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Visual Analytics in Digital Pathology: Challenges and Opportunities

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Abstract

The advances in high-throughput digitization, digital pathology systems, and quantitative image analysis opened new horizons in pathology. The diagnostic work of the pathologists and their role is likely to be augmented with computer-assistance and more quantitative information at hand. The recent success of artificial intelligence (AI) and computer vision methods demonstrated that in the coming years machines will support pathologists in typically tedious and highly subjective tasks and also in better patient stratification. In spite of clear future improvements in the diagnostic workflow, questions on how to effectively support the pathologists and how to integrate current data sources and quantitative information still persist. In this context, Visual Analytics (VA) - as the discipline that aids users to solve complex problems with an interactive and visual approach - can play a vital role to support the cognitive skills of pathologists and the large volumes of data available. To identify the main opportunities to employ VA in digital pathology systems, we conducted a survey with 20 pathologists to characterize the diagnostic practice and needs from a user perspective. From our findings, we discuss how VA can leverage quantitative image data to empower pathologists with new advanced digital pathology systems.

CCS Concepts

• ***Computer Graphics*** → *Applications;*

1. Introduction

The field of pathology informatics has grown substantially in the last 10 years. The increasing adoption of digital pathology is leading to an evolution of the practice of the pathologists and to promising breakthroughs in quantitative imaging. As it happened in radiology, the adoption of digital systems is changing the diagnostic routine in pathology and opening new research challenges and opportunities [AJHV12, Pan10]. Because of the advent of high-throughput digital scanners, glass tissue slides can be digitized in an acquisition process that generates so-called Whole-Slide-Images (WSIs) [Hig15]. Once created, WSIs can be viewed, annotated and manipulated by the pathologist with dedicated software. In clinical settings, WSIs are used for education, consultation, and quality assurance [Hig15, SVHvD13, FGZ*17] and most recently, primary diagnosis [HPM*17]. In the research context, WSIs large availability together with the developments in Artificial Intelligence (AI) and machine learning algorithms have established a new discipline named *Computational Pathology* that involves the development of computational methods for biological feature detection and biomarker discovery [LFC*16, Mad09, ML16]. In the last years, many research approaches have been proposed for computer-aided quantitative analysis systems for tissue evaluation, nuclear morphology assessment [HBW*14, JM16, VPvDV14] and visual support for the workflow of the pathologists [CWvDvW18].

In the coming years, it is expected that more computer-aided quantitative methods will be mature enough to assist pathologists in their diagnostic process and to evolve WSI examination [BFCDGR16]. There is a growing sentiment in the pathology and medical community that the role of radiologists and pathologists will need to be central to the development of new software solutions [JT16, Fin14, ML16, DZAD17]. Pathologists are the end-users of quantitative methods in diagnostics and therefore there is the need to tune the integration of such techniques with the diagnostic practice. In the first place, pathologists are likely to employ computational methods to quickly perform tasks that are time consuming and tedious [DZAD17]. This will enable them to focus on tasks related to management of the extracted information and analysis of patient profiling together with other data sources (*e.g.*, Electronic Health Records, genomics data, radiology reports, and automated quantitative measures, molecular profiling). Later, the progress of digital pathology systems might redefine the role of pathologists (and radiologists) [TP18]. Many challenges, how-

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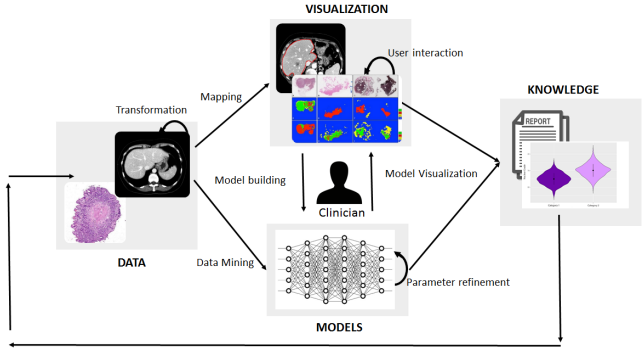

Figure 1: *The visual analytics process model conceived by Keim et al. [KAF*08] shows the deep integration between three pillars (data, models, visualization) towards the generation of knowledge. In medical imaging, this knowledge is represented by diagnostic reports or visual insights from models and output illustration.*

ever, still need to be addressed [JT16, DZAD17] to guarantee adequate integration and make effective use of AI-based analysis and quantitative image information in clinical settings. In this scenario of increasing data complexity and need for advanced diagnostics platforms, Visual Analytics (VA) can play a major role [CG15]. VA is typically described as an integral approach for decision-making by the combination of visualization, human capabilities, and data analysis [KAF*08]. Considering the characteristics of digital pathology, VA can provide more tools to achieve precision histology [DZAD17] and to assist pathologists in digital pathology platforms [Fin14, TP18]. Moreover, VA has shown significant results in addressing information overload challenges [CG15]. In this paper, we characterize digital pathology from a VA perspective, by identifying the challenges and the opportunities for employing VA techniques in the daily workflow of the pathologist. The paper is structured as follows: first, we introduce VA, the nature of pathology diagnosis, digital pathology and the significance of AI/machine learning techniques to the diagnostic process. In section 5 we distinguish WSIs from other medical images by defining four fundamental elements for VA. Next, a survey with 20 pathologists gives an overview of digital pathology practice and the main challenges that can be addressed with interactive visual analysis. Last, we propose five potential use cases to demonstrate how VA can be applied to enhance data integration in digital pathology systems.

2. Visual Analytics

Visual analytics is the field of *visualization* [WT04] that focuses on integrating and combining the strengths of human abilities for sense and decision making, with semi-automated methods for data analysis [Mun14, TM04]. In VA, the human is deeply involved in the exploration process (Fig. 1), which is steered by interaction and visualization towards the creation of some form of knowledge. In many domains, VA demonstrated to effectively support the user's reasoning to facilitate tasks towards new data insights. Among the decision-making applications, successful approaches have been shown to simplify the collection of findings [SvW08] by supporting the analytical reasoning of the user and to interactively guide the construction of decision trees to include domain-specific knowledge [vdEvW11]. These approaches may be translated to the medical domain as the integration of quantitative information and algorithmic support grows and users (pathologists and radiologists) acquire access to these techniques. Because of the increasing complexity of medical data collections [CG15], there is a strong need for VA solutions to help domain experts with novel techniques for exploration of clinical records [KPS16, ZGP14, PG13], identification of prognostic determinants in high-dimensional datasets [KPB14] and for clinical decision-making [MSS*16, VHE*16b]. By translating the VA overview of Keim *et al.* [KAF*08] to the area of medical imaging, we can depict a diagram that involves the use of digital medical images as the primary data source (Fig.1). Current medical platforms enable clinicians to digitally diagnose and researchers to review algorithm output but rarely allow to interact directly with data (and image) analysis models (*e.g.*, statistical techniques or deep learning models) to obtain new quantitative information. VA can provide a highly interactive environment where semi-automated methods can be manipulated by the users to acquire additional knowledge regarding the data source by means of derived data. Such derived data includes extracted quantitative data from AI-based and machine learning algorithms [KI18]. Typically, this data is in the form of 2D-3D spatial objects (*e.g.*, tumor cells, segmented lung volumes) that can be visualized in many ways on the digital medical images for Computer-Aided Detection (CADe) and Computer-Assisted Diagnosis (CADx). A way to manipulate this type of data has been presented by Raidou *et al.* [RvdHD*15] who presented a VA application for tumor characterization and knowledge discovery in association with clinical data. The authors showed that their VA approach promotes analysis of heterogeneous intra-tumor regions and particularly, supports hypothesis generation and confirmation.

