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Survey Paper

A Survey on Multi Modal Fusion for Histopathology Image Analysis

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Abstract: - For centuries, histopathology has gained a remarkable place in the medical field. The disciplines of histopathology have witnessed outstanding advancements in microscopic technologies. The interpretation of traditional histopathological images by pathologists presents several challenges: high inter-observer variability, stain variability and artifacts, and complexity of tissue microenvironments. The appearance of digital scanners has converted conventional histopathology into computational pathology (CPath) by providing Whole Slide Images (WSIs). CPath tackles the complexity and limitations inherent in conventional histopathological images. The digital histopathology imaging offers a new frontier for the integration of artificial intelligence in WSIs analysis. Deep learning-based approaches have been explored for the automated analysis of digital histopathological images. Notably, these approaches have been performed for tumor classification, and prognosis prediction. However, relying solely on histopathological images may not provide a comprehensive understanding of the disease mechanisms. Several studies have highlighted the potential benefits of combining histopathological images with multimodalities data distinguishing between intra-modalities and inter-modalities to enhance diagnostic accuracy and disease prediction. Multi-modal fusion integrates histopathology images with genomic, clinical, or radiological data to improve diagnostic and prognostic models. Specifically, neural networks represent and combine histopathological images and transcriptomic data into deep survival layer for prognosis prediction. This paper describes the history of histopathology and its complexity which is a challenge in interpreting clinical cases. This review offers a thorough overview of deep learning-driven multi-modal approaches in histopathology, highlighting how they might enhance prognostic modeling and diagnostic precision. Future research should concentrate on optimizing data fusion methods and guaranteeing the clinical applicability of AI models.

Keywords- Histopathology, WSIs, Inter-modalities, Intra-modalities, Multi-modal Fusion, IA systems.

1. Introduction

The medical domain is considered an appropriate environment for applied work in the discipline of decision-making. Indeed, this is explained by the increasing evolution of medical data handled daily with various modalities. Within this field, histology plays a core role by offering primary insights into tissue morphology and pathology, supporting data-driven clinical assessment. Histology's rich history, originating with simple microscopy, has progressed into advanced imaging tools. Digital microscopy, which incorporates optical methods with digital technology to enable real-time image acquisition, improved processing, and increased sensitivity, has emerged as

a solution to traditional microscopy's depth of field and magnification limitations, even though traditional microscopy offers useful diagnostic insight into cellular biology.

This innovation has enabled the incorporation of advanced AI algorithms such as full convolution neural network, generative adversarial network, long short-term Memory, recurrent neural networks, AlexNet, LeNet, and Holistically Nested Network in histopathology [87]. This integration has positive impacts such as increased diagnostic accuracy, more standard diagnostics, and grading of tumors, and increased complexity, completeness, and quality of clinical reports. Several scientific papers highlight the use of machine learning and AI approaches in medical histology applications, for instance identification of mitosis in breast cancer, automatic measurement of HRE2 gene amplification, classification of benign and malignant tumors, association between various immune cell populations [57].

WSIs provide complex and heterogeneous histopathologic phenotypes (cell level, tissue level, and phenotype level) that present a part of the trajectory of illness progression. Hence, they offer only a portion of information for a comprehensive understanding of disease. For instance, for cancer tumors, WSIs are unlimited to provide an overview of tumor biology which with Whole slide Images.

Indeed, the diagnosis of cancerous tumors such as breast cancer, ovarian cancer, etc. requires molecular alterations that involve changes in proteins, cellular pathways, deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA). This observation explains the importance given in the literature to the analysis of histological images with the integration of multi-omic data such as proteomics, metabolomics, transcriptomics and epigenomics. Furthermore, the analysis of radiomics imaging may provide additional insights into conventional tissue biopsy [8]. This fact has sparked growing interest in the idea of merging multiple data sources to improve the diagnosis of histological images.

Recently, several studies have focused on pathomics with radiomics for cancer prognosis. These papers have explored the correlations between histopathological images that provide micro scale details and radiological images that offer the macro scale information to analyze the tumor heterogeneity [41]. By aggregating these approaches, we can improve diagnostic accuracy and enhance the characterization of tumors, addressing the challenges posed by their various histological features and clinical behaviors.

In literature, multi-source models that combine histology images and genomic data, histology images and radiomics data or multi-modal algorithms that integrate multi-stains, or multi-magnifications WSI or both simultaneously offer more complete insights than an independent one-modality histology diagnostic. Consequently, the employment of histology, genomics, and radiomics fusion methods has resulted in the development of machine learning and deep learning algorithms that have been implemented in precision medicine. With an emphasis on both inter-modality and intra-modality differences, this paper examines the development in deep learning and machine learning methods for WSIs analysis. By automating the examination of WSIs, it highlights attention to deep learning models in the literature that strengthen pathology diagnostic efficiency and accuracy.

To support research in proposing new frameworks or improvements to current approaches, this study synthesizes the body of literature on deep learning applications in WSIs analysis and multi-fusion models. This could involve pointing out areas where existing research is offering best practices for successfully applying these strategies. This guidance is essential for promoting innovation in computational pathology and related disciplines. Highlighting the interdisciplinary nature of these technologies encourage collaboration between biologists, medical professionals and computer scientists. This is kind of cooperation is essential for converting theoretical advancements into practical clinical applications.

Hence, this review is organized as follows:

Section ”2” describes the history of histopathological imaging and how the emergence of digital scanning technologies has increased the adoption of artificial intelligence (AI) in histopathology analysis, and it underscores the importance of magnification levels for enhancing histopathological images analysis. It highlights also the significance of different stains in histology for elucidating tissue architecture.

Section ”3” emphasizes the critical role of multi-magnification models for interpretation WSIs.

Section ”4” illustrates deep learning multi-stains models for diagnosis WSIs.

The section ”5” underscores the deep learning and machine learning algorithms presented in the recent literature for combination histology imaging with genomics data.

Section ”6” demonstrates multi-fusion modals for incorporating WSIs and radiomics data.

Section ”7” reviews the papers that combine histopathology images with radiomics and genomics data simultaneously using deep learning techniques.

Finally, we discuss and present our future perspectives in the next works.

2. History and evolution of histopathology in medical imaging and the influence of artificial intelligence in modern pathology

2.1 Principals of histology imaging

Histology, the ex-vivo imaging modality, is an important field of biology that studies cell anatomy and normal tissue at a microscopic level. Histology has its origins from the composition of the Greek root words “histos (tissues) and logos (research)”. Histology first appeared in the 17th century through the work of scientist Marie François Xavier Bichat known as “the father of modern histology”. Bichat’s research

includes analyzing 21 different specimens by dissection, that is, without using a microscope [44]. In 19th-century, the German physiologist and anatomist, Johannes Peter Müller has worked in the integration of histology into medicine. He has underlined the importance of comprehending the microscopic architecture of tissues in relation to their physiological functions and roles in pathology. Hence, it enables the histology field to be a core of pathology diagnosis.

