

Overview of the potentials of multiple instance learning in cancer diagnosis: Applications, challenges, and future directions

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Abstract— The outcome of cancer patients mostly depends on the diagnosis process and the treatment strategies. Computer-aided diagnosis (CAD) methods have demonstrated the potential to handle accurate diagnostics using artificial intelligence techniques such as machine learning and deep learning. The nature of the data used in training the AI-based model determined the paradigm, often classified as supervised and unsupervised learning for scenarios with labeled and unlabeled data, respectively. Due to the cost of time and resources, most datasets are nowadays partially labeled and used for training. The weakly supervised learning approach enables the AI models to be trained with incompletely labeled, noisy, or imbalanced data. In recent years, multiple instance learning (MIL) has emerged as a promising weakly supervised learning approach in many fields, including cancer diagnosis. Unlike traditional supervised learning methods, MIL allows the classification of groups of instances, known as bags, where only the bag's label is available. This comprehensive review aims to provide an in-depth analysis of the applications of MIL in cancer diagnostic tasks, highlighting its advantages, challenges, and future directions. By examining these advantages, challenges, and future trends, the review aims to contribute to advancing MIL as a powerful tool in improving cancer diagnostic accuracy and patient outcomes.

Keywords— Bag, Cancer diagnosis, Instance, Multiple Instance Learning, Weakly supervised learning

I. INTRODUCTION

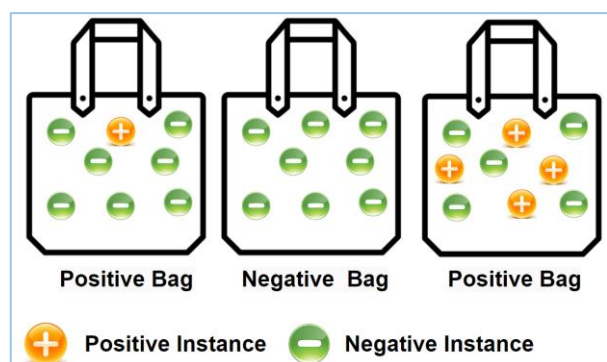
Cancer remains a global health challenge, with significant implications for patient outcomes and healthcare systems. According to a World Cancer Research Funds International report, 18.1 million cancer cases were estimated in 2020, with 1,806,590 new cases in the United States. Cancers are named for the area where the cancerous cells originated (breast, liver, colon, etc.), even if they spread to other body parts (metastasis). The most common cancers include breast cancer, lung and bronchus cancer, prostate cancer, colon and rectum cancer, melanoma of the skin, bladder cancer, non-Hodgkin lymphoma, kidney and renal pelvis cancer, endometrial cancer, leukemia, pancreatic cancer, thyroid cancer, and liver cancer [1]. Despite advances in cancer research, the mortality rate of cancer patients is still alarming, rendering it a severe threat to human life [2]. Accurate and timely cancer diagnosis is crucial in

determining appropriate treatment strategies and improving patient survival rates [3]. However, cancer diagnosis presents numerous challenges due to the complexity and heterogeneity of tumors and the limitations of traditional diagnostic methods. In recent years, advanced machine-learning techniques have emerged as powerful tools to address these challenges and enhance cancer diagnosis [4]. These techniques improve early detection of the condition, tumor classification, prognosis and survival predictions, risk assessment, and clinical trial matching, leading to a better patient outcome, thus reducing healthcare costs and advancing our understanding of the disease. Still, cancer diagnostic challenges arise from several factors, including the diversity of cancer types, the variability in disease manifestations, and the limitations of existing diagnostic approaches.