Finally, in our adapted VA diagram, the data and the insights collected by the clinician and the image-extracted information computed by the models are integrated into some form of knowledge (*e.g.*, a diagnostic report).

To understand how VA can be effectively applied to digital pathology and thereby, handle image-based features, we investigate three common key elements for successful VA applications: a) the characteristics of the data source used, b) how targeted users work, and c) the needs of the users. The last ones are obtained by means of a survey conducted with 20 pathologists.

3. Digital Pathology and WSI characteristics

Following years of validation studies to prove the equivalence of digital pathology to microscope based pathology for primary diagnosis [WBT17, STM*16, PSH*13, GRWT17], the Food and Drug Administration (FDA) [AP17, Boy17] allowed the first vendor to market their device for primary diagnostic use in the USA in 2017. Having achieved one milestone, the next goal is to integrate image analysis methods to aid pathologists in diagnostic tasks that suffer from reproducibility and accuracy [VPvDV14, VvDJ*16]. Some are already available. An example is an image analysis-based diagnostic system that has received 510(k) clearance from the US FDA [FDA19]. Similar methods will target tedious tasks such as

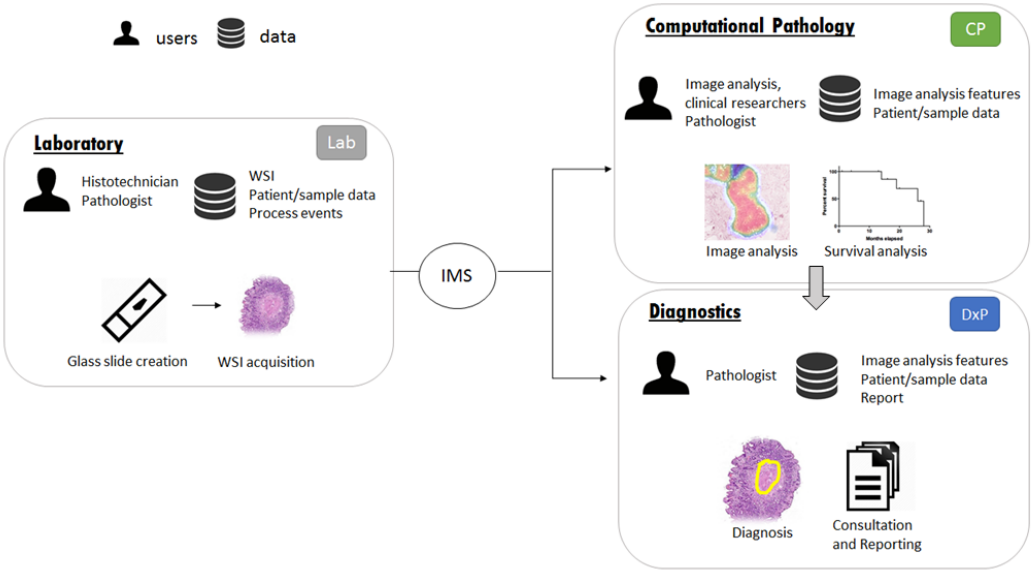

Figure 2: *Overview of three main areas where digital pathology technologies had an impact in the last decade. The workflow in the histology laboratory (Lab) has been adapted to whole-slide-imaging. The increasing digitization required technical adaptation of the Image Management Systems (IMS). Also, the availability of a vast amount of digital images boosted the field of computational pathology (CP). At the same time, the diagnostic process (DxP) is shifting to digital workstations augmented by image analysis, automated reporting, and telepathology.*

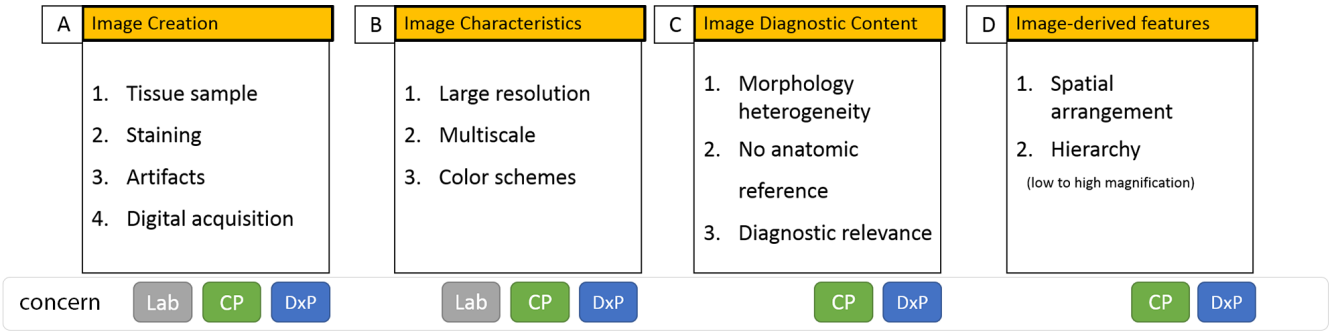

Figure 3: *A landscape of the main aspects of whole-slide-images compared to other medical images. A) a WSI is generated by surgical resection or biopsy that is fixed on a glass slide. Staining is applied and artifacts can occur. The digital acquisition consists of a scanning procedure. B) The digital slides are characterized by high resolution, multiscale view, and stain variability. C) Diagnostics deals with morphological heterogeneity and tissue architecture, absence of anatomic reference and difference in diagnostic content (high or poor), D) The derived features from image analysis are related by a spatial arrangement and belong to a hierarchy, from low magnification features (e.g., tissue region) to high magnification features (e.g., tumor cells, lymphocytes).*

detection of nuclei or calculation of percentages. Currently, support of more articulated diagnostic tasks (*e.g.*, grading steps for breast or prostate cancer) has still to be integrated into CAD systems [Fin14, CWvDvW18] even though researchers together with pathologists are collaborating to develop the necessary technological advances on future platforms [Fin14, CML16, MFMTL15].

Generally, the impact of a digital pathology system (Fig. 2) is visible in three main areas: the histological laboratory, in diagnostics and in research (Computational Pathology). In each of these settings, WSIs are central to the worflow of the users, and represent an additional sort of data that is used, shared and displayed on several platforms and in many ways.

