

## Chapter 3

# Applications

**Abstract** Despite the diverse appearances and usage scenarios, digital pathology applications can nevertheless be categorized into a number of distinct topics and fields. In this chapter, we start with the most obvious of these applications and move toward the least obvious. We limit ourselves to explaining the field of applications here. In practice, applied digital pathology most likely involves a combination of applications, as can be seen in Chap. 5, where we highlight certain specific use cases.

**Keywords** Digital pathology · Pathology applications · Primary diagnosis · Second opinion · Pathology education · Quality assurance · Tumor board · Biobank · DP

### 3.1 Education

Whole slide imaging is increasingly being used for a number of applications. In education, for instance, WSI has been successfully adopted for graduate education in medical, dentistry, and veterinary schools, for the training of pathology residents, as an educational tool in cytotechnology, for virtual tracking and tutoring, at tumor boards, and on examinations [1].

Education may very well be the area in which the application of digital pathology is easiest, with the lowest risk, yet at the same time offering a high payoff. Every year, thousands of students go through a variety of histology and pathology courses. Viewing reference slides is expected to prepare them for their future careers. While high-quality slide sets exist, they are expensive and are typically not available to everyone. Oftentimes, a waterfall system is installed, whereby the best slides are used by medical school students, and more worn slides are used by

nursing school students. Those slides that are the most worn—typically consisting of incomplete collections—end up in bachelors-level anatomy and physiology courses.

The reasons for this are practical, as well as economic: It takes a lot of time and effort to develop high-quality reference slides. Purchasing them from a third party is an alternative to save time, but obviously has a financial cost associated with it. Depending on the histological condition/disease that one wants (or needs) to capture, it may be more difficult (and more costly) to obtain the right slides, as well. With purchased slides, one does not usually get a sufficient number of identical slides (sliced at same level or even the same tissue sample) for a large class. Such variability makes teaching difficult. “Look for...” or “it resembles...” do not apply to all students’ slides. With WSI, all students will have the same slide.

Once the slides are available, they are only available to a limited number of lecturers or students at a given time. During histology laboratory sessions, students typically must pass slides from one station to the next. Even with a multi-head microscope, there is limited viewing time (and multi-heads require frequent calibration, as well). In addition, coverslips become smudged, and occasionally slides break or are dropped due to improper (or careless) handling.

Compare this with a collection of digital slides. The slides are always available at any time to as many concurrent users as needed (albeit, limited by computer network and server constraints). Since slides no longer need to be physically handled, they cannot break or be dropped or misplaced. Furthermore, they do not fade or degrade over time. Assuming that quality assurance (QA) occurs before digital replicas are included in the reference collection, the colors will be as true and vibrant 10 years from now as they were on the 1 day the slides were stained. On the other hand, image color and quality vary, depending on the settings and quality of the student’s computer/laptop. In a survey of screens during an actual digital pathology classroom session, one cannot deny that different students will observe very different presentations.

The construction of a collection for teaching purposes or as a reference set becomes easier as well, once the digital route is chosen. The preparation of physical glass slides for preservation purposes requires more attention to detail than is prescribed in daily pathology laboratory practices. This brings up an interesting dilemma (which also explains the high cost of purchasing these off the shelf): A prepared slide needs to be examined before inclusion. Clearly, not all slides will “make the cut,” which means that a lot of effort and time is lost in preparing unfit slides. At the same time, interesting cases may turn up occasionally that are unfortunately unfit for inclusion, because the wrong preparation protocol was used. Contrast and compare this to going digital, with which any slide of interest that passes through a pathology or research laboratory can now be flagged, scanned, and included in any collection. Finally, a large number of digital WSI collections can also be accessed at other institutions.

Two great examples of WSI use in action within a medical education context are detailed in Chap. 5, the first at the New York College of Podiatric Medicine (NYCPM), and the second at the Italian Hospital in Cairo.

## 3.2 Remote Consultations and Second Opinions

Telepathology is probably the oldest form of digital pathology, especially since the practice need not necessarily incorporate digital pathology. Different types of telepathology exist: The content can be static or dynamic (either with or without robotic control), and combinations of static (reference) content and dynamic content exist as well. Whole (virtual) slide imaging is the most recent addition to the portfolio. WSI is nevertheless not a “capture it all” replacement for what existed previously: While virtual slides can be saved and edited, a mounted camera, converted into a video stream, can be sent to any remote site in a similar fashion that cable television signals are distributed. As such, the requirements for digital pathology are probably more demanding than for telepathology.