Histology has a long and fascinating history, beginning with observations under a conventional microscope and progressing to advanced imaging techniques used today. Traditional optical microscopes had limits, particularly in context of depth of field and magnification, which resulted in fuzzy images at higher magnifications. To overcome this, digital microscopes were introduced. This innovation has enabled the digitization of specimen slides, which can now be examined on computers, increasing the accuracy of histological examination. On account of new advancements in imaging technology for instance the late appearance of whole slide computerized scanners, histopathology has been converted to digital pathology (DP). DP's cornerstone lies in providing a digital replica of the histological slide designated as a Whole slide image (WSI) [27].

Recently, a significant number of articles use histopathology instead of histology. The concept of histopathology and histology are interconnected because it is important to initially analyze normal tissues to create a baseline for detecting structural aberrations. Understanding the complex architecture and function of normal tissues lays the foundation for diagnostic and identification of abnormalities that contribute to disease and tumor growth. Understanding what constitutes 'normal' tissue allows for more efficient detection of pathological alterations, making it a crucial step in disease analysis and treatment [51]. Indeed, histopathology examines microscopic samples to observe cellular morphology based on the arrangement of cells and background extracellular material. This process aims to identify cell types, including normal or abnormal types, to detect cellular abnormalities namely shape, size, color and organization. Also, it aims to diagnose cancer growth and tumor features for instance tumor subtype, growth, margins, invasion into neighboring tissues, grade and stage. That said while accentuating the difficulty of the medical diagnostic process, particularly when pathologists diagnose hundreds of thousands of cells in each sample [9].

WSIs can be viewed at high and low magnifications and from different angles and planes like the navigation in Google Maps [49]. The WSIs have been saved as a pyramid structure. This pyramidal structure consists of many layers of the same image, each with a different magnification factor. The base level (level 0) includes the highest magnified slide, whereas succeeding levels contain down sampled versions of that image [50]. While magnifying histopathological slides enables histopathologists to visualize cellular components, tissue architecture, and other fine-grained details that are essential for accurate diagnosis, the ability to appropriately interpret these structures is partly dependent on the staining procedures used. Actually, to highlight different biological structures in tissue sections, stains are frequently used to modify the colors of specific tissue components to contrast with those located next to or in contact with them.

The 19th and 20th centuries were productive in the context of developing new staining techniques in histopathology. There were various histology dyes to choose from, and selection was according to the type of specimen to be examined. Furthermore, the story of stains has started with Prussian blue, the first stain, which was introduced in 1774. In the modern area of histology, the Hematoxylin and Eosin H&E staining technique which was first discussed in 1875–1878, is commonly used in light microscopy [27]. Furthermore, the employment of various stains allows pathologists to diagnose tissues and cells for the first time under light microscopy and distinguish between their architecture. As a result, pathologists can diagnose sickness by observing morphological changes in cells or identifying pathogenic agents in tissue samples with the naked eye.

The sheer size of digital pathology images, often several terabytes for uncompressed whole-slide images, poses significant computational issues. Furthermore, the heterogeneity in tissue staining, which is vital for providing the necessary color and contrast in the slide, is also a critical source of complexity. Tissue staining can vary depending on the type of tissue and the specific components being analyzed, with a range of staining techniques employed. Another important factor contributing to the variability in histopathology is the magnification factor used during imaging, which can also influence the diversity analysis and diagnostic capabilities. Different magnification levels bring complexity and variety, which can provide considerable issues. Magnification can add complication since the increased degree of detail makes it more difficult for histopathologists to manually analyze and understand the images. This intricacy is exacerbated by the vast volume of digital whole-slide images generated in current pathology practice, which can be prohibitively time-consuming to manually analyze. Therefore, this variability and complexity make manual histopathology analysis limited since many histopathological features are difficult for the human visual system to examine and understand.

Manual analysis in histopathology has shown significant diversity and errors. One of the fundamental sources of errors in disease diagnosis based on histopathology is the subjective character of human evaluation. Pathologists might analyze the same sample differently depending on their experience, training, and prejudices. This might cause discrepancies in diagnosis, especially in complicated or confusing cases. Hence, variability in the visual inspection of histopathology images is a well-known issue. Both inter- and intra-observer variability may have a major influence on image diagnosis [29]. Numerous papers have found high rates of diagnostic error due to significant disagreement among clinicians and the pathology community on case target diagnoses.

To address these challenges, researchers have explored the

use of deep learning and IA and other advanced computational techniques to assist in the analysis of histopathological images. WSIs provide a platform to employ computer vision to introduce a certain level of objectivity to diagnosis. Computer vision solutions would be extremely useful in modern histopathology diagnostics. AI algorithms may be trained to interpret digital pathology images in a consistent and objective manner, mitigating the influence of human variability. Hence, digital tissue histopathology slides can be integrated into medical artificial intelligence systems, known as computational pathology which was introduced in 2011 [6]. Digital pathology has been integrated into the studies and research in the pathological anatomy laboratories. The approaches based on machine learning and deep learning algorithms to comprehend digital histopathological images, improve the histology details provided to histopathologists resulting in much higher consistency and precision than standard optical microscopy [49].

Digital pathology combined with IA systems demonstrates robustness in addressing significant challenges in pathological analysis medicine. It permits the essentially automated diagnosis of large histological pictures. It can detect unusual cell types despite a lack of labeled data. Pathologists and medical professionals can run any of these algorithms efficiently on large WSIs. AI research in histopathology began in the 1960s, with the analysis of cell pictures to diagnose diseases. Over the last decade, computational pathology (CPATH) has advanced significantly. Early AI models, such as convolutional neural networks (CNNs), analyzed small sections of WSIs to perform tasks such as mitotic counting. As technology advanced, increasingly sophisticated models were developed to evaluate complete WSIs, resulting in applications such as breast cancer segmentation, glioma classification, non-alcoholic fatty liver disease assessment, and prostate cancer detection. Along with these developments, the complexity of AI jobs and the availability of huge datasets have increased, stretching the limits of what AI can do in histology [76]. The integration of AI into digital pathology workflows can take various forms. In summary, modern histology applications in the medical field include detecting tumors, tumor grading, mitosis detection, segmenting images, counting cells and study of kidney transplant biopsies, [76].

Examining histopathological images from a single modality, such as one stain or magnification, with AI systems is a limiting technique in histology. Combining multi-stain histology images and multi-magnification WSIs help to maximize the volume of information available for understanding and diagnosing illnesses. Furthermore, relying exclusively on histopathological images is insufficient for a comprehensive diagnosis, incorporating incremental data modalities such as genomes and radiomics is critical for capturing disease complexity and improving diagnostic accuracy. Actually, the cancer research community has long recognized the importance of merging multiple data types, such as radiography, multi-modalities in histology, genomes, proteomics, and clinical records, to increase diagnosis and treatment accuracy and dependability. In the context of histology, integrating morphological and molecular information from genomics can provide a more comprehensive view of the tumor microenvironment. The "pathomic fusion" approach can use deep learning to create image-omic assays for early diagnosis, prognosis, patient stratification, survival prediction, and assessing therapy response and resistance [81].

