure 2. Philips Digital and Computational Pathology Solutions did not offer any incentives or financial support and was not involved in the content of this article other than technical support.

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