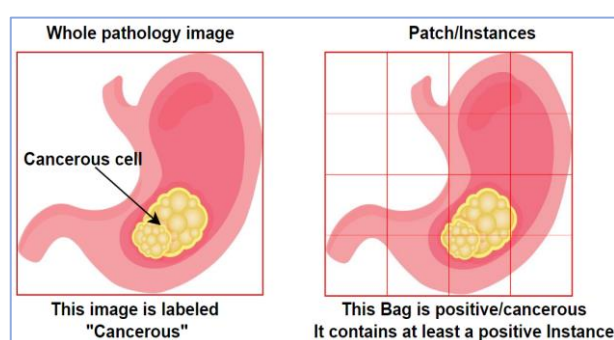
Traditional diagnostic methods, such as histopathological analysis, imaging techniques, and biomarker assessments, rely on subjective interpretations and may have limitations in terms of sensitivity, specificity, and reproducibility [5]. Additionally, while using Computer-aided diagnosis (CAD) and machine learning methods, cancer datasets often exhibit characteristics such as class imbalance, noisy labels, and complex interactions between features, further complicating accurate diagnosis [6]. Overcoming these challenges enables a growing need for advanced machine-learning techniques in cancer diagnosis. Advanced machine learning algorithms can analyze large volumes of complex data and extract meaningful features and patterns to make accurate predictions. By leveraging computational power and advanced algorithms, machine-learning approaches can improve the sensitivity and specificity of cancer diagnosis, enhance risk stratification, and aid in treatment decision-making [7].

Multiple instance learning (MIL) is a machine learning paradigm that has gained attention for its applicability in many areas, including image classification, drug activity prediction, text classification, and object recognition in computer vision, among others [8]. MIL is a weakly supervised learning approach that deals with specific types of problems and is helpful in cases where the supervised methods are unsuitable because of the lack of colossal labels or annotations in the dataset. In MIL, training data is organized into bags with instances. An instance is a small data point, e.g., a patch image.

An instance can be either positive (belonging to a specific target class) or negative (not belonging to the target class). A bag is a collection of instances. A bag is said to be positive if it contains at least one positive instance and negative in the opposite case. Figure 1 illustrates the concept of bags and instances.



(A)



(B)

Figure 1. Illustration of the concept of bags. A bag is labeled positive if one or more instances are positive.

Unlike traditional supervised learning, where each instance is labeled individually, MIL operates on groups of instances known as bags. A whole slide image can be represented in histopathological imaging as a bag of instances and its patches as instances using MIL [8]. Similarly, a bag could represent a region of interest in an image, a patient's medical record, or a collection of molecular features [9]. The fundamental key concept of MIL is the above-mentioned: bags are labeled as positive if at least one instance within the bag is positive, and the bag is labeled negative if all instances are negative. This allows MIL to handle situations where the exact localization or identification of cancerous regions within a bag may be challenging or uncertain. The MIL algorithms are therefore designed and implemented to learn a model that can accurately classify bags of instances based on the tumor's presence/absence, considering the ambiguity and flexibility within the bags [10]. In this review, we highlight the benefits of MIL in cancer diagnosis with applicable use cases. We further discuss challenges associated with MIL and propose strategies to overcome them. The review also suggests future research directions for cancer diagnosis using MIL.

II. FUNDAMENTAL OF MULTIPLE INSTANCE LEARNING

Multiple Instance Learning (MIL) is gaining interest from industry and academia because it fits a variety of problems and allows us to leverage weakly labeled data. MIL finds applications in computer vision, natural language processing, drug activity prediction, bioinformatics, CAD, and document and text classification [8]. It appears that almost every field can use the MIL approach for problem-solving since the bag and instance representation can be reproduced in real-life scenarios. Multiple Instance Learning (MIL) is a form of weakly supervised learning where training instances are arranged in sets called bags, and a label is provided for the entire bag. MIL organizes its data into bags containing multiple instances; this can be replicated in the medical domain, where a bag can be considered as medical report and, an instance, a clinical test result. MIL uses bag-level labels, which can be either positive or negative. A positive bag contains at least one instance of the target class (positive instance), while a negative bag does not contain any instances from the target class (negative instance). Each individual instance is described by a set of covariates (or features). The instance label is ambiguous in practice as it may not be directly observed or clearly identified. This ambiguity is the primary challenge of MIL since there is no evidence of individual precise labels of instances (positive or negative). Therefore, MIL algorithms are responsible for handling this doubt. MIL uses the relationship between bags and instances through a learning process to predict the bag-level labels. The learning process is weakly supervised due to ambiguous instance labels and aims to predict whether a bag is negative or positive. MIL uses various classifiers on bags to predict the bag-level label; the prediction output depends on the aggregation method.

