Towards a Deeper Understanding of How a Pathologist Makes a Diagnosis: Visualization of the Diagnostic Process in Histopathology

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***Abstract*—Advancements in Artificial Intelligence (AI) and Machine Learning (ML) are enabling new diagnostic capabilities. In this paper we argue that the very first step before introducing AI/ML into diagnostic workflows is a deep understanding of how pathologists work. To contribute to a deeper understanding of the diagnostic process in histopathology, we developed a visualization concept, including: (a) the sequence of the views observed by the pathologist (Observation Path), (b) the sequence of the spoken comments and statements of the pathologist (Dictation Path), (c) the underlying knowledge and experience of the pathologist (Knowledge Path), (d) information about the current phase of the diagnostic process and (e) the current magnification factor of the microscope chosen by the pathologist. We implemented the proof-of-concept prototype as HTML5/CSS3/JavaScript application.**

***Index Terms*—microscopic pathology, histopathology, diagnostic process, diagnostic path, diagnostic phases, visualization concept, workflow analysis**

I. Introduction

Traditionally, histopathologists examine glass-slides containing thin-cut tissue samples through optical microscopes. In the last years, advancements in AI/ML along with increased computational power and storage foster the field of digital pathology , enabling new diagnostic possibilities [1]. Glass slides are digitized by WSI (Whole Slide Imaging) scanners and the digital slides can be further processed via AI/ML [2], or directly examined by the pathologists on computers via virtual slide viewers [3]. Turning glass slides into digital slides brings numerous advantages [4], e.g., multiple users can view the slides simultaneously in different locations; obtaining diagnosis results from histopathology experts quicker and independent from geographic location. Bringing AI/ML into the workflows can help to improve the accuracy, reliability and efficiency of histological tests. However, for creating AI/ML solutions that can successfully augment the work of pathologists [5], it is essential to follow an integrated approach [6], and the first step of bringing AI/ML (Artificial Intelligence/Machine Learning) into digital pathology workflows is to obtain a deep understanding of the pathologists workflows.

II. Background

Currently, more and more researchers emphasize the importance of explainability in AI/ML which is the property of a system and fosters transparency and trust [7]. In contrast, causality is the extent to which an explanation of a statement to a human expert achieves a specified level of causal understanding with effectiveness, efficiency and satisfaction in a specified context of use [8], which is very similar to the concepts of usability and user experience. A detailed design, user experience and usability study for Next Generation Sequencing applications with a special focus on clinical and diagnostic settings can be found in [9]. The study is based on a data driven GUI, eye tracking methods [10], [11] and a visualisation framework parameterized by (a) the user role and experience and (b) the outcome of the patient counselling and attributes of related medical events.

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III. The Process of histopathological decision making

Each histopathological diagnosis starts with a medical question and a corresponding underlying initial hypothesis. The pathologist refines this hypothesis in an iterative process, consequently looking for known patterns in a systematic way in order to confirm, extend or reject his/her initial hypothesis. Unconsciously, the pathologist asks the question *”What is relevant?”* and zooms purposefully into the - according to his/her opinion - essential areas of the cuts. The duration and the error rate in this step vary greatly between inexperienced and experienced pathologists. Through a precise classification and quantification of selected areas in the sections, the central hypothesis is either clearly confirmed or rejected. In this case, the pathologist has to consider that the entire information of the sections is no longer taken into account, but only areas relevant to the decision are involved. It is also quite possible that one goes back to the initial hypothesis step by step and changes their strategy or consults another expert, if no statement can be made on the basis of the classifications. Finally the pathologist combines the recognized features to a diagnosis.

IV. The Visualization Concept

The first step in the course of the project was to develop a visualization concept, which takes into account all relevant aspects of the diagnostic process. Following the findings from literature research the visualization concept was based on the following elements:

- Diagnostic Path - setting the observations obtained from the video recording into context.
- Phases and milestones - providing orientation along the timeline of the diagnostic process.
- Global and focal search - indicating the pathologist’s intentions.