This review paper categorizes fusion techniques in histopathology into various groups: multi-stain WSIs fusion, multi-magnification histopathological image fusion, integration of virtual histopathological slides with genomics data, fusion of WSIs with radiomics, and comprehensive fusion of WSIs with both radiomics and genomics.

2.2 Multi staining modalities used for improved visualization in histology and histopathology

In the histopathology tissue preparations, the objects of interest in the tissue, for instance nuclei and cytoplasma are needed to be dyed with different types of stains [78]. Each stain binds to specific cellular structures as it is illustrated in Figure 1. The color reaction of a dye may diverge across tissue architecture. The most common laboratory dyes used in the staining protocol is Hematoxylin and Eosin (H&E). It has been widely implemented as a fundamental tool for the assessment of diseases and understanding biological processes by examining cellular arrangements and tissue morphological alterations. Indeed, H&E has been employed, for over a century for determining tumor shape and architecture, cell types and their morphological features, invasion, and mitotic activity which reveals information about the tumor's proliferative rate, and tumor grade [2].

Fischer [18] elucidates the color response of H&E across a range of cytoplasmic, nuclear, and extracellular matrix characteristics. Hematoxylin is a deep blue-purple dye that stains components of cells known as nucleic acids whereas Eosin stains proteins in shades of pink. H&E staining shows the way nucleic acids are condensed in the nucleus. H&E staining reveals variations in how nucleic acids are condensed in the nucleus across different types of cells, which is critical for diagnosing illnesses such as cancer. Small components of the nucleus, called nucleoli, are stained pink by Eosin. However, some components of the tissue such as collagen and elastin fibers are not stained well with H&E stains. Hence, special stains Picro Sirius Red (PSR) and Verhoeff van Gieson (EVG) are used to observe these specific components. Thus, for a complete understanding of tissue compositions in carotid atherosclerotic plaques, it is impractical to perform multiple stains on the same atheroma tissue section [86]. Therefore, special stains are utilized to recognize specific microorganisms such parasites or bacteria, nucleic acid minerals, lipids, carbohydrates, mucosubstances as well as connective tissues [70].

Table 1 provides a comprehensive review of numerous special dyes employed in histologic protocols in laboratory settings, detailing the specific histologic characteristics they

target and the corresponding color responses they exhibit.

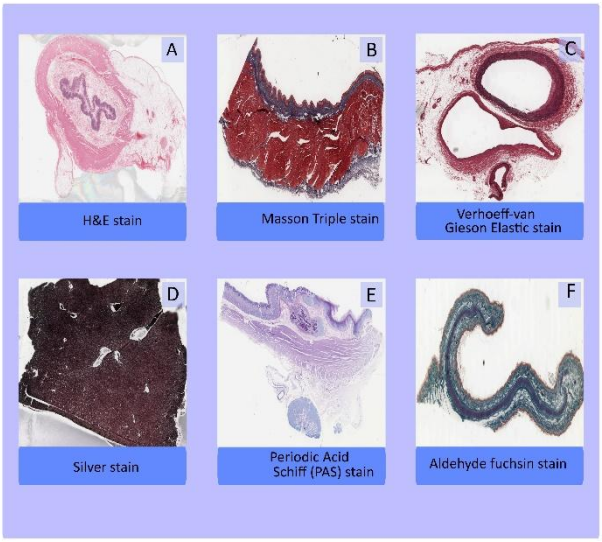

Fig 1. Images from "A" to "F" illustrate different dyes used in histology to highlight various tissues. the slides are download from the michigan histology collection available on [1] : A- histological section tissue of the small intestine stained with h&e. B- histological section tissue of oral pharynx stained with masson triple or trichrome stain. C- histological section of artery and vein stained with verhoeff-van gieson elastic stain. d- reticular fibers in the space of disse in the liver stained with silver. E- histological section of gastro-esophageal junction stained with periodic acid schiff (PAS) stain dye with azure, blue counterstain. F- Histological stain of ear pinna stained with aldehyde fuchsin which is a deep purple stain [45].

TABLE 1. An overview of histopathological stains and their architectural tissue highlight

Reference Paper	**Stain**	**Histological features**	**Color Response**
[70]	Periodic acid Schiff (PAS)	Carbohydrates. The PAS recognizes the presence of carbohydrates in different substances such as neutral mucoprotein, basement membrane, fungi glycogen, glycoprotein, cerebrosides, and phosphorylated sugar.	The tissue stained with PAS exhibits shades of purple and magenta, suggesting a positive result, while the nuclei look blue
	Alcian Blue	Hyaluronic acid, sialomucin, proteoglycansthe and the nucleus.	Alcian Blue stains Hyaluronic acid, sialomucin, proteoglycans in blue, and the nucleus in red.
	The Mucicarmine Technique	Acidic mucins	Acidic mucins are stained in pink or red color by the Mucicarmine dye.
	Combined Alcian blue-PAS method.	The micro-organisms that are highlighted are mucin such as the respiratory digestive tracts	Neural mucin will be dyed red.
	Feulgen Stain	The nuclear morphology and ploidy of cancer cells	Feulgan stains DNA in red-purple and the cytoplasm in green
	Methyl Green pyronin Method	Methyl Green pyronin Method stains DNA in green-blue color and RNA in red color.	DNA, RNA, mucins, and cartilage in tissue samples.
	Ziehl Nielsen ZN stain.	Mycobacterium	ZN stains mycobacterium in red color and background in pale blue
	GMS Gomori methenamine silver nitrate	Pneumocystis and fungi, melanin mucin andglycogen	GMS stains pneumocystis fungi and melanin in black color. It stains the mucin and glycogen in dark grey whereas the background in pale green.
	Masson's Trichrome Technique	Nuclei, RBC, muscle, cytoplasm	Masson's Trichrome stains nuclei, RBC, in blue or black, muscle in red color and cytoplasm in yellow color
[53]	Gram staining	The Gram technique distinguishes between Gram positive and Gram negative. It stains the cells into red (Gram-negative) or violet (Grampositive)	Grain staining identifies essentially organisms causing pneumonia. Also, Gram dye provides an overviewof the morphology and organization of bacteria. It is also utilized to detect various fungi and parasites
[64]	Congo Red	Amyloid	Under polarized light, CongoRed stains amyloid in green color
	Van Gieson Method	It is used to distinct between the structures of smooth muscle and collagen fibres. Also, it highlights collagen increase in the tissues	Van Gieson stains the collagen in red color

[1] histology.medicine.umich.edu/resources/introduction-histology-stains

2.3 Improving histopathological insights: the critical need for different magnification factors

Under a microscope, the pathologist examines the specimens at different levels of magnification to differentiate benign from malignant and to extract the distinctive cell features. Magnification levels are classified as low, medium, high. Magnification varies from 2x to 10x for low power, 10x to 40x for medium power, and 40x to 400x for high power [3]. Indeed, every magnification factor provides some pieces of histopathology information. Particularly, the expert switches between different magnifications to find the optimized magnification factor at which he identifies the presence or absence of malignant tissues is important [83].