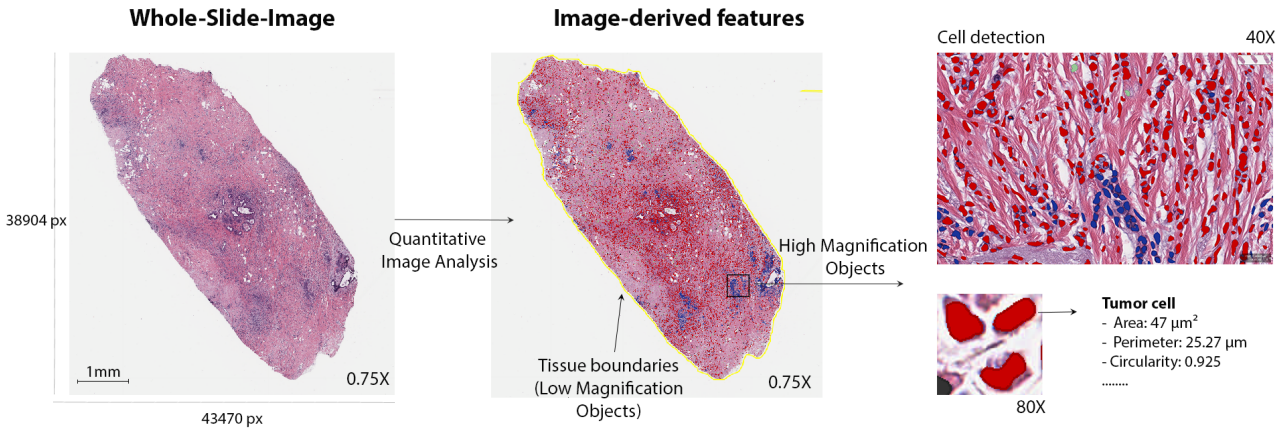

Figure 4: *An example of image-derived features. From a WSI, tissue boundaries and cell objects are detected by algorithms. For each cell object, morphological properties are computed. Pathologists may use these measurements to deliver precision diagnostics.*

WSIs have different characteristics than other medical images. We distinguish four aspects: *a) image creation, b) image characteristics, c) image diagnostics*, and *d) image-derived features*.

Image creation works differently than in radiology, in which images show portions of anatomic structures and organs of the patient's body. In fact, a WSI is generated from a tissue glass slide. This is derived from a specimen, typically a surgical resection or biopsy, which is sliced, stained and fixed on glass according to a standardized protocol [FGZ*17]. Therefore, the histological workflow remains the same, despite the introduction of digital technology [Fin14]. A major tedious task in this phase is carried out by histotechnicians who examine the glass slides manually to avoid artifacts, bubbles, or folds that would make WSI unusable for diagnostic interpretation [SVHvD13, FGZ*17, PPP12, AJHV12]. Recently, many labs have started to track tissue glass slide preparation as an additional way to oversee WSI quality [AJ13, FGZ*17, SVHvD13, BBvL*18]. Data collection can increase quickly, as in a standard digital pathology lab, the production of WSIs can reach numbers higher than 500/day, resulting in daily needed storage of hundreds of Gigabytes [SVHvD13]. WSIs present challenging *image characteristics*. WSIs can have a resolution of a hundred thousand pixels in each dimension and are built on a 40x scale. Generally, pathologists can view images up to a factor 40 magnification and interact in a similar way as with digital maps [MFMTL15]. The average file size of a 40x (0.25 um/pixel) WSI is 1-2 GB/image and the uncompressed image size is 50 GB. This is a remarkable contrast to radiology images such as a CT exam, which size is typically only 100-200 MB [YYK*12, RCL*13]. Moreover, WSI appearance depends on the glass preparation and digital acquisition. According to the applied staining, the WSI presents a specific color scheme (*e.g.*, blue to violet tones with H&E).

Once the tissue glass slide is ready and digitized, the pathologist can proceed with the examination of the *image diagnostic content*. We can discriminate WSI content from other medical images by considering three aspects. First, there is high variability in structure appearance and morphology, for instance in cell size and tissue architecture. Another aspect concerns the absence of anatomic references which is the basis of radiology examination. The last element to consider concerns the percentage of diagnostic relevance of WSIs. Pathologists spend most of their time looking at (many) slides with normal tissue or benign lesions [Fin14]. Hence, one of the envisioned goals of digital pathology is to triage slides and to focus the expertise of a pathologist on high-priority slides: abnormal tissue and aggressive tumors [SPT*13]. Because WSI is a digital duplicate of glass slides [Boy17], their real value consists in the opportunity to extract diagnostic information in novel ways [Fin14]. Quantitative image analysis (Fig.4) aims to generate a vast range of *image-derived features* that can be used to discriminate WSIs [DIO*14], prioritize cases and to make diagnosis more objective and reproducible [VPvDV14, ML16]. The detected objects such as tumor cells and lymphocytes are characterized by a spatial arrangement that can incrementally explain tumor growth and presence of tissue patterns. Cells and other biological components such as tissue regions (fat, stroma, tumor) can be seen as belonging to a hierarchy [KPSW13], where the first ones (low magnification features) interact with the others (high magnification features). The heterogeneity of tissue architecture represents another difference with radiology image analysis, where the output typically concerns the detection and the localization of a malformation in the anatomic reference. Therefore, the analysis of WSI-derived features introduces new challenges. The analysis of 2D spatial data the process of discovery of relations between biological components and correlation with clinical data can reveal new important features for diagnosis and prognosis [ML16, DZAD17, NY16, ADT*17, WCJ*18], but can be extremely tedious and difficult to obtain. After that the image analysis features are accepted and validated for clinical purposes, the combination of multiple features can support the workflow of the pathologists in dedicated CADx tools.

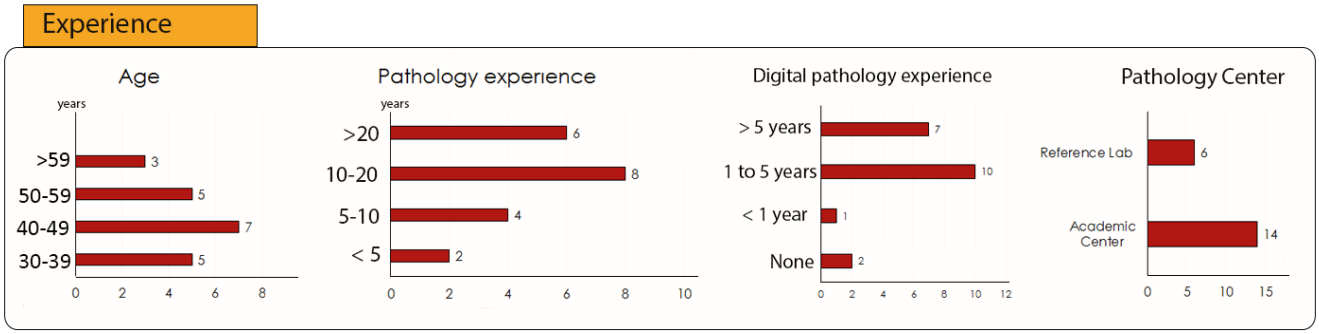

Figure 5: *View on age, pathology and digital pathology experience of participants of the survey.*

In light of this, we present the responses of a survey conducted with 20 pathologists. Differently from previously published surveys on digital pathology [WLOT18, CVC*16] that mostly focus on the adoption and future trends, we addressed the participants regarding diagnostic challenges and their expectations of technological advances from a software perspective. We want this survey to be indicative of the current digital pathology workflow and not a thorough investigation of the many facets of the technology in practice.