These three basic elements of the visualization concept are explained in more detail in the following sections.

A. The Diagnostic Path - Setting into Context the Observations Obtained from the Recorded Video

a) The Concept of the Diagnostic Path: Connecting Visual and Audio Information: For a meaningful visualization of the diagnostic process, it is essential that the visual and audio information derived from the video-recording of the diagnostic process is shown in context. To achieve this, the visualization concept developed in the course of this mini project is based on the concept of the Diagnostic Path: As described in [12], a Diagnostic Path connects the Observation Path, which is the sequence of images seen by a pathologist during his slide viewing, and the corresponding Dictation Path, which is the sequence of the pathologists oral statements regarding his findings. The time set-ups of speech and image views constitute the link between these two sequences. Schrader et al used the concept of the Diagnostic Path for the development of a storage system for annotated WSI, where single views from the WSI could be retrieved via keywords in the corresponding oral statements of the pathologists.

b) Enhancing the Diagnostic Path: Adding a Knowledge Path: Studies, such as [13] and [14], have shown that the expertise of a pathologist in microscopic diagnostics has a big influence both on the diagnostic process as well as on the final diagnosis. In order to take this aspect into account in the visualization of the diagnostic process, in the course of this project the original version of the concept of the Diagnostic Path was enhanced by adding a Knowledge Path as depicted in Fig. 1. This Knowledge Path is the sequence of experience and knowledge, which (implicitly) influences and guides the pathologists decisions during the diagnostic process.

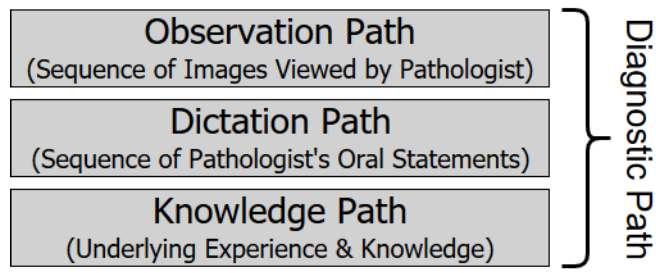

Fig. 1. The enhanced Diagnostic Path comprises of the Observation-, Dictation- and Knowledge Path.

c) Reconstructing the Elements of the Diagnostic Path from the Video Recording: The video recording of the diagnostic process shows many similarities with a ”Thinking Aloud Test”, a widely used Usability Evaluation method: Similar to the observer in a Thinking Aloud Test, who watches the activities of the test-user, the viewer of the video watches the activities of the pathologist (*Observation Path*) and simultaneously listens at the pathologist’s verbalized thoughts (*Dictation Path*). This helps to understand the pathologist’s mental models and reveals information about the pathologist’s (non-verbalized) related knowledge and experience (*Knowledge Path*). So, all elements of the Diagnostic Path can be reconstructed from the video recording of the diagnostic process.

B. Phases and Milestones in the Diagnostic Process - Providing Orientation along the Process

In [13] the authors report that a similar sequence of main milestones and achievements in the timeline of the diagnostic process could be found in all diagnostic processes they had analyzed. Crowley at al. found that the sequence of these milestones was independent from the experience level of the pathologist, although the time which was needed to achieve a certain milestone varied according to the experience level of the pathologist. According to Crowley et al., the main milestones in the diagnostic process include:

- Final statement of anatomic location
- Lesion detected
- First statement of any hypothesis
- Final diagnosis

- End of case (when final diagnosis was dictated by the pathologist)

Based on these main milestones, 4 phases can be distinguished in a diagnostic process: the Orientation Phase, the Search Phase, the Reasoning Phase, and the Closure Phase. Fig. 2 shows the sequence of these 4 phases in a diagnostic process.

Each of these 4 phases is dedicated to achieve a certain objective:

- The aim of the Orientation Phase is to get an overview of the slide's content and determine the anatomic location of the tissue sample(s) under inspection.
- The aim of the Search Phase is to find a clue for a pathologic condition / disease
- The aim of the Reasoning Phase is to develop the diagnosis.
- The aim of the Closure Phase is to state / dictate the final diagnosis in detail.