In a diagnostic process, pathologists usually start with low magnification to identify regions of interest such as vessels, blood, connective tissue or muscle fibers and contribute to the preliminary analysis. Then, they switch to higher magnification to emphasize further details about the cell nucleus and the intra- and extra- matrix [46].

Basically, digital scanners use multiple magnification factors (2X, 10X, 20X, 40X and 100X) to increase the proportion of biological structures from pixel to object and tissue levels, thus enabling a comprehensive analysis of tissue structures. The whole slide image is very large, and we can consider each image as a collection of tens of thousands or hundreds of thousands of smaller images. The whole slide images are stored as a multi-resolution pyramid where the microscopic image series are structured at different levels of magnifications as shown in the Figure 2. Therefore, this structure allows the pathologist to dynamically visualize, navigate and magnify specific areas through the computer screen without compromising the overall context of the sample. Furthermore, fine microscopic features that were hidden at the original magnification might nonetheless be revealed at digital magnifications higher than those used for digitizing. Lower magnification allows the assessment and analysis of glandular and tissue context, including architectural patterns, while higher magnification reveals more detailed cellular components such as nuclei and cytoplasm [60], [79]. tissue at different magnifications from 40X to 200X structured in WSI's multi-resolution pyramid available in the dataset the Breast Cancer Histopathological 2

3. Multi-stains WSIs approaches implemented in computational pathology

Recent research on staining modalities in histopathology emphasizes the use of multiple stains to highlight different architectures and complex compositions of biological tissues. This complexity makes it difficult to fully capture relevant information using a single staining technique. For instance, three distinct stains HE, PAS, and Sirius red are applied jointly to dye virtual esophagus tissue by FCS for inspection of possible morphological modification [38]. Therefore, it is essential to apply multiple staining techniques to different sections of the same tissue sample to correctly examine and interpret the histological sample. Consequently, this "multiple stain fusion" approach is implemented in deep learning algorithms for the global analysis of histopathological images.

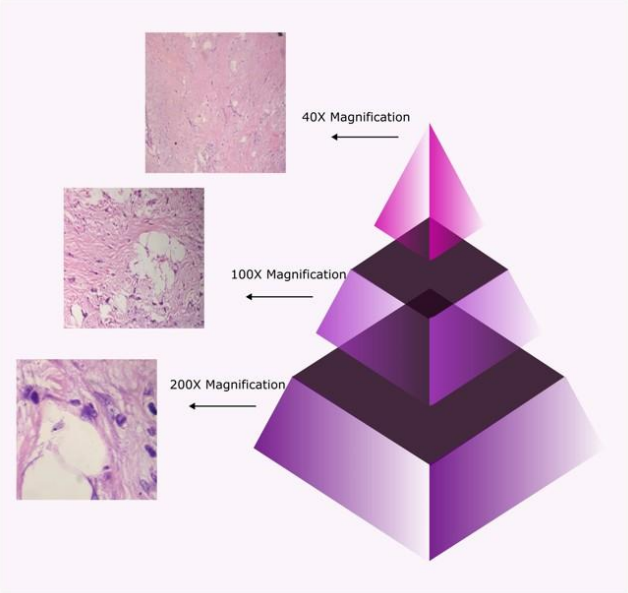

Fig 2. Malignant microscopic images of breast tumor

In this section, we propose a review of the combination of multiple modalities, where each modality represents a distinct staining technique applied to the same tissue section. The implementation of a multi-stain approach in the most automated histopathology image analysis has demonstrated promising results, particularly in segmentation, classification, and object detection tasks that aid in clinical diagnosis, patient classification, prognosis, treatment response, survival prediction, and biomarker identification. For example, segmentation is the process of partitioning histological slides into two categories of structures of interest for the regions or objects of the pathological community. Therefore, regions are homogeneous areas derived by segmentation based on similar features such as shape, size, and color in histopathological images. Thus, the partitioning of objects resulting from segmentation aims to detect objects such as gland and cells in the histological image [75].

Many articles illustrate different histological segmentation approaches in histology, such as cell segmentation, gland segmentation, and epithelial tissue segmentation [13]. In this context, the paper [48] presents the essence of the multi-staining model to improve the accuracy of the stroma segmentation task.

Therefore, we identify in table 2 several publications that confirm the effectiveness of deep learning and artificial intelligence (AI) frameworks that integrate multi-staining multi-tissue classification, instance and semantic segmentation, and detection in histological diagnosis.

[2] https://web.inf.ufpr.br/vri/databases/breast-cancer-histopathological-database-breakhis/

TABLE 2. A review table of AI-Driven fusion of multi-stain WSIs

Publication	Methods	Sains	Task	Dataset	Learned features
[34]	Incorporation of Color Deconvolution into UNET for learning CD parameters during training	H&E, Carcinoembryonic Antigen CEA, Forkhead box P3 (FoxP3), Ki67/CD3, Cluster of Differentiation 163 (CD163)/CD68), Ki67/CD8, Platelet-Rich Fibrin (PRF)/CD3	Segmentation	WSIs of colorectal carcinoma metastases stained with H&E and 8 immunohisto-chemistry (IHC) dyes	-
[28]	Cascade Mask region-based convolutional neural net architecture.	PAS, PASM, Masson	Individual Glomeruli identification and segmentation	WSIs and Snapshot Images from patients with kidney disorders at Peking University People's Hospital	-
[48]	Multi-Stain UNet including Co-Attention Recurrent Unit (CARU) approach for the simultaneous segmentation .	Hematoxylin and Eosin (H&E), Masson's Trichrome, Alcian Blue	Segmentation of stromal regions	Private dataset	Features common to H&E, Masson's Trichrome and Alcian Blue
[40]	Novel few-shot generative self supervised meta-learning framework, MSMTSeg	Hematoxylin and Eosin (H&E) stain, Periodic acid–Schiff (PAS), Periodic acid silver methenamine (PASM), Masson trichrome (Masson)	Renal histology segmentation	WSIs from the Shanxi Provincial People's Hospital	The domain-invariant feature representation across different dyes
[16]	Minimization technique based on graph cuts for segmentation	Hematoxilin and Eosin H&E , PAX5	Segmentation and classification of Nuclei in Follicular Lyphoma Tissue	Private dataset	Textural characteristics identified by H&E stain. The nucleoli structures identified by PAX5
[17]	Multimodal CNN-GNN based graph fusion method including Hadamard product, GIMP network, GAIMP network	Trichrome TC, Hematoxylin and Eosin H&E	Forecast NAFLD Activity Score (NAS) and CRN Fibrosis Stage	Private data	Nuclei and Cytoplasmic Features and Steatosis, Inflammation, and Ballooning features revealed by H&E. Fibrosis level highlighted by Trichrome

4. Integrative IA approaches for multi-magnification Whole-Slide Images fusion in medical diagnostics

In a diagnostic routine, pathologists in oncopathology, inflammatory pathology, cytopathology, anatomic pathology, clinical pathology, and molecular pathology review histopathology images in a hierarchical approach, starting by examining slides at low magnification to select areas of interest and zooming in at high magnification to detect more detailed tissue architecture. Indeed, at a low magnification of 40x, the histopathology image provides a wider Field of View (FOV).