MIL algorithms are usually divided into two main parts: An instance-level classifier and a bag-level classifier. An instance-level classifier provides information about the individual instances within each bag. The instance-level classifiers help to access the features of instances within each bag, and their training results in differentiating between positive and negative instances without directly using bag-level classification. Instance-level classifiers can assist in understanding the characteristics of instances associated with positive or negative bags and provide additional insights into the underlying patterns [9]. Instance-level classifiers can be very effective in certain situations, especially when the data is highly variable or complex. However, they can also be sensitive to noise and outliers, which can affect the accuracy of the classification results. Implementing instance-level classification uses various algorithms such as SVM, logistic regression, or k-nearest neighbors. For instance, the k-nearest neighbor algorithm finds the k-nearest instances to a given example and then assigns the class label that is most common among those instances. Another example is the support vector machine, which finds the hyperplane that separates the different data classes. On the other hand, A bag-level classifier is responsible for making predictions at the bag level based on the collective information of the instances. The output of the bag-level classifier is typically a probability or confidence score indicating the

likelihood of a bag being positive or negative. MIL uses majority voting, average probability, max probability, and clustering techniques to achieve bag-level classification. In majority voting, the class of the bag is that of the majority of its instances. For all instances in a bag, the average probability technique computes the average probability of belonging to a class. It sets it as a threshold λ used to classify the bag as of class c if $P(\text{inst} \in c) \geq \lambda$. The max probability uses the highest likelihood of an instance belonging to a class for bag-level classification. Clustering methods group instances per cluster according to their similarities. Various machine learning algorithms can be employed as bag-level classifiers, including support vector machines (SVM), decision trees, random forests, and neural networks [9].

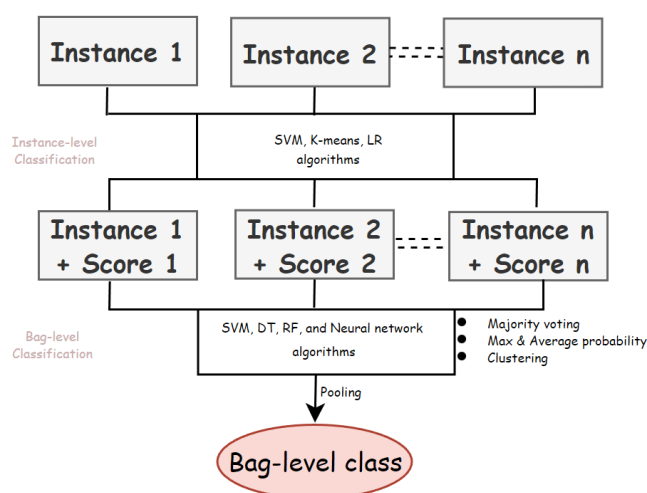


Figure 2. Overview of MIL algorithm

MIL algorithms can be classified into various types depending on their application areas. Regarding cancer diagnosis, some standard MIL algorithms include CNN-based, Deep-MIL, and attention-based MIL, among others, and each has its strengths and weaknesses. However, the advantages of MIL are numerous, as it appears to be a promising solution in the field of cancer diagnosis and prognosis. Due to the combination of approaches and methods, the MIL hybrid algorithms are countless reasons why we will present a few applied to cancer diagnosis tasks.