As described in [13] search, perception, and reasoning activities constitute the main components of the diagnostic task. The pathologist focuses on these activities especially during the Search Phase and the Reasoning Phase. The objectives of the 4 phases of the diagnostic process and the associated activities of the pathologist to achieve these objectives are summarized in Tab. I.

Information regarding the current phase of the diagnostic process is included as an element of the visualization concept. On the one hand this information gives orientation with respect to the current progress in the diagnostic process, and on the other hand this phase information is also an indication of the intermediate objective the pathologist is focusing on at this stage of the diagnostic process.

C. Global and Focal Search - Indicating the Pathologist's Intentions

As explained in [14] pathologists extract feature details from complex images by utilizing a global and a focal search mode. The global search mode, where the image is inspected in low resolution, reveals image content such as symmetry, color and grayscale. In the focal search mode, image details are inspected sequentially in high resolution. During the inspection of the slide the pathologist cycles between global and focal search modes. The findings from both, the global and the focal search mode, are compared with the pathologist's cognitive schema, that is information contained in the long-term memory, in order to determine for example whether or not a cell structure is physiologic.

Thus, the pathologist's choice of the microscopes magnification provides an indication of the pathologist's current intention: low resolution is characteristic for the global search mode, which is used to identify general aspects such as patterns and shapes; high resolution is characteristic for the focal search mode, which is used when the pathologist is looking for specific details in a certain area of the slide.

Information regarding the currently applied magnification factor is included in the visualization concept. On the one hand, this information is crucial for the interpretation of the visual information shown in the Observation Path, and on the other hand the magnification factor indicates whether the pathologist is currently utilizing global or focal search mode to look for general patterns and shapes or for details on cell level respectively.

Furthermore the duration of the observation concerning a specific area within the tissue has to be taken into account. Magnification factor combined with the observation period may indicate findings within the examined section that are relevant to the final diagnosis.

D. Overview of the Elements of the Visualization Concept

In order to achieve a comprehensive visualization of the diagnostic process, all information that can be derived from the video-recording of the diagnostic process was taken into account in the development of the visualization concept, as described in the previous paragraphs. As a result, the developed visualization concept for the diagnostic process in microscopic pathology comprises of the following elements:

- Observation Path (sequence of images viewed by the pathologist)
- Dictation Path (sequence of the pathologist's oral statements)
- Knowledge Path (the pathologist's underlying experience and knowledge)
- Magnification Factor (current magnification factor chosen by the pathologist)
- Diagnostic Phase (current phase of the diagnostic process)
- Observation Duration (the observation period of a certain area)

Fig. 3 gives an overview of the elements of the visualization concept for the diagnostic process in microscopic pathology.

V. Prototype Implementation of the Visualization Concept

As a next step in the course of the project, following the development of the visualization concept, a visualization prototype of the diagnostic process was implemented as a proof of concept. The prototype visualizes all available information and allows the rearrangement of certain paths.

A. Preparatory Work: Retrieving the Necessary Information from the Video

In order to derive the input data for the visualization, as a first step the pathologist's speech was transcribed from the recorded video. For the prototype implementation this was done manually. However, if the audio recording quality is high, transcription can be automated, as there are already quite mature speech to text applications available.

After transcription, the text was analyzed, and the Milestones and Phases of the Diagnostic Process were marked. Then the transcribed text was split into small, thematically related chunks, which were copied into a spreadsheet. For each of these chunks the timestamp (at the start of the chunk) was