The benefits of telepathology systems are numerous and include enhancing medical services, allowing for increased specialization, saving money and time, enhancing both teaching and learning, and facilitating the exchange of knowledge. In terms of costs, the average cost of sending physical slides to only one American or European center (approximately US\$100) plus the average fee for the consultation (approximately US\$150) imply that the total costs for consulting on our specialized complex cases for this one center was US\$12.500 annually. As usually two or three centers are consulted for each case to gather more opinions, this figure should be multiplied two to three times, up to US\$37.500 annually. Compare this to the cost, once a digital system is set up, of a few simple mouse clicks to send images digitally.

Transmitted images may be used for multiple purposes, including aiding in establishing primary diagnoses, collecting second opinions, facilitating QA, testing personnel and system proficiency. Offsite learning is another application, which includes learning at “extreme” distances. The latter applies particularly to developing countries, which may lack sufficient resources or personnel to establish and maintain their own high-quality pathology services.

Preparation for telepathology requires several steps. Costs need to be evaluated, and funds to cover them need to be identified. Depending on which location one is in, the best available and qualified instruments need to be identified. This is not always straightforward, as telepathology is often deployed in remote and/or underdeveloped regions of the world. Practicality is therefore an important factor to consider, and it may be desirable to select somewhat less advanced equipment that is easier to operate or more durable. Furthermore, a consensus must be reached on the software that will be used, and the availability of connections for sending and receiving (live) data-feeds must be verified. A problem that is unique to digital pathology is its bandwidth requirements. At the 2013 20th International DICOM conference in Bangalore, India, several practitioners of rural medicine were pleading for applications that could also run over limited bandwidth (such as dial-up or ISDN). This is still a challenge for digital pathology, as color image streams are more difficult to compress. This may actually limit the application of digital pathology initially.

Once in place, however, service can be provided to any pathology department at any university, any research center, and any pathologist. Digital pathology

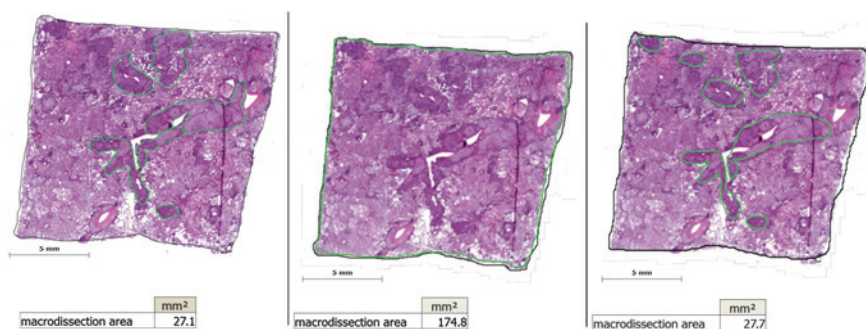
allows for the creation of a countrywide and international network for clinical and teaching purposes, as well as for research. Asynchronous viewing also becomes possible, in that two or more pathologists can view and comment on the same slide on their own time, rather than having to coordinate so that the slides are viewed together.

### 3.3 Tumor Boards and Pathology Reviews

A tumor board can be defined as a group of physicians  $\pm$  other healthcare providers with different specialties meeting to discuss specific cancer patients to determine the best course of management. Typically, this includes medical, surgical, and radiation oncologists [2], though other specialists may become involved as well; for example, a general internist may be included to provide input on comorbid diseases or a psychologist or social worker to address personal and interpersonal issues. Such boards have been in use for decades, the first description of one having been published as early as 1952 [3]. However, recently, there has been a push not only to increase their use, but to systematize them to enhance patient outcomes [2–5]. The rationale behind such boards is obvious: If two heads are better than one, why not have three or more extremely experienced and well-educated heads come together with the common goal of optimizing patient management? In recent years, such an approach is starting to fit particularly well with the emerging concept of “individualized” patient care, especially in light of so many cancer biomarkers and genomics-based therapies [6–9]. This inevitably increases the role of histopathology in treatment-related decisions.

In the past, tumor boards had little choice but to meet in person, usually at a hospital where most members, if not all, had their practices. But with teleconferencing and communication networks such as Skype now viable options, this is no longer as necessary. Such technology, combined with digital pathology, allows specialists miles and sometimes even countries apart to “meet” while having the slides in question immediately visible and interpretable (e.g., with pathologist annotations) right before them on their computer screens [5]. Even when boards do meet in person, it is helpful to have digital slides  $\pm$  pathologist annotations available for review. Nonetheless, the ability to have virtual tumor boards creates countless opportunities for collaborations between departments, hospitals, and even countries [2].