- **Multiple Instance Learning via Embedded Instance Selection (MILES):** The MILES algorithm selects representative instances from each bag and transforms the problem into a standard supervised learning task. MILES has been applied in breast cancer histopathology image analysis for cancer detection and grading [11].
- **Deep Multiple Instance Learning (DMIL):** DMIL combines deep learning architectures with MIL to handle complex, high-dimensional data. DMIL has been used for breast cancer subtype classification, leveraging molecular data to predict breast cancer subtypes [12]. Moreover, Pal et al. and Chang et al. used DMIL for abnormal cell detection in cervical histopathology images [13] and the

prediction of chemotherapy response in non-small cell lung cancer using pretreatment CT images [14].

- **Multiple Instance Learning Neural Network (MILNN-MILCNN):** MILNN utilizes a multiple instance neural network and CNN to classify bags. These algorithms are applicable in a variety of cancer diagnosis tasks. Wei et al. [15] proposed a cluster-based MILNN called the CBMIL model for binary classification (benign or malignant) of lung and breast cancers using WSI. Li et al. also developed a Dual-Stream MILNN for WSI classification; the approach learns from instances and bags while providing critical instances followed by an attention score representing the similarity of the critical instance and other instances [16].
- **Attention-based Multiple Instance Learning:** This approach extends the classical MIL approach using the attention mechanism [17]. Lu et al. [18] proposed a clustering-constrained attention multiple instance learning (CLAM) that uses attention-based learning and MIL to identify subregions of high diagnostics value to classify WSI effectively. CLAM approach is applicable to various cancer types and provides an interpretable weakly supervised deep-learning method for data-efficient WSI processing and learning that only requires slide-level labels.

These MIL algorithms, among others, demonstrate the applicability of MIL in cancer diagnostic tasks, leveraging bag-level labels to effectively identify cancerous regions, subtype classification, and risk prediction. The choice of algorithm depends on the specific cancer diagnostic task and the characteristics of the available data. However, it should be noted that the few types and examples of MIL algorithms presented are a non-exhaustive list because medical imaging and cancer diagnosis are rapidly evolving, and new research papers and methodologies are continuously being published.

III. APPLICATIONS OF MULTIPLE INSTANCE LEARNING IN CANCER DIAGNOSIS

The attention MIL gets can be justified by its ability to fit in various problems and allow it to leverage weakly labeled data. The challenges encountered in getting labeled data are alarming and raise the need for methods dealing with partially labeled data, such as MIL. In cancer diagnosis, pathologists are expected to provide labeled data that can be used for model training. The labeling process is time-consuming and cost-effective; pathologists can successfully achieve partial annotation of the medical images. MIL algorithms use bag and instances representation to handle the classification of partially annotated data. Here, we discuss the applications of MIL in breast cancer diagnosis, lung cancer diagnosis, and prostate cancer diagnosis, highlighting some studies and research that have utilized MIL techniques.

A. Breast Cancer Diagnosis using MIL.

MIL has been applied to breast cancer diagnosis tasks, including subtype classification, mammogram analysis, and lesion detection. In a study by Sudharshan et al., MIL was

employed for breast cancer subtype classification using histopathological images [19]. The MIL-based approach captured bag-level representations of breast tissue samples, enabling accurate classification into different molecular subtypes such as luminal A, luminal B, HER2-enriched, and basal-like subtypes. MIL algorithms have also been utilized for mammogram analysis in breast cancer detection. Cheplygina et al. investigated MIL methods for detecting and classifying breast lesions in mammograms [20]. The MIL framework allowed bag-level labels to identify regions of interest and accurately classify mammograms as positive or negative for cancerous lesions.

Furthermore, Wang et al. [21] developed a prediction model for HER-2-positive breast cancer prognosis patients using WSI and MIL. The patient's histopathological whole slide was considered a bag and was split into thousands of patches (instances) and clustered using the k-means algorithm. The clustered instances were aggregated into bag feature-level representation through graph attention networks to predict the prognostics of the patients. This research showed MIL's potential effectiveness and efficiency in analyzing unlabeled gigapixel WSI to predict Her2-positive breast cancer prognosis. Applications of MIL for breast cancer are diverse and extend beyond ordinary diagnosis. Piumi et al. [22] used MIL on histopathological images for survival prediction in triple-negative breast cancer. A WSI is cropped before the feature extraction process. A pre-trained encoder is used to extract the features before clustering. Each cluster is composed of a group of instances that is fed into a prediction model. The proposed model can output the risk score, a useful biomarker in triple-negative breast cancer prediction.