4. Survey

We structured the survey in a similar fashion as done in the work of Lundström *et al.* [LP11] where the authors characterize VA in radiology and medical image diagnosis in general. Participants were contacted from a total of 11 academic centers and reference laboratories from 6 countries: The Netherlands, Spain, Italy, United Kingdom, Finland, United States. A maximum of two pathologists from each site was included in the study. When we interviewed the pathologists, six labs had already a digital pathology system in place, four were going digital and four had still conventional microscopy. Figure 5 gives an overview of the main characteristics of the participants. The survey consisted of a web questionnaire, organized in five sections: experience and background, diagnostic tasks, diagnostic routine, views on digital pathology, visualization and automation. We present the results and compare the responses with the findings from the survey on VA for radiology conducted by Lundström *et al.* [LP11].

4.1. Task overview

Identification of user tasks is a primary step for successful VA applications. Hence, we collaborated with a pathologist to identify the main activities involved in the examination of a pathology case. The tasks identified were:

- To collect all the required (patient/case) information prior to doing the primary diagnostics;
- To assess staining quality and tissue slide preparation (*e.g.*, if the staining was applied in a correct way to discern tissue from cells and highlight histological patterns without artifacts);
- To plan case examination (collection of the necessary image types for the diagnosis, previous clinical data and reports);
- To identify findings relevant for the primary diagnostic conclusion (*e.g.*, Histologic Type or Architectural Patterns);
- To assess the morphology of histopathologic features (*e.g.*, how tumor cells appear in size and shape);
- To make the required measurements;
- To identify additional findings requested by the protocol
- To make a final characterization of the disease;
- To fill in the final report;
- To be efficient;

We asked participants to score the grade of difficulty for each diagnostic task on a scale from 1 to 5. We assigned 1 to not challenging and 5 to extremely challenging.
Finding #1. The global results (Fig. 6) show that pathologists consider being efficient the most challenging aspect of their work. This concern is likely as a result of time-consuming tasks such as examination of morphology of histology features (the second most challenging task) together with a work overload. Identification of additional findings requested by the protocol and also to provide the necessary measurements are seen as tasks that affect the comfort of diagnostic routine.
Finding #2. The assessment of staining quality and plan examination are considered the simplest tasks (Fig. 7). Plan examination usually requires the collection of all the necessary data sources and it follows standardized protocols. Therefore pathologists consider this step as a routine task.
Finding #3. We looked at the correlations with the answers given for the ten tasks. When a pathologist defined the morphology task as challenging he was also likely to give a high score for the other tasks involving the tissue slide examination (*e.g.*, primary findings, to collect additional findings) .
The other tasks were poorly correlated. A reason can be that diagnosis ancillary tasks such as data collection or reporting may be dependent by the characteristics and functionalities of the histology workstations, software and LIS used in the lab.

We divided the responses of the participants in two groups according to the experience in digital pathology: *more experienced* pathologists with more than 5 years experience in digital pathology (N=7) and *less experienced* in between 1 and 5 years (N=10). The three pathologists with less than one year of experience were then discarded from the comparison. In this scenario, we define digital

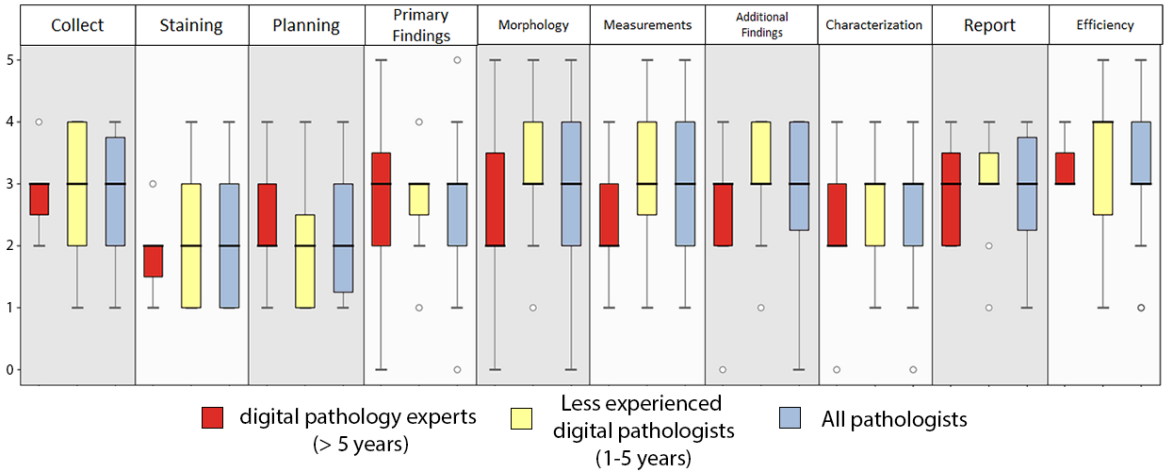

Figure 6: *Overview on diagnostic tasks. Pathologists were asked to score each task from 1 (not challenging) to 5 (highly challenging). To make measurements, morphology assessment, staining assessment and obtaining primary features seem the most variable tasks in these two groups.*

Task	Median/Range		
Most demanding Tasks	All (N=20)	Experts (N=7)	Less Experienced (N=10)
To be efficient	3 (1-5)	3 (3-4)	4 (1-5)
Morphology	3 (1-5)	2 (1-4)	3 (1-5)
Additional Findings	3 (1-4)	3 (1-4)	3 (1-4)
Measurements	3 (1-5)	2 (1-5)	3 (1-5)
Less demanding tasks	All (N=20)	Experts (N=7)	Less Experienced (N=10)
Staining	2 (1-4)	2 (1-4)	2 (1-4)
Planning	2 (1-4)	2 (1-4)	2 (1-4)

Figure 7: *Summary of the most difficult and easiest tasks according to the responses of the participants.*

pathology experience as usage of WSI systems for diagnosis and clinical research.