In contrast, at a higher magnification of 400x, it focuses on a smaller region with finer and more critical details that are relevant for final diagnostic judgment and therapeutic decision-making [20]. In this pathological diagnosis process, the practitioner combines and integrates all the detailed histological profiles from different magnifications to obtain the macro and micro level features essential for an accurate diagnosis, leading to an understanding of the pathological conditions. Inspired by this process, several papers have developed a reliable diagnostic artificial intelligence model by combining multiple features from different magnifications.

In table 3, we present different research papers that integrate multi-magnifications histopathological images based on advanced deep learning algorithms.

TABLE 3. A review table of fusion approaches for multi-magnifications WSIs analysis.

Publication	Methods	Magnification	Learned features	Task and disease	Performances	Dataset
[21]	Cross-magnification attention	20×, 10×, 5×	Local and global features from patches from WSI at various magnifications	Predicting the gene mutation for clinical treatment.	AUC	TCGA-LGG and TCGA-GBM public datasets from The Cancer Genome Atlas (TCGA) portal

	model: CroMAM.					
[32]	Novel graph-structured multi-magnification framework: GRASP	Multiple magnifi-cations	Classification	Balanced Accuracy, F1 Score		Ovarian Carcinoma Cancer dataset Bladder Cancer dataset
[79]	Novel fast dual magnification framework.	10×, 40×	Low-dimensional and high-dimensional compact feature vectors	Detecting lymph node metastasis for breast cancer diagnosis	Free Response OperatingChara-cteristic (FROC)	Camelyon16: breast cancer WSI dataset
[15]	Deep multi-magnification similarity learning (DSML) approach.	40×, 20×, 10×, 5×	-	Classification	Area under curve (AUC) , Fscore (F1), Accuracy (ACC), Recall (REC),Preci-sion (PRE)	Nasopharyngeal carcinoma NPC2020 andBreast cancer BCSS2021 dataset https://github.com/PathologyDataScience/BCSS
[52]	Multi-Magnification Ensembles (MME). Multi-magnification ensembles of Vision Transformers (ViTs)	20×, 40×, 10×, 5×.	-	Breast cancer detection and classification.	Matthews Correlation Coefficient (MCC), Area Under the Receiver Operating Characteristic (AUROC)	CAMELYON16 dataset
[59]	TransEM-Net	20x, 10x, 5x	-	Segmentation	Dice score	Lung Cancer Dataset. Public Prostate Cancer Dataset: PANDA
[73]	ZOOMMIL	20×, 40×.	Slide-level representations across different magnifications	Classification	Accuracy, weighted F1-score.	CRC, BRIGHT, and CAMELYON16 datasets.
[66]	Multi-Magnification Organ Network (MMO-Net)	1.25x, 5x	Organ segmentation and detection in preclinical pathology (Animal research)	AUROC, Dice DSC	-	WSIs dataset available at https://doi.org/10.7303/syn30282632.
[25]	Deep Multi-Magnification Network.	20×, 10×, 5×.	Cellular features from a higher magnification, Architectural growth patterns from a lower magnification	Precision, Recall, Intersection-over-union (IOU)	Multi-Class Breast Cancer Image Segmentation	Two private breast datasets
[26]	MULTI-SCALE CNN (MSCN).	20×, 40×.	HCC detection	mIOU	-	WSIs of hepatocellular carcinoma (HCC).
[20]	Densely-Connected Multi Magnification hashing (DCMMH) framework.	40x, 100x, 200x, 400x	Discriminative Binary Codes, accumulated Similarity in Low-Magnification Images, Information across different magnifications	Mean Average Precision	Computer-aided diagnosis: Histopatholo-gical Image Retrieval	BreakHis dataset.

5. Bridging medical data: fusion approaches of incorporating histopathological imaging and genomic data to revolutionize medical pathology

Many research papers have achieved considerable efficiency in implementing a single modality or source for accurate diagnosis or prognosis through deep learning algorithms in histopathology [89]. Nevertheless, a single modality or source is not enough for a comprehensive understanding of complex diseases. Different medical source data are used to capture different perspectives of a patient's organ. Each source provides a unique visualization and observation of the same medical problem and multiple sources can show multiple information about a target tumor, organ or tissue). Thus, the precise analysis of these various sources increases the potential for more accurate and informed medical decisions. In this section, we conduct a systematic review of the publications that discuss the fusion of histopathological images and omics data.

While histopathological images determine the morphological and microenvironmental characteristics of tumors, omics information reveals underlying genetic factors and molecular signatures. Omics information is diverse and comes from genomic, epigenomic, transcriptomic, proteomic and metabolomic data. The convergence of histopathological slides and omics data is essential because of the synergistic potential of data fusion. By merging this information that allows us to have complementary perspectives on the same biological

phenomenon, the accuracy and robustness of inferential analysis is improved, thus overcoming the limitations of single-source approaches and reducing the risks of errors and variability.

Hence, studies approved that histopathological slides and genetic data combined complement each other and offer better performance of patient stratification. As an illustration, in a cancer diagnostic process, tumor-derived genomic data identifying oncogenic driver mutations, serving as a template to understand the molecular structure of the tumor while the histological slide of the same tumor reveals a detailed illustration of the histopathological architecture of the tumor and its microenvironment. These two sources are indirectly complementary, as they provide enriching multidimensional information as well as the overall understanding of the disease. [71], [69]. Integrating two data sources into a decision-making approach requires a fusion step. The fusion of two different sources based on early or late combinations. Depending on the type of inputs for multimodal fusion, the fusion strategies can be divided into feature-level fusion and decision-level fusion.

Decision-level fusion integrates the probabilistic or categorical predictions of unimodal models to make a final multimodal prediction. For decision-level fusion, the prediction of unimodality can be learned separately and be independent of the fusion step. It can fuse any combination of multimodalities without further adjustment in the testing phase. Thus, it can be preferred for flexibility and simplicity. and it can tolerate the missing modality situation. On the other hand, feature-level fusion fuses the original data or features extracted from heterogeneous multimodalities into a compact and informative multimodal hidden representation to make a final prediction. [12]. Early fusion algorithms (feature-level fusion) combine histological and genomic data at the beginning of the framework, allowing for the simultaneous training of a single model across all modalities, while late fusion trains models for each modality individually, allowing for the collection of relevant structural information but preventing the algorithm from learning correlations between histological and genomic sources Ren et al. [63].

Table 5 presents a multi-source medical image fusion algorithm based on histological images and genomic data. This table therefore provides an overview of multi-source algorithm (MSA) fusion that aims to develop approaches that can process information from histological imaging and genomic data, allowing us to learn dependencies between the two different sources.