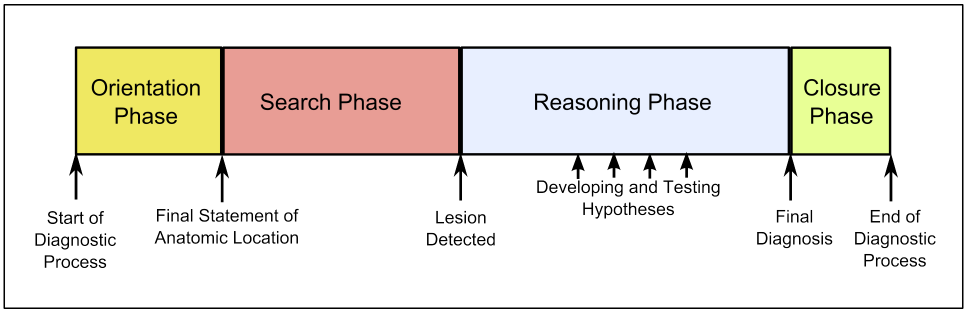

Fig. 2. The Diagnostic Process can be structured into 4 phases: Orientation-, Search-, Reasoning- and Closure Phase.

TABLE I
OBJECTIVES OF THE 4 PHASES OF THE DIAGNOSTIC PROCESS

Phase of the Diagnostic Process	**Objective(s) of this Phase**	**Activities Performed in this Phase**
Orientation Phase	(1) Get an overview of the slide's content (2) Determine the tissue sample's anatomic location	(1) Inspect the slide globally to find out the number of tissue pieces, and to get a first impression of the quality of these tissue samples (2) Find out to which organ and which part of that organ the tissue sample belongs
Search Phase	(1) Find a clue for disease	(1) Search for a lesion (abnormal damage or change in tissue)
Reasoning Phase	(1) Develop the diagnosis	(1) Develop hypothesis for disease and hypothesis for etiology (2) Test the hypotheses (3) Search for clues confirming hypothesis for etiology and reason for disease (4) Search for clues contradicting the hypothesis (5) Explore additional aspects for further refinement of diagnosis
Closure Phase	(1) State the diagnosis in detail	(1) Final summary of the diagnosis

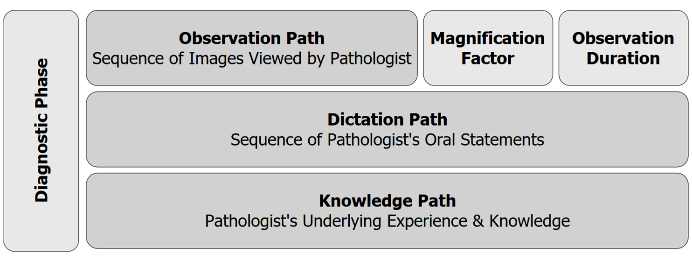

Fig. 3. Elements of the Visualization Concept for the Diagnostic Process.

retrieved from the video and added to the spreadsheet. These timestamps serve as the link between the video (Observation Path) and the text (Dictation Path). Furthermore, also the respective diagnostic phase was indicated for each text chunk in the spreadsheet. Then, these text-chunks were simplified and shortened, so that they expressed the main content of the pathologist's speech in an easy displayable and easy readable way and thus could serve as the basic elements in the visualisation of the Dictation Path. In addition, wherever applicable, notes regarding the underlying knowledge were added to the spreadsheet. These, formed the basic elements for the visualisation of the Knowledge Path.

As a final step, the information was transformed into JSON (JavaScript Object Notation) format to serve as input data for the visualization prototype. Fig. 4 shows a schematic overview of these preparatory steps for the input data of the visualization prototype, and the code snippet depicted in Fig. 5 gives an impression of the structure of the input data for the visualization prototype.

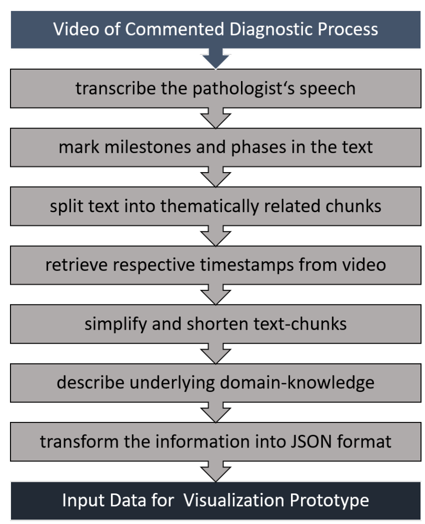

Fig. 4. Retrieving the input data for the visualization prototype from the video recording of the diagnostic process.