B. Lung Cancer Diagnosis using MIL.

MIL techniques have been applied to lung cancer diagnosis tasks, focusing on nodule detection and risk prediction. Dou et al. proposed an MIL-based approach for false positive reduction in lung nodule detection from computed tomography (CT) scans [23]. By considering the entire CT scan as a bag, the MIL model effectively detected and classified lung nodules, aiding radiologists in identifying potentially cancerous regions. Furthermore, MIL-based models have been developed for lung cancer risk prediction by integrating diverse clinical and imaging data. The MIL framework captured bag-level relationships between imaging and clinical variables, providing accurate patient risk estimation. Junhua et al. [24] proposed a lung cancer diagnosis model using deep attention-based MIL. The proposed approach uses the radiomics feature to feed the deep-attention MIL module, which is equipped with an attention mechanism that provides higher interpretability by estimating each instance's importance in the final diagnosis set. A total of 103 features were extracted per nodule to generate a bag of features that were used for model training. The results of this study demonstrate that the proposed approach will serve as a reliable indicator of the importance of each nodule in the diagnosis process. The module will support medical personnel

and patients in interpreting medical results better and handling the disease.

Similarly, Fadre et al. [25] used MIL lung pathophysiological CT scans to detect nodules, fibrosis, and emphysema. Each CT scan was a bag, and the various sections of the scan were considered as instances to adapt to the MIL problem structure. The Radiomic Bag Generator and Hounsfield Units Bag Generator were used for the implementation, and the obtained bags were labeled positive and negative according to the presence of an instance of the target class. A Kernel Density Estimation (KDE) was used to select the most positive instance in the bag, and a sampling method was applied before classification. The model could classify the presence or absence of tumor cells, making it useful for pathologists to handle the disease characterization.

C. Prostate Cancer Diagnosis using MIL.

MIL techniques have been employed in prostate cancer diagnosis, particularly in histopathology image analysis and detection in multiparametric MRI. MIL can potentially use an artificial immune recognition system based on classifying histopathological images into different Gleason scores to facilitate prostate cancer grading. MIL approach allowed the analysis of entire tissue slides as bags, capturing relevant patterns and providing valuable information for cancer diagnosis. MIL-based methods have been developed for prostate cancer detection and localization in multiparametric MRI. Litjens et al. proposed a MIL framework for automatic prostate cancer detection in multiparametric MRI, achieving improved sensitivity and specificity compared to traditional supervised learning methods [26]. The MIL model effectively captured bag-level interactions and relationships among different MRI sequences, enabling precise identification of cancerous regions. Li et al. [27] proposed a multi-resolution MIL model for Gleason grade group classification using MIL. Their model uses end-to-end training with slide-level labels (bags labels) and an aggregated bag-level feature vector clustered and trained to predict cancer grade using slide-level attention distribution. Unlike most classification algorithms focusing on patch segmentation, the proposed MIL-based approach uses multi-resolution instance learning algorithms that can detect suspicious regions accurately for a fine-grained grade. In addition, Golar et al. [28] used ultrasound images from systematic prostate biopsy to develop a deep network for cancer detection using MIL. The MIL enabled learning from ultrasound image regions associated with some statistically labeled data. This approach showed promising results and could be used as a generic extension to other similar cases.

D. Other Cancer Diagnosis using MIL

In practice, providing an exhaustive list of the applications of MIL techniques in diagnosing various cancer types is impossible. In this section, we underline some studies that have employed the MIL approach to achieve diagnosis or related tasks in other cancer types. The baseline remains the same; in the case of partially annotated images, MIL is one of the best and most famous approaches for machine learning-based solutions.