TABLE 4. Integrating Histology and Genomics Data: A review table of IA fusion methods for improved diagnostics

Pap -ers	Models	Perfor-mances	Data Types	Learned features	Fusion strateg y	Task	Data Source
[55]	Federated Multi-Modal (FedMM) learning framework.	Accuracy, ROC Curve	WSIs, CNV data	WSI level representation	Early fusion	Classification of subtypes of lung and kidney cancers	Two datasets: non-small cell lung cancer NSCLC , renal cell carcinoma RCC
[68]	IMO-TILs, Cox model	C-index, AUC	WSIs, Genomic data (mRNA, miRNA)	The spatial interactions between TILs and tumors across WSIs, Gene coexpression modules derived from ImQCM	Early fusion	Survival prediction	Three cancer datasets: BRCA, KIRC and LUSC
[31]	Random Survival Forest (RSF) algorithm based on generated prognostic features	AUC	H&E-stained WSIs, Transcriptome, somatic mutation, Clinical information	Co-expressed modules as an eigengene. object intensity, object size, object shape, image granularity, and image texture from WSIs.	Early fusion	Survival prediction for Papillary Renal Cell Carcinoma patients	Genomic data from GDAC
[23]	Hybrid Early-fusion Attention Learning Network (HEALNet).	C-Index	H&E-stained WSIs, Multi-omic data (gene expressions,whole genome sequencing), Mutations (RNAseq), Clinical variables	Dimensional feature vectors extracted from each patch of WSI	Early fusion	Survival analysis	Cancer datasets from The Cancer Genome Atlas TCGA : BLCA, BRCA, KIRP, UCEC
[39]	Mutual-Guided Cross-Modality Transformer MGCT	C-index	WSIs, Genomic data: transcript abundance (bulk RNA-Seq), gene	Bag representation from WSIs, Genomic feature embedding	-	Survival analysis	Cancer datasets BLCA, BRCA, LUAD, GBMLGG and UCEC

			mutation status, copy number variation				
[72]	Multi-modal fusion framework based on multi-task correlation learning (MultiCo-Fusion)	C-index, The ROC curve, micro-AUC, microAP, micro-F1	WSIs, mRNA expression data	Gene-gene interactions from mRNA expression data	Early fusion	Survival analysis and cancer grade classification	mRNA expression data for brain lower grade glioma and gliob-lastoma multiforme from TCGA, Pan-Cancer Atlas
[7]	AJIVE	-	H&E WSIs, gene expression	Visual characteristics extracted from patches of a WSI	-	Exploratory analysis	Dataset from the Carolina Breast Cancer Study
[10]	Integration model: random Forest SRC	Time-dependent ROC curve, Kaplan-Meier method, Logrank test	Histopathological images, Mutations, transcri-ptomics, and proteomics data	Object size, shape, correlation, neighbors, and texture modules from WSIs; transcriptional subtypes (PI, PP, TRU) and genetic aberrations (ALK, BRAF, EGFR, ROS1)	Early fusion	Predict Molecular Charac-teristics and Survival LUAD	H&E histopathological images of LUAD patients, multi-omics data from The Cancer Genome Atlas (TCGA)
[36]	Random forest (RF) approach with 1,000 decision trees	Kaplan-Meier analysis, Logrank test, Decision curve analysis	Histopathology slides, mRNA expression data	Coexpression-gene modules	Late fusion	Prediction of the survival of COAD	WSIs provided by TCIA and the HTSeq-count mRNA expression data and clinical informationof COAD patients from TCGA: https://portal.gdc.cancer.gov/
[54]	Cascaded convolutional neural network model, Residual neural network ResNet	Accuracy	WSIs, Molecular data: (IDH1/ 2,1p/19q, ATRX, and MGMT)	Cellularity features from WSIs	Early fusion	Glioma Classifi-cation and Grading	WSIs from the Cancer Genome Atlas TCGA, molecular informationfrom the Genomic Data commons (GDC)
[82] [42]	Correlation Analysis. k-means clustering algorithm	The log-rank	Histopathological images, ATAC-seq, mRNA expression data	The epithelial tissue proportion from histopa-thological images, the chromatin accessibility from the ATAC-seq data	Early fusion	Prognostic prediction for breast cancer	Chromatin accessi-bility data, gene expression data, H&E WSIs clinical information
[84]	Integrative prognostic model including the Random Forest (RF)	Time-dependent receiver operating characteristi c curve, Kaplan-Meier survival curve, Decision curve analysis	Histopathological images, Genetic mutation, RNA sequencing, Protein expression, Clinical characteristics	Area occupied, cell density, cell neighbors, radial distribution, size shape, objective texture from WSIs.	Early fusion	Survival analysis in head and neck squamous cell carcinoma (HNSCC)	Clinical and multi-omics data from the Cancer Proteome Atlas (TCPA), WSIs from the cancer Imaging Archive TCIA
[37]	Conditional autoencoder. The Deephit network for survival analysis	Pearson correlation coefcient, AUC, FROC, C-Index, CI	WSIs, Gene expression data	Tumor probability and tumor regions from WSIs and gene features	Early fusion	Breast Cancer survival prediction.	Data from The Cancer Genome Atlas Program Breast Invasive Carcinoma TCGA-BRCA project

[11]	Multimodal Tensor Fusion via Kronecker Product and Gating-Based Attention	C-Index,AUC, AP, F1-Score	WSIs, Genomics data (mutations, copy number variation(CNV),RNA sequencing (RNA-Seq expression)	Morphometric cell from histology images	-	Detailed patient classification and interpretation for finding prognostic features, Survival outcome prediction.	Glioma and clear cell renal cell carcinoma datasets from the Cancer Genome Atlas TCGA.
[69]	Generalized sparse canonical correlation analysis framework (GSCCA) including Ordinal multi-modal feature selection (OMMFS) framework.	Concordance index, AUC.	Pathological images,Multi-modal genomic data (copy number variation, mRNA transcription, DNA methylation data)	Histology features: nuclear axes lengths, area, distances to neighboring nuclei, axis ratio, and RGB pixel values. Eigengene modules. Methylation level from DNA Methylation. Copy number estimation from CNV	Early fusion	Prognosis of early-stage cancer patients	Cancer datasets: KIRC, KIRP and LUSC from TCGA. Genomic data from the Cancer Genome Atlas TCGA portal
[47]	Genomic survival convolutional neural network (GSCNN), Survival convolutional neural networks (SCNNs)including Visual Geometry Group (VGG) convolutional network architecture within a Cox proportional hazards model	Harrell's c-index	Genomics data (IDH mutation status, and 1p/19q codeletion), Histology data	Regions of interest (ROIs) from WSI, Visual features from the high power field HPF	Early fusion	Predicting cancer outcomes	Gliomas data : LGG and GBM from The Cancer Genome Atlas TCGA
[62] [63]	CNN-LSTM for combining histology features and omics data	-	WSIs, Illumina-RNA seq gene expression data	Local and global tissue properties from WSIs, Pathway Scores from on gene expression	Late fusion	Patients recurrence of disease in prostate tumors	Data from the TCGA/ GDC data portal
[35]	Supervised Multi-view Canonical Correlation Analysis (sMVCCA) including Random forest classifier and Wilcoxon rank sum test(WRST)	-	WSIs, Proteomic data.	Histomorphometric Feature: glandular morphology, Protein expression profile.	Early fusion	Prediction of the likelihood of prostate cancer returning after radical prostatectomy	WSIs and a set of proteins from the Hospital at the University of Pennsy-lvania HUP
[22]	Pathology and Genomics NETwork PAGE-Net.	C-index	Histology images, Genome data, Biological pathways and Clinical data	Survival-discriminative features identified from patches of a histopathologcial image	Late fusion	Survival prediction.	WSIs from TCGA and the gene expression data of GBM from TCIA and KEGG and Reactome pathway databases from MSigDB
[43]	Transformer-based survival analysis model TransSurv for fusion of intra-modality and	C-index	Histopathological images, Genomic data, Clinical information	Region level features, slide level features, and patch-level features from WSI. Genes from the	Late fusion	Survival analysis for Colorectal Cancer	Colorectal cancer dataset from TCGA

	intermodality features of histopathological, genomic, and clinical data			RNA-seq expression and gene level copy number alterations CNAs			