Finding #4. We can see that pathologists perceive the diagnosis-related tasks differently. Experienced digital pathologists find it easier to perform the typical diagnostic tasks of pathology work than their less experienced colleagues (Fig. 6). For instance, tasks such as morphology assessment, making measurements and exploring additional findings seem to be less challenging and time-consuming for digital experts. The only tasks that show a comparable difficulty in both groups are the examination of primary findings and the completion of the final report.

4.2. Diagnostic resources and usage

One of the aims of VA is to facilitate the combination of heterogeneous information from different resources in visual interfaces. We were interested in investigating which resources pathologists currently use in diagnosis. From Figure 8 we see that reference tissue slides and radiology images are rarely used at this stage. The difficulty in retrieving this material might play a role in the habits of pathologists. Well-integrated PACS systems might foster the use of available material and information of the patients as shown by Mongan *et al.* [MA18]. In this study, the authors show that the connection with an electronic medical record leads to radiologists making more use of medical notes.

Finding #5. Currently, pathologists seem to rely mostly on their own experience and only in some cases on other people's experience, even if telepathology makes remote review easier [CVC*16]. One reason can be that pathologists prefer to optimize the workflow and accelerate the sign-out for normal cases. The participants don't explicitly express the desire to use these additional resources, but they might follow a similar attitude to radiologists, especially for complex cases.

4.3. Diagnostic routine

To understand how pathologists deal with the *image characteristics* of WSIs we questioned participants on their diagnostic routine. Generally, pathologists follow protocols but have their own exploratory strategy to examine tissue slides and collect the requested information. We asked participants about the range of unexpected findings on a sample of 100 cases. We defined these as for instance uncommon locations for particular malignancies or specimen type.

Finding #6. According to the responses of the participants (Fig. 8), unexpected findings happen mostly in a range between 0-10%. Seven participants indicated a number in the range of 11%-20%. This indicates that current protocols cover most of the aspects of diagnostic examination but unexpected findings may still occur in large percentage. Nonetheless, pathology examination, contrary to radiology, relies on the exploration of large images where magnification steps are required. According to our survey, pathologists mainly make a diagnosis in a range between 5X and 20X. Five participants indicated 40X as an essential step. This is the case for breast cancer, which protocol explicitly dictates the use of this specific magnification level for mitotic counting [CAP18]. Pathologists are used to observing specific biological components at corre-

Figure 8: *Use of resources in diagnostic pathology: pathologists mostly rely on their own experience or on second opinions, previous material, literature and radiology sources are scarcely used. In routine practice pathologists examine WSIs mostly at a magnification level in a range between 5X to 20X. The number of unexpected findings is mostly in the range between 0% and 20%.*

sponding magnification levels. For instance, architectural patterns at 5X-10X; lymphocyte invasion at 10X-20X, cellular morphology and mitotic counts at 20X-40X [CWvDvW18, MFMTL15].

4.4. Automation

One section of the survey concerned the view on automatic algorithms. Since many digital pathology solutions are integrating image analysis tools, we first asked for which purposes pathologists are currently using them. Half of the participants do not use automatic algorithms for diagnostics. For the majority, the reasons are the cost of the technology. Other pathologists answered that the available tools are time-consuming and complex and then the efficiency may be affected. On the other hand, 9 participants use automatic algorithms in the diagnostic work for counting, measuring, and comparison. Most of the subjects use such algorithms for research work. Typically, the output of algorithms is displayed as overlays on top of the WSI (see Fig. 4). We asked how many cases are usually needed to get accustomed to a new type of visualization (*e.g.*, in the case of detected nuclei).

Finding #7. Seven pathologists felt confident of requiring less than 10 cases; seven more than 30 cases and five in between 10 to 30 cases. One pathologist did not provide an answer.

Finding #8. From the responses, we see that the perception of the quality of detection of specific *image derived features* to use in clinical practice is quite diverse. Generally, the expectation is that an algorithm should be reliable at a threshold of 95% accuracy for the primary source of diagnosis or for one of its components (*e.g.*, mitotic counts). First, we asked participants which grade of reliability they would expect if image analysis were provided as input for their own judgment. In this case, the pathologists seem prone to accept also lower reliability levels. Next, we asked whether their answer would change if image analysis were provided as a primary source for a diagnosis component (Fig. 10). In this case, the responses were closer to the highest threshold of 99%.

The final questions regarded automatic reporting in the diagnostic work. It usually consists of forms that are automatically filled with case information besides data collected during the diagnostic examination.

Finding #9. Eight participants do not use automatic reporting. Among the users, seven pathologists underlined that the attachment of measurements and the link with annotated regions are still weak aspects in reporting software. According to three pathologists, dictation is another aspect to be improved.

4.5. Pathology vs radiology

From previous work of Lundström *et al.* [LP11], we can extract the main findings from the field of radiology and compare them with pathology. The most difficult tasks expressed by the radiologists in the survey were: to be efficient, to make the diagnosis and to identify primary findings. Also in our survey, the participants indicated as being efficient the main challenge in their work (**Finding #1**). Differently, to make a diagnosis and to examine primary findings do not seem to concern the pathologists. However, dealing with the *image diagnostic content* to determine morphology, to assess geometries and to make measurements is seen as a tedious and challenging aspect. In the coming years, CADe support addressing these tasks may highly augment the process and increase efficiency.

Radiologists use patient data and previous material more than pathologists who rely on their own experience in 80% of cases (**Finding #5**). This may not surprise as radiology transitioned to

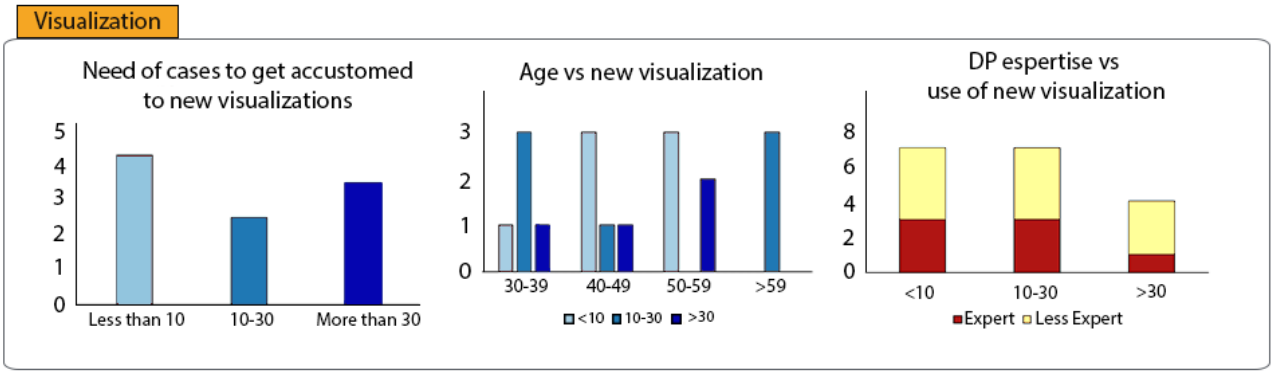

Figure 9: *Tendency of pathologists to get accustomed with new type of visualizations (e.g., overlays). Pathologists between 40 and 59 years old tend to be confident in becoming accustomed to new types of visualization in comparison to less experienced or older pathologists.*