Another tumor board-like application relates to research, especially in the context of multicenter clinical trials or cohort studies, which often are required when studying rare forms of cancer and/or rare outcomes (e.g., an uncommon but serious side effect of a drug or other treatment). Since such studies often involve centers some distance apart, sometimes in separate countries, having collaborators meet in person to collectively decide upon patient eligibility often is infeasible. And yet, the more assured everyone is that every subject entered into the study is truly appropriate for entry, the more confident the investigators themselves will



**Fig. 3.1** Observations on the same tissue sample from three different pathologists

be—as well as grant application reviewers, journal reviewers and, ultimately, readers—that the ultimate results are generalizable to real-life practice. Digital pathology allows for collaborators from multiple centers to agree upon a histological diagnosis by all seeing, or having all their departments of pathology review, relevant slides. This helps them to reach a consensus regarding a given patient’s eligibility for the study and, in studies in which the treatment arms entail some degree of flexibility, the most appropriate course of action.

WSI also is expected to play an important role in central pathology reviews, both in clinical trial settings and in second-opinion cases. This is likely to result in a substantial reduction in the overall turnaround time required for slide reviews at central locations [10].

Interesting extensions lie in the recruitment of new pathologists and in the evaluation of practicing pathologists. It can also offer a novel way of choosing pathology service providers. Figure 3.1 shows annotated lung tissue. Three pathologists were asked to select appropriate regions for macrodissection, assuming subsequent downstream DNA extraction for mutation analysis. Clearly, the three pathologists came to different conclusions. This exercise can have far-reaching implications for the patient: Indicating the wrong area for mutation analysis can lead to misdiagnosis and the patient receiving incorrect therapy.

### 3.4 Biobanking and Collection Hosting

Translational biomedical research is based on large collections of high-quality samples combined with large sets of well-documented, up-to-date epidemiological, clinical, and/or molecular data from large numbers of patients and controls. Such collections are of the utmost importance in both investigator-driven and company-driven clinical trials. Biobanks are therefore considered essential for the advancement of research and development in the life sciences [11–17]. The term “biobank” is generally defined as an organized collection of human biological

material and associated information stored for research purposes. As the term infers, collections of plants, animals, microbes, and other non-human materials could also be labeled biobanks. However, the term is generally reserved for collections of human specimens. Specimen types include blood (in all its forms; e.g., serum, plasma, isolated PBMCs), urine, saliva, skin cells, organ tissue, and other materials taken from the body. Specialized biobanks exist, such as the Network for Pancreatic Organ Donors with Diabetes (nPOD) biobank that houses pancreatic tissues (<http://www.jdrfnpod.org>) and biobanks that focus on heart valves. The primary task of the biobank is to maintain specimens in good condition for future analysis. For this purpose, biobanks usually have cryogenic storage facilities for the samples, ranging in size from individual refrigerators to warehouses, maintained by institutions such as hospitals, universities, and other non-profit organizations [11–21], but also by pharmaceutical companies (e.g., Astra Zeneca Global Biobank). Disease-oriented biobanks, usually located at a university-based hospital, often have formalin-fixed paraffin-embedded (FFPE) tissue available, next to fresh frozen tissue. Although many collections of human biological materials are present in European countries, these collections often suffer from (geographical) fragmentation, undefined access rules, lack of uniform quality standards, and the absence of any uniform legal and/or ethical framework, thereby hampering international collaboration.

Increasingly, the focus of cancer therapy is shifting toward personalized medicine. For optimal application of targeted molecular drugs, an improved understanding of the underlying molecular mechanisms may help to identify biomarkers that can be used clinically to predict response and establish new treatment options to overcome resistance. For this kind of research, FFPE tissue is the specimen most widely available. Moreover, in contrast with prospective studies, long-term clinical follow-up is an implied characteristic of a biobank. However, the use of high-quality, fresh-frozen biospecimens with appropriate clinical annotation would be preferable. Collections of human biological materials together with associated clinical data are key resources when investigating genetic and environmental factors underlying (multi-factorial) disease, with the aim of improving diagnosis and treatment and ultimately preventing or mitigating disease.