6. Fusion of histopathology images WSIs and radiomics: MRI, CT, PET scans: pioneering precision medicine

Radiomic data such as magnetic resonance images (MRI), computed tomography (CT), positron emission tomography (PET) poses another challenge for digital representations in the field of medical imaging, as pathophysiological information can be highlighted via deep learning analysis using radiomic images. Furthermore, with the support of the NCI Cancer Imaging Program and the National Cancer Institute (NCI) Quantitative Imaging Network (QIN) initiatives, radiomic data has been integrated into the field of oncology. Radiomic data has been combined with genomic data, called radiogenomics. Indeed, several radiomic properties can be correlated with certain genetic mutations or expression patterns, providing more details on tumor aggressiveness, responsiveness to treatment, and helping in survival prediction [19].

Like genomics, histological images with radiomic data can be integrated to develop the concept of historadiomics. This fusion approach aims to reveal the significant correlation between cell density pathomics and radiomic features. Therefore, this section focuses on publications that represent historadiomic methodology. As an illustration, the authors in [14] describe a radiopathomic analysis approach for survival prediction such as progression-free survival (PFS), overall survival (OS), and CD8 cell count distribution, in the context of non-small cell lung cancer (NSCLC) patients treated with immunotherapy. The radiophonic diagnosis of this study is based on an early fusion strategy.

The observation of correlations between these multi-sources traits highlights the possibility of fusion pathomics with radiomics. This integration has the potential to considerably increase the value of medical imaging as a sophisticated “in silico biopsy,” enabling a more accurate and effective way to controlling immunotherapy therapies. Furthermore, authors proposed in [33] to extract and evaluate radiomic features from 120 pre-treatment MRI scans were compared with the final analysis of tissue samples acquired during surgery (postoperative histology). In this scientific publication, the researchers investigate whether radiomic features can predict what histology would reveal. Indeed, radiomics, as a noninvasive analysis, can identify tumors in the form of MRI images at an early stage, thus, radiomic imaging, such as MRI images, can increase the accuracy of the initial diagnosis that is not revealed by histology. Radiomics can therefore complement histology by providing additional information that refines the histological findings. In cases where a complete histological examination is not possible before surgery, radiomics can fill in the gaps by providing information that would otherwise require surgical intervention.

Table 5 summarizes current publications about the fusion of pathomics and radiomics data.

TABLE 5. A review table of IA fusion approaches that merge virtual histopathological slides and radiomics data.

Pap-ers	Models	Perfor mances	Data Types	Learned features	Fusion strategy	Task	Dataset
[1]	Quantitative correlation analysis including Spearman’s rank correlation coefficients and Haralick correlation and homogeneity	AUC	H&E WSIs, ComputedTo mo-graphy (CT)	Cellular density from WSIs, Haralick textural features from radiomics data	Early fusion	Classification of non small cell lung cancer (NSCLC)	Publicly available datasets: WSIs and Computed Tomo-graphy: TCGA, CPTAC
[61]	Radiopathom ics pipeline including Support Vector Machines (SVM) and Regression models	Accura cy, Sensiti vity, Specifi city, AUC	Digital pathology images, Radio-graphic images :T1, T1-Gd, T2, T2-FLAIR, overall-survival outcomes	Size, morphometry, nuclear intensity and gradient statistics, and texture descriptors from WSI. Radiomic texture features from MRI images	-	Prognostication in glioblastoma .	Datasets (MRI and WSIs) from TCIA and TCGA, overall-survival outcome from clinical records from TCIA

[67]	Radopathomics strategy: the eXtreme Gradient Boosting framework for building radiopathomics signature (RPS), Spearman test, Cox proportional hazard model	ACC, Kappa coefficient, ROC, AUC, NRI test	H&E WSIs, Multiparametric MRI (mp-MRI), (T2WI and ADC) images	Pathomic features. Texture differentiation from WSIs	Early fusion.	Prediction of response to Neoadjuvant Chemoradiotherapy treatment in Rectal Cancer	Private dataset from four hospitals in China the Sixth Affiliate Hospital of Sun Yat-sen University
[85]	Clinical radio-histopathologic CPH model (ModelCRH), Prognostic multiscale nomogram	Harrell's concordance index	H&E WSIs, MRI images, Clinical data	Histopathologic signature, Radiomic features groups: histogram, gray level cooccurrence matrix, gray level run length matrix	Late fusion	Failure-Free Survival (FFS) estimation in nasopharyngealcarcinoma	Private dataset

7. Cross-Modality Integration: pathomics meets radiomics and genomics data in modern healthcare discipline

In the context of computational medicine based on deep learning and machine learning networks, the integration of multisource "pathomic, genomic and radiomic" data in the assessment of the tumor environment demonstrates a promising improvement in the understanding of the heterogeneity and complexity of the tumor microenvironment (TME). These three sources provide excellent complementarity. Genomic data provides quantitative details on molecular alterations highlighting cancer development and progression, radiomic data captures quantitative information from medical images that can be correlated with tumor biology and clinical outcomes while WSIs provide essential qualitative information regarding the morphological characteristics of tumor cells and the tumor microenvironment.

The integration of these three data sources using artificial intelligence and deep learning algorithms to improve cancer diagnosis, prognosis and treatment strategies. Thus, decision support tools based on this fusion approach are developed to accentuate this promising and stimulating direction [30]. Figure 3 below illustrates an example of the fusion architecture of these three types of data. The table 6 illustrates different research papers that highlight the significant interconnection between pathomics, radiomics, transcriptomics, and genomics in clinical use cases.

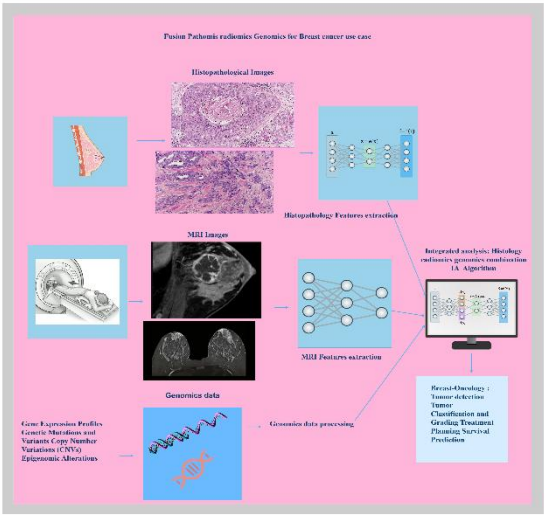

Fig 3. Illustration of integrative IA approaches for the combination of pathomics, radiomics and genomics data.