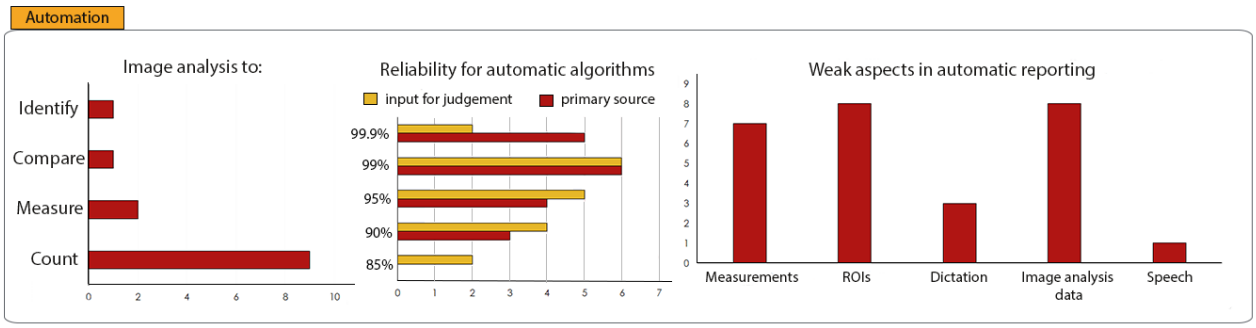

Figure 10: *Range of responses for the question which reliability for image analysis as input to diagnosis or primary source.*

digital almost 20 years ago and therefore current systems have been optimized for the retrieval and exchange of stored clinical information. For instance, a recent study [ASH*18] demonstrates that nowadays neuroradiologists access and use reports more frequently than images. A fact that may have contributed to building trust in radiology reports is a strong integration of structured digital reporting systems in the last decade [Eur11, LTPD13]. Studies show that pathologists would benefit of systems capable of retrieving similar images representing tissue patterns that are difficult to distinguish [OSA*18]. According to the responses of the radiologists, unexpected findings occur up to 60% of cases, whereas in pathology they occur in less than 30% of diagnoses (**Finding #6**). As Lundström *et al.* [LP11] mention, radiologists need to maintain an exploratory approach for all cases, in pathology about 70% of cases are routine tasks where protocol features (*e.g.*, cell morphology, tissue margins, and lymphocytes invasion) have to be examined and assessed repeatedly [VPvDV14]. From our survey, we see that pathologists are more confident in mastering a new type of image/visualization (**Finding #7**) and they consider themselves more conscious of the hardware and software capabilities of the digital pathology technology.

On the question concerning the required reliability of an automatic algorithm to be used in clinical practice, most of the radiologists answered they would expect a range between 90% and 99%. In our case, pathologists aligned on similar values (**Finding #8**), expressing more concern in the case where the automatic algorithm provides the primary source for a component of the diagnosis (*e.g.*, tumor size). Despite the survey on radiology was conducted in 2011, we can conclude that the responses are comparable in many aspects. This indicates that pathology is still at the beginning of the digital evolution. Pathologists are mostly concerned with identification of the relevant information from the tissue examination, while radiologists are careful in collecting all the necessary evidence to make a final diagnosis. At the same time, pathologists seem prepared to embrace new technologies and actively use them.

5. Data challenges and Opportunities with Visual Analytics

According to our WSI characterization (Fig.3) and the findings from our survey, we can list four data-challenges to consider to

apply VA in combination with *image-derived features* to digital pathology:

- **Data-Challenge A**. The *Image creation* process and the final WSI quality can affect the clinical workflow (*e.g.*, delays, new digitization, identification of artifacts) and algorithm output [JT16]. Despite being a simple task, pathologists and histotechnicians spend part of their time in assessing the staining quality and in defining the prioritization of the cases, Ideally, image quality information and tissue content detection should be accessible to the pathologists on lab software in the first stage after digitization.
- **Data-Challenge B**. The *image characteristics* of WSIs bring new challenges in user interaction, exploration, and visualization in medical imaging. Pathologists are used to recognizing specific colors, patterns and to examine the tissue area at particular magnifications [CWvDvW18, MFMTL15]. Therefore, it is essential to respect their cognitive/perception abilities and diagnostic strategies when additional information is integrated [CWvDvW18].
- **Data-Challenge C**. The combination of additional visualization and interaction of image analysis data on such large resolution images is hard to achieve and requires optimization of *image diagnostic content* support.
- **Data-Challenge D**. The *image-derived features* range in the number of thousands-millions features per image. Therefore, initially, it is necessary to address the needs of the pathologists (*e.g.*, protocol requirements [CAP18]) and concrete use cases (*e.g.*, most robust techniques) to gradually integrate quantitative information in the diagnostic workflow [JM16].

In this scenario, we can outline the opportunities for digital pathology and pathologists by employing VA:

- **Opportunity #1. Multidimensional data exploration:** pathologists are used to deal with multi-resolution and 2D spatial data. VA is typically built to facilitate insight discovery and data exploration in large and heterogeneous volumes of data.
- **Opportunity #2. Interactive Approach:** pathology examination is based on the dynamic examination of tissue samples. Traditionally, pathologists have been trained to collect data and insights in an interactive way which is also the common approach in VA applications.
- **Opportunity #3. Hypothesis-driven environment:** likewise radiologists, pathologists work by following protocols [CAP18] and standard decision trees to discard disease subtypes and binary classifications [DZAD17, PAF09]. Many applications show how VA can promote human reasoning and facilitate hypothesis generation and validation [vdEvW11, SvW08, TLLH13].
- **Opportunity #4 Visualization:** pathologists are trained to use their cognitive and perception capabilities to associate morphological patterns to shapes and color scales (tissue staining) which are common principles in VA and information visualization in general [KAF*08, vW05].

To make these challenges and opportunities more concrete, we present a list of use cases (Fig. 11) where VA can be beneficial for the pathologist and for the digital pathology practice.

6. Visual Analytics for Digital Pathology Practice

We focus on four main areas for employing VA in digital pathology practice: a) support for WSI quality assurance, b) advances in Image Management System (IMS), and c) quantitative imaging integration in diagnostics, and d) reporting.

6.1. WSI quality assurance

In more advanced laboratories, the process involving the creation of the glass tissue slides (tissue fixation, specimen transfer to cassettes tissue processing, sectioning, staining) and the time for issuance of pathology reports are monitored [TCSL14]. This process can be compared to a manufacturing pipeline in which the main goal is to optimize the final product by minimizing cost, time and waste. In pathology, the final product is a representative histological sample to render a definitive diagnosis. Mistakes in the process lead to a new request for sampling or biopsies [SVHvD13]. Meanwhile, the variability of image properties between different WSI scanners may highly affect the performances of computer algorithms in accuracy and precision [KCO*13].