B. Visualization Prototype

The prototype visualization of the diagnostic process was created utilizing HTML5, CSS3, and JavaScript. Fig. 6 shows an annotated screenshot of the visualization prototype, where

```
{
   "timestamp": "01:42",
   "timestampMilliseconds": 102000,
   "diagnosticPhase": "Orientation Phase",
   "activity": "identify anatomic location",
   "dictationPath": "Man sieht hier: das ist eine
   Magenmukosa vom Antrumtyp…",
   "knowledgePath": "Domain knowledge: How do cells
   of the mucosa in the stomach look like, when seen
   through the microscope?",
   "milestone": "first statement of anatomic
   location"
 },
```

Fig. 5. Code snippet showing the structure of the input data for the visualization prototype.

all elements, which were described in the visualization concept, are marked and labeled.

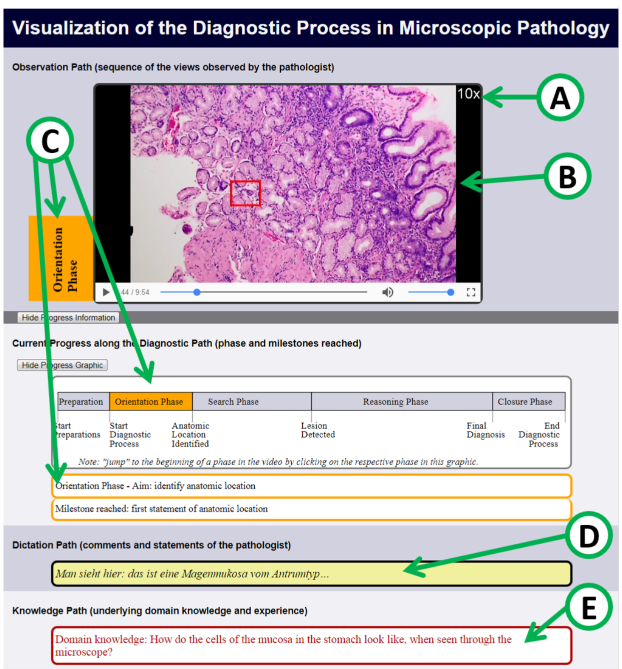

Fig. 6. Annotated Screenshot of the Implemented Visualization Prototype.

a) Functionality of the Visualization Prototype: As can be seen in Fig. 6, in the visualization prototype all elements of the visualization concept are implemented:

- The *Observation Path*, that is the sequence of the views observed by the pathologist, is realized by embedding the recorded video of the diagnostic process. (see (B) in Fig. 6) The user can start and stop the video by clicking on the respective control elements.
- In the *Dictation Path* the respective comments and statements of the pathologist, which fit to the current view of the video, are shown. (see (D) in Fig. 6) This information is linked to the time-stamp of the video and updated automatically according to the progress of the video.
- In the *Knowledge Path* the underlying domain knowledge and experience of the pathologist, which is relevant for the current view of the video, is shown. (see (E) in Fig. 6) This information is linked to the time-stamp of the video and updated automatically according to the progress of the video.
- The current *magnification factor* chosen by the pathologist is shown in the upper right corner of the video. (see (A) in Fig. 6) This information is an integral part of the embedded video.
- The current *phase of the diagnostic process* is shown in a colored field to the left of the video, and in addition a more detailed information-block regarding the current progress along the diagnostic path is shown below the embedded video. (see (C) in Fig. 6) The phase information to the left of the video as well as the information included in the graphic and the phase- and milestone-text-fields are linked to the time-stamp of the video and updated automatically. By clicking on any phase in the graphic, the user can jump to the beginning of that phase in the Observation Path, as the playing-position of the video is then set to the beginning of that phase automatically.

In order to make the visualization of the Diagnostic Path more clear and avoid an overloaded screen, or in order to adjust the visualization prototype to smaller screen sizes, the progress graphic as well as the whole progress information-block can be hidden.