TABLE 1: OTHER CANCER TYPES DIAGNOSED BY MIL

SN	Cancer type	Description	Ref.
1	Bladder cancer	Using hierarchical deep multiple-instance learning with double-stage attention mechanism for high precision of gene mutation prediction.	[29]
2	Lymph node metastasis in various cancers	Two-stage MIL for Lymph Node Metastasis (LNM) Classification. The first stage consists of a double Max-Min MIL to select suspected top-K positive instances. The second stage consists of a transformer-based MIL aggregator combined to achieve classification in LNM.	[30]
3	Ovarian tumors	MRI-Based multiple instance convolutional neural networks for increased accuracy in the differentiation of borderline and malignant epithelial ovarian tumors	[31]
4	Gastritis	Attention MIL and network-based MIL are combined to diagnose chronic gastritis. WSI label is based on the gastritis pathology report, and the MIL is used for accurate diagnosis. The results were compared to the diagnosis results of pathologists and gave total satisfaction.	[32]
5	Colorectal cancer	Detect and grade lesions in colorectal cancer with higher sensitivity using multiple instance learning and feature aggregation methods.	[33]

IV. ADVANTAGES OF MIL IN CANCER DIAGNOSIS

MIL offers several advantages, and the primary one lies in its ability to handle weakly labeled or ambiguous data in cancer diagnostic tasks.

- *Reduced reliance on precise instance-level labels:* Obtaining accurate instance-level labels can be challenging in cancer datasets, especially when dealing with complex imaging modalities or heterogeneous tumor regions. MIL allows for the utilization of bag-level labels, reducing the dependence on precise instance annotations and accommodating the uncertainty inherent in cancer diagnosis [11]. This is particularly beneficial when only bag-level labels, like the case may be when dealing with whole-slide histopathology images or medical records.
- *Accommodation of inter-instance variability:* In cancer datasets, instances within a bag may exhibit variability in terms of size, shape, texture, or intensity. MIL models can effectively handle this variability by considering the collective information of instances within a bag, enabling the identification of common

patterns or features associated with the presence or absence of cancer [34].

- *Robustness to noisy or mislabeled instances:* MIL is inherently more robust to noisy or mislabeled instances compared to traditional supervised learning. Even if some instances within a bag are mislabeled or ambiguous, the bag-level label provides a more reliable indication of cancer's overall presence or absence. This robustness allows MIL models to handle imperfect or incomplete labeling in cancer datasets, improving their generalization performance [35].

V. CHALLENGES ASSOCIATED WITH MIL

Despite its advantages, MIL also poses some challenges in cancer diagnostic tasks:

- *Model interpretability:* MIL models often operate at the bag level, making it more challenging to interpret the specific instances or features responsible for the bag-level predictions. Interpreting the decision-making process becomes complex when the exact localization or identification of cancerous regions within a bag is uncertain. However, various interpretability techniques, such as saliency maps or attention mechanisms, can be employed to gain insights into the contribution of instances or features to the bag-level predictions [36].
- *Bag-level feature representation:* One of the critical aspects of MIL is the representation of bags as feature vectors. Designing effective bag-level feature representations that capture the relevant information from instances is crucial for the success of MIL models. This requires careful selection and extraction of informative features that discriminate between positive and negative bags. Incorporating domain knowledge or leveraging advanced feature extraction techniques, such as deep learning architectures or transfer learning, can improve the representation of bags and enhance the performance of MIL models [34].

To overcome the limitations and improve the performance of MIL-based cancer diagnostic models, several strategies can be employed:

- *Instance selection or weighting:* Selecting informative instances within bags or assigning instance weights can enhance the discrimination between positive and negative bags. Techniques such as instance selection based on confidence scores or importance weighting based on instance-level predictions can improve the model's performance by emphasizing more informative instances [37].
- *Ensembling and boosting:* Ensembling multiple MIL models or applying boosting techniques can enhance the overall performance and robustness of the models. Combining the predictions from multiple models or boosting the performance of weak MIL models through iterative training can improve the accuracy and generalization capabilities of the models [38].