Use Case #1. In fully digital labs, hundreds of slides are digitized per day. WSI data are tracked and this results in a vast amount of data that is arduous to monitor. We can envision dedicated VA dashboards **(Data-Challenge A)** for quality assurance. Histotechnicians and pathologists must be given an overview of the digitized slides (day, week, months), the success rate of the scanning process and the complementary information of the microscopic sections preparation (*e.g.*, sectioning and staining type). Moreover, visual analytics can be useful to show the results of algorithms to judge the quality of WSI pre-processing. For instance, the presence of artifacts such as blur [WPB*15] and tissue-folds [WKP13] may be reported and fixed, and the image tissue content (*e.g.*, % tumor tissue vs % normal tissue) could be already assessed in this stage [HLAT12]. The pathologists may already interact with the data to prioritize the slides for diagnostic assessment [LLD*12].

6.2. Image Management Systems

A digital pathology system deals with the *image characteristics* of WSIs. In the last decades, the main challenges comprised the management of large volumes of data (WSIs), PACS integration and DICOM standards that are currently maturing [MLSC17]. Performance and integration of these systems improved and new techniques are now needed to explore images and the image-derived features that will be associated with them.

Use Case #2. Biomedical informatics research strongly focused on Content-Based Image Retrieval (CBIR), an image search technique based on automatically extracted visual image features. Systems built with such functionalities [KNK*15, SDM15, ZJM*17, LWGB03, ARN*11] demonstrated to be of benefit for medical diagnosis, education and research. At the same time, VA offered a variety of approaches to facilitate the exploration and the understanding of the retrieval of similar images [KNK*15, vdCJvW16] on the basis of metadata and machine learning methods. These tools enable a guided visual exploration of the search space for new content. Many examples of medical VA and CBIR systems are present

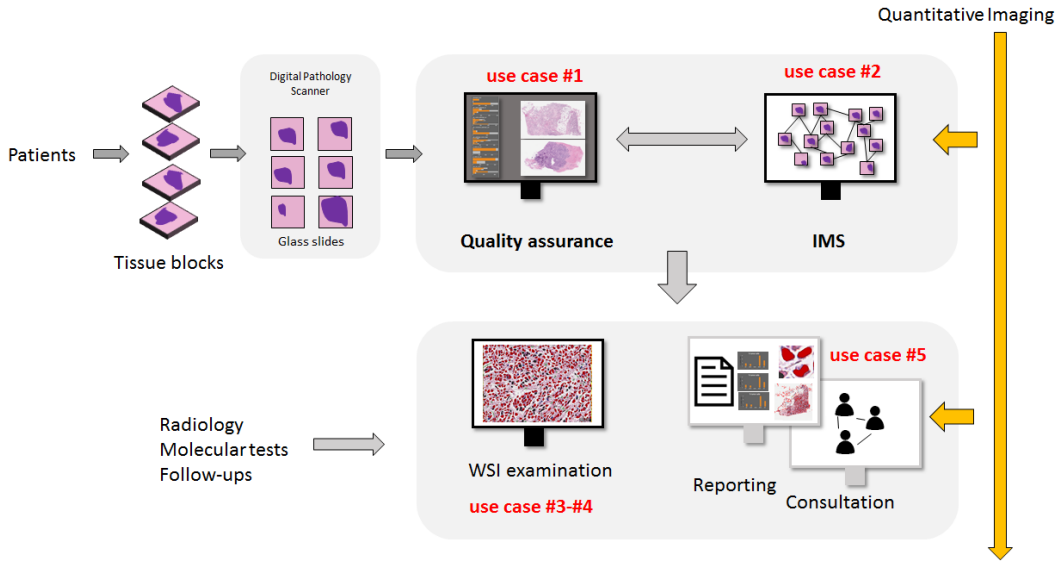

Figure 11: *A schematic view of five use cases for digital pathology practice. We envision VA applications in the quality assurance process, in the IMS to manage WSI on basis of quantitative image data and metadata and in diagnostics for integration of image analysis techniques and for communication (reporting and consultation).*

in literature, but only a few [QWR*14, SDM15, JdTOAM17] address the exploration and manipulation of large-scale histopathology images (**Data-Challenge B**). Recently, two studies addressed the challenge. The most recent work is GRAPHIE, presented by Ding *et al.* [DWHM15]. The application is a VA tool to discover potential relationships in histology image collections by interacting with tissue morphological features. A limitation is the lack of scalability of the tool but it strongly demonstrates the potential of VA for digital pathology image exploration. Previously, Marée *et al.* [MSR*13] implemented an application that enables pathologists and researchers to build histology and cytology atlases. The system is a combination of CBIR algorithms and visualization that allows the user to interact with WSIs and retrieve similar annotations based on visual content.

6.3. Visual Analytics for diagnostics

Many examples of AI/machine learning techniques [KI18, JM16] have been presented in the last years and numerous are expected to be used in routine pathology in the next generation of digital pathology systems [DZAD17]. The challenges for VA (**Data-Challenges B-C**) involve the development of suitable techniques to manipulate WSIs and to visualize image analysis features (**Data-Challenge D**) in an adequate manner, and to reduce the manual and cognitive effort of the pathologists during the examination of image diagnostic content [CGB05]. Nonetheless, transparency on the quality of WSI (**Data-Challenge A**) and image-derived features must be presented to the pathologists. This aspect falls in the domain of building CADe and CADx for trust and on the ways to improve the interaction between clinicians and automated aids [JCvO15, HMK*17].

6.3.1. Diagnosis

As discussed in Section 3, histopathology examination of *image diagnostic content* is characterized by a series of tasks that address the examination of cellular composition and tissue architecture of surgical biopsies. In diagnostics, the integration of quantitative information from AI-based/machine learning algorithms targets the subjectivity and tediousness of diagnostic interpretation to lead towards precision histology [DZAD17].

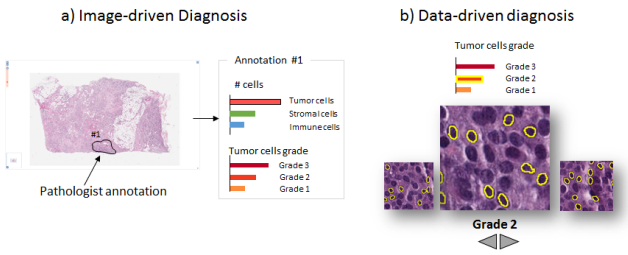

Figure 12: *Two examples for Computer-Aided quantitative analysis systems in pathology: a) a quantitative image-driven approach and a b) data-driven approach. In the first, the pathologist is supported by tissue and cellular quantification generated on request by interaction with the digital slide. In the second approach, the pathologist inspects image analysis data to triage WSI regions of interest.*

However, the quantity of computed information that can be extracted from each WSI may be nearly impossible to explore and to visualize (**Data-Challenge C**). Therefore, VA methods and a data-

driven approach can be applied to facilitate and optimize the integration of quantitative data.