TABLE 6. Review table: unified diagnostics approaches : fusion of pathomics, radiomics, genomics data for precision medicine.

Papers	Models	Performances	Data Types	Learned features	Fusion Strategy	Task	Dataset
[5]	DOF: the fusion model including: loss function: Multimodal Orthogonalization (MMO), attention-gated tensor fusion, Multi-parametric	Median C-index.	H&E WSIs, DNA sequencing, MRI exams, clinical data	Equally spaced crops per ROI, sample from middle of each quadrant from MRI	-	Prediction of overall survival (OS) of glioma patients	-

	Radiology FeatureNet, Cox Partial Likelihood Loss						
[4]	Cross modal integration including Coif wavelet-transformed images, SigMA (Signature Mutational Analysis), Cox proportional hazards models, A final Cox model for combining histology, radiomics, genomics and clinical data	Test concor-dance index	H&E WSIs, contrastenhanced computed tomography (CE-CT), DNA sequencing	Cell-type features and tissuetype features from histopathological images, omental and ovarian radiomic features, clinical HRD-DDR gene panels extracted from DNA	Late fusion	Risk classification of ovarian cancer	Private dataset prerepared during the diagnostic journey of patients with HGSOC, Clinical data from the TCGA CDR
[77]	Multi-source integration model: DyAM for estimating the survival probabilities. Overall score analysis: Kaplan–Meier survival analysis	AUC	Digitized PD-L1 IHC in tissue containing NSCLC, CT scans, genomic features.	PD-L1 texture features from histology images, radiomics features, genomics features: Somatic Gene, Transcription Regulators	Early fusion	Prediction of immune-therapy response in patients with NSCLC	Datasets available on https://www.synapse.org/!Synapse:syn26642505

8. Future directions and challenges

The fundamental reason for integrating multimodal histopathological images with multi-source data types such as genomics, clinical data, and radiomics is the complementarity of different information provided by each source. From histological images, we obtain the disease aggressiveness in cancer tumors while omics data provide basic details. Therefore, this fusion approach is implemented in precision medicine.

In this review, we have explained how we can build AI systems that can enable the advancement of precision medicine or the new way to advance precision oncology by combining histological images (WSI), omics data, and radiomics. The similarities, nuances, differences and complexities of clinical information from different organs at the cellular and tissue level are considered to detect or treat a disease, or even to discover new drugs. In addition, the fusion of low and high magnification histopathological images helps to reduce the loss of structural and contextual information throughout the training process thanks to the high resolution of the slides.

The main objective of this fusion is to unlock the correlations between different multiple sources of medical data where histopathological images or digital pathology constitute the central and most significant component, functioning as the cornerstone of the AI model. Furthermore, we have presented and discussed the approaches that have proposed the fusion of different modalities from histological images in terms of staining or magnification. Yet, we have not found in the literature any existing article that integrates multi-staining and multi-magnification histopathological images into machine learning and deep learning algorithms for clinical applications.

In this context, the author has developed in [58] an algorithm that transforms virtually H&E stained WSIs to IHC stained WSIs. Given that cellular arrangements and morphologies become visible at higher magnification (40x). However, the broader microenvironment and tumor boundaries are more obviously viewed at lower magnification (5x), it is crucial to implement the details obtained from these different magnifications. This integration improves diagnostic precision by guaranteeing appropriate translation of pictures from H&E staining to IHC. Therefore, the authors propose an “attention-based multi-magnification feature interaction module” for the translation of histopathological images from H&E staining to IHC staining. This module provided details about different magnification factors in histopathological images for the virtual translation process from one staining to another [58]. This involves developing an algorithm that extracts inter- and intra-magnification information from different stained histopathological images. From the results of this paper, ambitious perspectives can be proposed. For example, we can try to implement this perspective in tumor ecosystem diagnosis to extract complex correlations.

We will conduct trials of deep learning consensus algorithms guided by histopathology, genomics, and radiomics for precision medicine and oncology. The biggest challenge is the translation of histology-genomics-radiomics deep learning algorithms into the real routine in oncology. In this context, it is therefore evident that AI algorithms based on the fusion of histopathology images with other multiple imaging data and genomic data differ from the operation of the real clinic and the confidence they

have in their answers, which is related to the enormous diversity of data and the great variety of the fields of histology, radiomics and genomics.

To create reliable computational systems for pathologists, radiologists and geneticists, our next research paper discusses the implementation of uncertainty quantification ("epistemic uncertainty", "random uncertainty") in the construction of fusion models that integrate multimodal histological images, genomic and radiomic data for tumor identification or treatment response estimates, which guide treatment choices. Thus, models become more interpretable. Clinicians and pathologists can assess the confidence associated with certain predictions, which is essential to trust computer-aided systems. Recent research studies have already been conducted on quantifying uncertainty in digital pathology. Indeed, in [65], different uncertainty quantification models for histopathological image analysis have been introduced such as "expected calibration error (ECE)", "Bayesian DenseNet-169 model", "DCNN entropy-based elastic ensemble (3E-Net)", "Multi-level Context and uncertainty awareness (MCUa)". In [88], the authors review uncertainty estimation methods for radiomics imaging analysis such as "MC Dropout" for stroke diagnosis based on MRI images[24], "Probabilistic Unet" for "glioma growth prediction " [56].

9. Conclusion

This study has explored the various articles illustrating the different fusion techniques in histopathology: multi-stain or multi-magnification histopathology image fusion, integration of WSIs with genomic data or radiomics data, and comprehensive WSIs fusion with radiomics and genomics. The successful combination based on deep learning algorithms is considered as computational systems that help the medical community in decision-making for disease analysis, treatment routine, and survival probability estimation.

One of the key challenges of multimodal integration is ensuring that each data modality complements the others, thereby enhancing the overall information content beyond what can be gleaned from a single source. Specialized computational approaches are required to address data heterogeneity, missing data, and scalability issues inherent in integrative analytics. The limitations of the methodologies presented in this review article may not be feasible for real routine clinical implementation because of the lack of relevant and robust approaches that integrate the uncertainty estimation methods in the fusion algorithms for histopathology-radiomics-genomics IA frameworks for medical applications. Further, more experiments are needed to overcome this limitation and develop adequate fusion-algorithms for the real implementation in journey care.

Author Contributions

Mariem Arbi (1) conceptualized the study, developed the methodology, and wrote the original draft; Hedi Yazid (2) performed formal analysis, implemented software, and validated results; Mohamed Ali Mahjoub (3) supervised the research, provided resources, and reviewed/edited the manuscript. All authors contributed to investigation, data curation, and approved the final version.

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