To provide a forum to address the integration of scientific, technical, legal, and ethical issues relevant to repositories of biological and environmental specimens, the International Society of Biological and Environmental Repositories (ISBER, <http://www.isber.org>) and its chapter covering the region encompassing Europe, the Middle-East, and Africa (ESBB, <http://www.esbb.org>) were established. These societies aim to create opportunities for sharing ideas and innovations in biobanking, as well as the harmonization of approaches to evolving challenges for biological and environmental repositories. Educational resources and meetings focus on technical issues such as QA and control, regulation, human subject privacy, and confidentiality issues and provide information about sources of equipment and expertise.

However, despite the development of strict protocols for the inclusion of material into biorepositories, specimens may still prove to be of little value for

downstream testing. In one large study investigating 1,138 samples from the University of Indiana tissue bank, only 59 % were found to be at least 65 % tumor versus non-neoplastic tissue. Meanwhile, 23 % had a tumor volume that accounted for less than 65 % of the gross specimen, 17 % was entirely negative for tumor, and 1 % was completely necrotic. These findings underscore the importance of instituting adequate measures for histological sample quality control before the release of banked samples for downstream testing [22]. In fact, the availability of an online database of whole slide images for all specimens in a biobank would make it possible for researchers to preselect specimens based on tissue composition.

Finally, a fully digital workflow within pathology departments is within reach [23]. Since whole slide imaging is increasingly used for applications such as education and pathology reviews, it is likely that more laboratories will have access to digital pathology systems which will make whole slide image repositories as add-ons of existing biorepositories more feasible and, in the long term, even mandatory. A whole slide image database accompanying biorepositories should therefore be feasible. This can be taken even one step further by combining WSIs with digital pathology. Image analysis tools can be used to derive objective quantification measures from digital slides. Pattern recognition and visual search tools can be used to classify specimen imagery and identify medically significant regions of digital slides. Incorporating digital pathology into biobank QA procedures, using automated pattern recognition morphometric image analysis to quantify tissue features in digital WSI of tissue sections, can minimize the variability and subjectivity associated with routine pathologic evaluations in biorepositories. Whole slide images and pathologist-reviewed morphometric analyses can be provided to researchers to guide specimen selection [24]. As a specific example, unique spatial-spectral algorithms were developed for applying automated pattern recognition morphometric image analysis to quantify histological tumor and non-tumor tissue areas in biospecimen tissue sections. Measurements were acquired successfully for 75/75 (100 %) lymphomas, 76/77 (98.7 %) osteosarcomas, and 60/70 (85.7 %) melanomas. The percentage of tissue area occupied by tumor varied among patients and tumor types and was distributed around medians of 94 % for lymphomas, 84 % for melanomas, and 39 % for osteosarcomas. Within-patient comparisons from a subset, including multiple individual patient specimens, revealed  $\leq 12$  % median coefficient of variation (CV) for lymphomas and melanomas. However, due to phenotypic heterogeneity, the median CV for osteosarcomas was much higher. These data suggest that quantitative image analysis automation can minimize variability associated with routine biorepository pathologic evaluations and enhance biomarker discovery by helping to guide the selection of study-appropriate specimens [25]. An online histopathology system will be an important tool in the valorization of any biobank sample collection. An excellent example is the previously mentioned tissue repository installed by the nPOD-JDRF consortium ([www.jdrfnpod.org](http://www.jdrfnpod.org)), an initiative of the Juvenile Diabetes Research Foundation International, a large US patient organization. nPOD biobank houses pancreatic tissues from several hundred organ donors, including patients with



diabetes [26]. It has proven to be a highly efficient concept that has attracted researchers and industry from all over the world. The online repository not only provides detailed patient data, including donor demographics and laboratory assays, it also permits digital microscopy access to scanned slides, allowing potential customers to choose and inspect tissue and patient characteristics before ordering tissue sections via their online system [27].

### 3.5 Primary Diagnosis

Primary diagnosis has been described by some as the Holy Grail of digital pathology. However, like the mythical artifact, it has been difficult to achieve.

#### 3.5.1 *In the USA: The Role of the FDA*

Under the Food, Drug, and Cosmetic Act, the US Food and Drug Administration (FDA) recognizes three classes of medical device, based upon the level of control necessary to ensure their safety and effectiveness [28]. Classification procedures are described in the Code of Federal Regulations, Title 21, part 860 (usually known as 21 CFR 860) [29]. Class I devices are those that the FDA deems safe for use with minimal regulatory control. They generally are not intended to help support or sustain life or to be substantially important in preventing impairment to human health and are believed not to place patients at any unreasonable risk of illness or injury. Examples of Class I devices include elastic bandages, examination gloves, and handheld surgical instruments. Class III devices, meanwhile, are those devices the FDA deems most in need of regulatory control. Unlike Class I devices, they can help support or sustain life or be substantially important in preventing impairment to human health and could place patients at an unreasonable risk of illness or injury. Examples include implantable pacemakers, pulse generators, and diagnostic HIV tests.