To date, VA applications for digital pathology are lagging behind in comparison with radiology, where visualization techniques are routinely used for characterization, diagnosis and treatment planning. An example, already mentioned is the exploration of tumor tissue characterization [RMvE*14]. In their work, several scenarios are illustrated by using real patient data demonstrating the singularity and feasibility of such an approach in a clinical setting. In the field of magnetic resonance imaging (DCE-MRI) of the breast, Graber *et al.* [GSO*09] show a region merging method to split tumors into different regions according to different perfusion characteristics. The tool enables the user to explore tumor heterogeneity and to derive a more quantitative characterization of the lesion. Nevertheless, these studies do not take the protocol-based strategy of diagnostic work into account. In this scenario, we can envision two different diagnostic approaches: a) image-driven exploration and b) data-driven exploration (Fig. 12).

Use Case #3. In the first scenario, the pathologist interacts with tissue regions and receives quantitative information, in form of different visualizations, from the Computer Aided quantitative imaging system. An example of this strategy is given by Voglreiter *et al.* [VHE*16a] in a visualization-guided evaluation supporting radiologists in minimally invasive cancer treatment. In their work, the authors provide visual support of different parameters such as tissue temperature and tissue vulnerability by means of a texture-based iso-contour representation. The user study reveals the advantages of such a technique and that the system is applicable in medical practice.

Use Case #4. In the second diagnostic approach, the pathologist directly interacts with image analysis data, for instance matching specific protocol definitions (*e.g.* cell grade) to review relevant portions of the tissue slide. Standard techniques such as interactive bar charts and scatterplots may already empower pathologists with the necessary tools to manipulate digital images in a seamless way. In the next chapter, we present a first data-driven implementation designed in a protocol-based approach. In this work, the task analysis based on protocol routine that addresses the assessment of common diagnostic elements (*e.g.* morphology examination, cell grading). In the same way, protocol-based visualizations may facilitate the integration of image analysis data in clinical practice in other histopathology cases (*e.g.*, prostate cancer, liver).

6.3.2. Consultation, reporting and multi-site review

Digital pathology intensified and facilitated intra-departmental and remote consultation of cases [CVC*16]. Since the early adoption, streamlined navigation and review of WSI for reporting and for discussion in multi-disciplinary tumor review boards has represented the main use of digital pathology in clinical settings. Regarding the reporting stage, as pathologists responded in our survey **(Finding #9.)**, the weak points are the lack of integration of measurements and ROIs together with quantitative image analysis data. By combining this information, the practice of the pathologists would see an increase in *data provenance* along the diagnostic process. For tumor board review and consultation, VA can also play a major role to support the acquisition of findings and for better communication on dedicated interfaces.

Use Case #5. A substantial amount of research in visualization has been dedicated to the provenance of findings [RESC16] to improve the quality of insights and of the discovery process. Similarly, new consultation and reporting dashboards conveying tracked measurements and ROIs can be conceived and integrated into next digital pathology platforms. For instance, Cervin *et al.* [CML16] designed an interface to optimize the reporting workflow by automatic collection and organization of measurements. This application was successfully evaluated on standard clinical routine in breast cancer diagnosis. With the advent of image analysis, the reporting routine can be enriched by image-derived quantification and digital portions for an increased provenance of findings. Corvò *et al.* [CvDW17] designed and implemented the first reporting dashboard based on VA of image analysis data. The authors observed the diagnostic tasks characterizing the pathology diagnostic process and elicited the requirements to apply VA methods to the domain. The tool provides support for diagnosis and collection of findings in combination with a tracking component and a diagnostic trace visualization. Amabili *et al.* [AKM*18] also propose an application to diminish the information overload generated during medical imaging examination. The authors suggest an authoring and visual storytelling approach to increase knowledge gathering.

As digital pathology evolves, many more advanced solutions can be conceived with adequate task analysis and with the involvement of pathologists for diagnostics purposes.

7. Conclusion

In this work, we characterized digital pathology from a VA perspective. First, we introduced VA and we started investigating the practice of the pathologists. By interviewing 20 pathologists, we collected a list of findings that can favor VA application development. A group of pathologists was more experienced in digital pathology. This fact may add some bias in our data that at the same time led to interesting observations. We found that diagnostic tasks like morphology assessment, the collection of primary, additional findings and measurements are the most challenging tasks even if still considered manageable tasks. Overall, more experience in digital pathology software seems to reduce the perception of the needed effort. However, it is still evident that the main pressure lies on being efficient, a concern expressed by almost all participants. Furthermore, we verified that pathologists are less used to review previous resources than radiologists. This might change with the diffusion of digital pathology platforms that would facilitate access to similar cases and reports. It is noteworthy that pathologists will be more prepared than radiologists to use VA applications and to interact with data as their confidence, trust, and experience on hardware, software and visualization knowledge seems higher than in the case of radiologists in 2011.

In view of these findings, we discussed the challenges for VA to deal with WSI and image-derived data and the opportunities. We envisioned a list of VA applications that would integrate large volumes of multidimensional data, images into highly interactive platforms to perform quality assurance on WSI and algorithm output supervision. Here, also the role of histo-technicians may become central to assure WSI quality with respect to image analysis reg-

ulations and thereby, guarantee high precision and high accuracy in the diagnostic results. In general, new computational pathology algorithms can address the current pitfalls of the digital practice workflow and reduce the increasing workload. This last aspect may be addressed soon with dedicated CADe systems that will optimize the workflow of the pathologists and will increase the diagnostic confidence. More structured CADx systems will come as a consequence of the correct classification of features into malignant and benign. This would free pathologists to spend their time on more complex tasks where VA can facilitate data-driven exploration and diagnosis. Even if limited in the number of participants, we think that the presented survey covers the main aspects to apply VA to CADe/CADx. Moreover, the diagnostic patterns of the pathologists have been extensively analyzed [MFMTL15, MAS*16, BMWE17] in the last years and similar approaches can be applied to investigate the changes and accommodate the changes with quantitative analysis. This process will involve collaboration between scientists and pathologists to determine the correct discrimination to provide reliable primary sources for diagnosis that from our survey is expected to have reliability around 99%. Foreseeable Computer-Assisted digital pathology platforms will accommodate extracted quantitative information to facilitate review and to unify clinical, morphological and molecular information into diagnosis [DZAD17, TP18]. Another opportunity can be conceived in the creation of multi-site dashboards for increased provenance of findings in reporting with the integration of measurements, regions of interest, image analysis data and other medical resources. In addition, digital pathologists have familiarized with interactive visual interfaces, joysticks and other devices, and much more than physicians in the past. This will leverage the introduction and the demand of VA in new digital pathology platforms.

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