C. Visualize Diagnosis Process as Video Book

Further analysis of the given diagnosis video as well as the meta information allows the visualization of decision making by highlighting ”points of interest” (POI) and customizing of their presentation by the user. For realization of the prototype the recorded video is structured into cuts and scenes, where a scene represents a specific event in decision making. The scenes are shown as paragraph and annotated in a ”Video Book” viewer [15], [16], see figure 7.

The Video Book presents single images of the recorded video in chronological order and evaluates available annotations and meta information. Each extracted image shows a POI within the slide and has therefore be considered when ”tracking decisions”. Collecting those decision points allows systematic analysis of findings. While recording a microscopic examination the pathologist provides the highlights of the slide which reduces the data amount that has to be considered for the diagnostic process (in comparison to all available data in a WSI). Meta information like the magnification factor, examination duration of a specific area as well as other information along the diagnostic process can be used for alternative presentation of those POIs: single images can be categorized by all of those aspects. The cutouts of interesting tissue area are classified and allow further approaches to better comprehension of the whole diagnosis process.

Categories enable filtering of the available images due to their relevance to a certain examination path or phase within the diagnostic process. Rearrangement of the single video images puts findings in a new context and allows a new view on a slide as the diagnostic path can be followed individually. Figure 8 shows a rearrangement of the single images by high magnification which allow the assumption that those areas mark tissue features which are relevant for the final diagnosis.

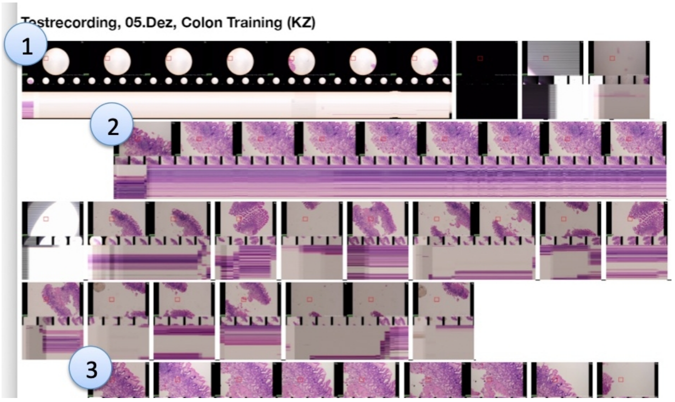

Fig. 7. Structure of the recorded video, each items represents a cut, a paragraph denotes one event in the decision making.

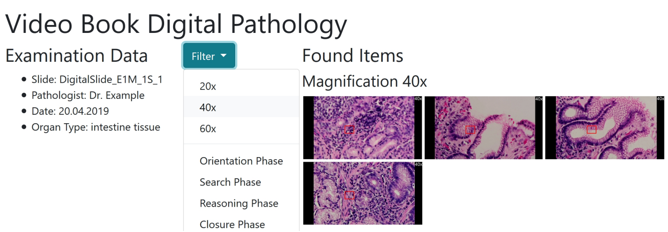

Fig. 8. Single images rearranged according to the magnification 40x.

VI. Conclusion

In the course of this project a concept for the visualization of the diagnostic process in microscopic pathology was developed, and a proof of concept prototype implementation of the visualization of the diagnostic process was created.

For this prototype implementation the input data was retrieved from the video recording manually. However, for future implementations of such a visualization tool, retrieval of the input data from video recording could be partially automated, at least as far as the transcription of the spoken comments of the pathologist is concerned.

Furthermore, for future implementations of such a visualization tool, the target group for this application should be defined more clearly, and usability evaluation of the visualization tool with test-users from the target group should help to adjust the application to the needs of the (future) users.

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References

[1] A. B. Levine, C. Schlosser, J. Grewal, R. Coope, S. J. Jones, and S. Yip, "Rise of the Machines: Advances in Deep Learning for Cancer Diagnosis," Trends in cancer, 2019. 10.1016/j.trecan.2019.02.002.