Laboratories in the USA are currently prevented from using digital pathology for primary diagnosis, because the FDA has ruled that digital pathology is a Class III medical device. This is in contrast with traditional microscopes, which are considered a Class I medical device.

Some in the community are rather upset with this decision, because it arguably impedes the progress that can be made integrating digital pathology into daily practice. At the same time, however, the FDA had very good reasons to rule the way it did.

The reason that WSI is deemed to require a more comprehensive approach is that a traditional microscope is one component in a diagnostic system that only involves a light source and imaging optics. In contrast, WSI involves a slide scanner before the traditional microscope, followed by digital image capturing



techniques, followed by the use of image processing software. These image acquisition, processing, and display capabilities are new technology with respect to the clinical assessment of tissue sections. Therefore, WSI systems cannot be considered Class I exempt.

The FDA is also not blind to reality. It recognizes that the technological advances associated with WSI make its use a reality and makes no attempt to regulate or comment upon any of the other applications mentioned earlier in this chapter.

At the end of the day it means that, before being embedded into daily clinical practice, since WSI systems are not Class I exempt, they are subject to premarket requirements. Current in vitro diagnostic tests (IVDs) that utilize digital imaging for limited applications are not applicable to the WSI paradigm.

It is hoped that parallels can be drawn with other areas of medicine that already have gone through digitization. Digital mammography may provide useful lessons, but does not address all of the concerns that exist for WSI. One problem is that, in order to speed up performance and reduce scan time, scanners do a pre-scan of a sample and auto-detect the presence of tissue. They then only scan the areas that they assume have tissue on them. Lightly stained areas can be missed in this way, and to date, there is no good way, besides manual inspection, to determine whether a scanner has indeed scanned all the tissue within a section under investigation. One of the main concerns of the FDA is that this process can result in the omission of diagnostically relevant tissue and thereby impact patient management.

Such issues should not prohibit parties from starting to explore digital pathology. Though the FDA has a say in the application of technology to US patients, a US laboratory can still apply digital pathology techniques for primary diagnosis in patients located outside the USA. We have observed many examples of this, both in profit and non-profit scenarios. It is interesting to note that, in an interesting twist on the outsourcing paradigm, a laboratory in the USA can now serve very well as a nighthawk service for developing countries, whereas traditionally this has occurred in the other direction.

### ***3.5.2 Throughout the Rest of the World***

At conferences, it is clear that digital pathology is starting to be used for primary diagnosis elsewhere. In some cases, practitioners want to adopt its use before a regulatory framework is in place, hoping to establish best practices from which regulations can follow, rather than the other way around.

The University Health Network (UHN) in Toronto, Canada, is at the forefront of this. Over the course of a decade, they have fully adopted the practice of digital pathology, one digital pathology niche at a time [30, 31]. Each implementation step was brought on by a specific need; but no particular application involved a huge volume of slides/cases at any given time. Therefore, it was possible to build up expertise and learn necessary lessons along the way, before eventually scaling up to handle larger volumes.

In 2004, an initial program was started for frozen section telepathology. Learning from its successes and failures, the program was expanded to transplant biopsy telepathology in 2007. In 2012, a collaboration was set up with the Kuwait Cancer Control Center. Also by 2012, slides were being routinely scanned at 20X, and 300–400 slides were being sent to UNH on a daily basis. By 2013, the center received 600–800 slides per day for primary diagnosis.

Over the period between November 2012 and August 2013, almost 10,000 slides were evaluated digitally, of which only about 3 % were deferred to glass review. Reasons for the latter varied and included pathologists still getting accustomed to working digitally, IT performance issues, the difficulty of the particular cases, and sub-optimal image quality or poor focus of the scanned area under investigation [30].

### 3.6 Birds of a Feather

While digital pathology is definitely a niche in the medical imaging universe, its applications can be wide and diverse. In this chapter, we have categorized the most important domains in which digital pathology plays a role. In practice, we find that most installations combine two or more of these. This is logical outflow from the fact that once the hardware is in place, it is usually versatile enough to facilitate various scenarios. One example is a university that not only uses digital pathology for second opinions from specialists, but also for teaching histology in its medical school. In addition, the pathology department might run an outreach program with another country. There is one big use case for digital pathology that we have not yet discussed, but that we feel is important enough to warrant its own chapter.

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