- *Integration with other techniques:* Combining MIL with other machine learning techniques, such as active learning, transfer learning, or domain adaptation, can further improve the performance of cancer diagnostic models. Active learning can be used to select informative instances for labeling, reducing the labeling effort required for training MIL models. Transfer learning and domain adaptation methods can leverage knowledge from related datasets or pre-trained models to enhance the generalization capabilities of MIL models in different cancer diagnostic tasks or datasets [39].

VI. FUTURE DIRECTIONS AND EMERGING TRENDS

- *Integration of MIL with deep learning for enhanced cancer diagnostic accuracy:* Integrating multiple instance learning (MIL) with deep learning techniques holds great potential for advancing cancer diagnostic accuracy. Deep MIL models, which combine the representation learning capabilities of deep neural networks with the bag-level learning framework of MIL, can effectively capture complex patterns and relationships within bags of instances. By leveraging the hierarchical representations learned by deep models, MIL can potentially improve the discrimination between positive and negative bags in cancer diagnosis tasks. Future research efforts should focus on developing deep MIL architectures designed explicitly for cancer diagnostic applications, exploring convolutional neural networks (CNNs), recurrent neural networks (RNNs), and attention mechanisms within MIL frameworks.
- *Exploration of MIL in other cancer types and clinical domains:* While the application of MIL in breast, lung, and prostate cancer diagnosis has shown promising results, there is a need to explore the potential of MIL in other cancer types and clinical domains. Each cancer type presents unique challenges and characteristics that can benefit from the MIL framework. For instance, using dermoscopy images, MIL can be applied to skin cancer diagnosis to classify melanoma, non-melanoma, and benign lesions. MIL can also be employed in gastrointestinal cancer diagnosis to detect and classify polyps or tumors in endoscopic videos or images. Exploring MIL in these and other cancer types will expand its applicability and impact in diverse clinical scenarios.
- *Incorporating domain knowledge and expert annotations into MIL frameworks:* To further improve the performance and interpretability of MIL-based cancer diagnostic models, incorporating domain knowledge and expert annotations into MIL frameworks is crucial. Domain knowledge can guide the selection of informative features, the design of appropriate bag-level representations, and the definition of task-specific constraints. Expert annotations, such as region-of-interest annotations or weak instance-level labels, can provide additional supervision during model training. Combining MIL with domain knowledge and expert annotations can help overcome model interpretability challenges and enhance the model's ability to capture clinically relevant patterns. Future research should focus on developing MIL frameworks that

seamlessly integrate domain knowledge and expert annotations to improve cancer diagnostic accuracy.

VII. CONCLUSIONS

The potential impact of MIL in improving cancer diagnosis and patient outcomes is substantial. By leveraging bag-level labels and capturing complex patterns within bags, MIL models can aid in early detection, accurate classification, risk prediction, and personalized treatment planning. Developing reliable MIL-based diagnostic tools can enhance clinical decision-making, reduce inter-observer variability, and improve patient outcomes. This review has discussed the challenges associated with MIL, such as model interpretability and bag-level feature representation. Strategies to overcome these limitations have been explored, including instance selection or weighting, ensembling, and integration with other techniques. These strategies can improve the performance of MIL-based cancer diagnostic models and enhance their interpretability and generalization capabilities. Integrating MIL with deep learning is a promising direction to improve cancer diagnostic accuracy. Exploring MIL in other cancer types and clinical domains will expand its applicability and impact in diverse clinical scenarios. Additionally, incorporating domain knowledge and expert annotations into MIL frameworks can further improve the performance and interpretability of cancer diagnostic models. With further advancements and research, MIL-based approaches are promising to improve cancer diagnostic accuracy, ultimately leading to better patient outcomes.

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