[2] S. T. Wong, "The Adoption of Artificial Intelligence in Cancer Pathology and Imaging," in Cancer and Society: Springer, 2019, pp. 113-120, 0.1007/978-3-030-05855-5-8A.

[3] N. Farahani, A. V. Parwani, and L. Pantanowitz, "Whole slide imaging in pathology: advanteges, limitations, and emerging perspectives," Pathology and Laboratory Medicine International, vol. 2015:7 , pp. 23-33, June 2015.

[4] A. Huisman, A. Looijen, S. M. van den Brink, and P. J. van Diest, "Creation of a fully digital pathology slide archive by high-volume tissue slide scanning," Human pathology, vol. 41, no. 5, pp. 751-757, 2010. 10.1016/j.humpath.2009.08.026.

[5] A. Holzinger, B. Malle, P. Kieseberg, P. M. Roth, H. Müller, R. Reihs, and K. Zatloukal, Towards the Augmented Pathologist: Challenges of Explainable-AI in Digital Pathology, arXiv:1712.06657, 2017.

[6] A. Holzinger, B. Malle, P. Kieseberg, P. M. Roth, H. Müller, R. Reihs, and K. Zatloukal, "Machine Learning and Knowledge Extraction in Digital Pathology needs an integrative approach," Towards Integrative Machine Learning and Knowledge Extraction, Springer Lecture Notes in Artificial Intelligence Volume LNAI 10344, pp. 13-50, Cham: Springer, 2017.

[7] Holzinger, A., and Biemann, C., and Pattichis, Constantinos S. and Kell, Douglas B., "What do we need to build explainable AI systems for the medical domain?", CoRR,vol. abs/1712.09923, 2017.

[8] A. Holzinger, G. Langs, H. Denk, K. Zatloukal, and H. Müller, "Causability and Explainability of AI in Medicine," Wiley Interdisciplinary Reviews: Data Mining and Knowledge Discovery, 2019. 10.1002/widm.1312

[9] H. Müller, R. Reihs, A. E. Posch, A. Kremer, D. Ulrich, and K. Zatloukal, "Data driven GUI design and visualization for a NGS based clinical decision support system", in 2016 20th International Conference Information Visualisation (IV), IEEE, [Available:] https://doi.org/10.1109/iv.2016.79, 2016

[10] M. Pivec, A. Preis, V. Garcia-Barrios, C. ütl, H. Müller, C.Trummer, F. Mödritscher, "Adaptive Knowledge Transfer in E-Learning Settings on the Basis of Eye Tracking and Dynamic Background Library", Proceedings of EDEN 2004 Annual Conference, 2004.

[11] A. Preis, H. Müller, "Eye Tracking in Usability Research & Consulting: What Do the Eyes Reveal about Websites & their Users", European Congress of Psychology: Psychology in Dialogue with Related Disciplines, 2003.

[12] T. Schrader, S. Niepage, T. Leutold, K. Saeger, K. Schluns, P. Hufnagl, et al. "The diagnostic path, a useful visualisation tool in virtual microscopy," Diagnostic Pathology 2006, I:40, 2006.

[13] R. Crowley, G. J. Naus, J. Stewart, C. P. Friedman, "Development of Visual Diagnostic Expertise in Pathology: An Information-processing Study," Journal of the American Medical Informatics Association, vol. 10, Number 1 , pp. 39-51, Jan/Feb 2003.

[14] E. A. Krupinski, A. A. Tillack, L. Richter, J. T. Henderson, A. K. Bhattacharyya, K. M. Scott, et al. "Eye-movement study and human performance using telepathology virtual slides. Implications for medical education and differences with experience," Human Pathology 37, pp. 1543-1556, 2006.

[15] Heimo Müller, Ed Tan, "Movie maps", International Conference on Information Visualization, 1999

[16] Herwig Rehatschek, Heimo Müller, "A Generic Annotation Model for Video Databases",Visual Information and Information Systems, pp. 383–390, Springer Berlin Heidelberg, 1999