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Insight into deep learning for glioma IDH medical image analysis

A systematic review

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Abstract

Background: Deep learning techniques explain the enormous potential of medical image analysis, particularly in digital pathology. Concurrently, molecular markers have gained increasing significance over the past decade in the context of glioma patients, providing novel insights into diagnosis and more personalized treatment options. Deep learning combined with imaging and molecular analysis enables more accurate prognostication of patients, more accurate treatment plan proposals, and accurate biomarker (IDH) prediction for gliomas. This systematic study examines the development of deep learning techniques for IDH prediction using histopathology images, spanning the period from 2019 to 2023.

Method: The study adhered to the PRISMA reporting requirements, and databases including PubMed, Google Scholar, Google Search, and preprint repositories (such as arXiv) were systematically queried for pertinent literature spanning the period from 2019 to the 30th of 2023. Search phrases related to deep learning, digital pathology, glioma, and IDH were collaboratively utilized.

Results: Fifteen papers meeting the inclusion criteria were included in the analysis. These criteria specifically encompassed studies utilizing deep learning for the analysis of hematoxylin and eosin images to determine the IDH status in patients with gliomas.

Conclusions: When predicting the status of IDH, the classifier built on digital pathological images demonstrates exceptional performance. The study's predictive effectiveness is enhanced with the utilization of the appropriate deep learning model. However, external verification is necessary to showcase their resilience and universality. Larger sample sizes and multicenter samples are necessary for more comprehensive research to evaluate performance and confirm clinical advantages.

Abbreviations: attMIL = an attention-based MIL model, CNN = convolution neural networks, GAN = generative adversarial networks, GBM = glioblastoma, H&E = hematoxylin and eosin, IDH = isocitrate dehydrogenase, IHC = immunohistochemical, LGG = lower grade glioma, MIL = multi-instance learning, ROI = regions of interest, SSL = self-supervised learning, TCGA = The Cancer Genome Atlas, WHO = World Health Organization, WSI = whole slide images.

1. Introduction

Glioma is the most prevalent primary malignant brain tumor in adults. The World Health Organization currently classifies gliomas (grade I-IV) through a combination of histological observation and genetic molecular detection (including IDH, 1p/19q, and ATRX).[1–3] Regarding gliomas, a patient's prognosis, diagnosis, and course of therapy are significantly influenced by their molecular genetic status. Certain genetic variations, such as isocitrate dehydrogenase (IDH) and 1p/19q, respond differently to targeted treatment.[4] Mutations of isocitrate dehydrogenase gene IDH1 and IDH2 are common in diffuse and anaplastic astrocytic tumors, oligodendrocytic tumors, and secondary glioblastoma.[5] Research indicates that patients with IDH mutations generally experience a more favorable prognosis compared to those with IDH wild type.[6] Furthermore, knowledge of IDH status may be linked to how well anti-IDH medications and vaccines work in advance.[7] IDH serves as a crucial biomarker for the diagnosis, treatment, and prognosis of glioma. At present, the gold standard for IDH mutation detection is immunohistochemical (IHC) and high-throughput molecular sequencing. These methods usually require additional reagents and specialized equipment, with professionals required to explain the test results.[8] These factors significantly impede how quickly doctors can diagnose patients, particularly in places where there is a scarcity of medical personnel. In contrast

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to histopathological examination, molecular biology detection offers greater objectivity and reliability; Nevertheless, its cost is frequently considerable, and its availability may be limited in less developed economies.

Using a complete scanner to digitize histopathological sections and computational techniques to analyze the resulting whole slide images (WSI) is known as digital pathology. Recent advancements in deep learning technologies, particularly convolutional neural networks (CNN),[9–11] have made computational image analysis tasks such as tissue categorization, cell segmentation, and feature recognition increasingly feasible. Comparing the deep learning method to the machine algorithm, which requires laborious labeled data,[12] the latter is less flexible and adaptive. Currently, deep learning is progressively employed in research to predict the condition of IDH based on histopathological pictures or to classify gliomas molecularly based on IDH.

In this review, we examine research focused on predicting IDH status for improved glioma diagnosis using various deep learning frameworks. Multiple deep learning methods, sample sizes, and performance metrics are examined. We delve into the limitations of these recent studies, the challenges associated with implementing them in clinical settings, and provide recommendations for future study.

2. Method

2.1. Ethical review

No ethics committee approval was required for this review.

2.2 Retrieval strategy and inclusion criteria

The PRISMA reporting requirements were applied in our systematic review. The literature search covered the period from October 31, 2019, to 2023. 2 impartial reviewers examined and assessed the studies. The search phrases encompassed terms such as deep learning, CNN, histological pictures, histology, hype, digital pathology, glioma, IDH, GBM, and LGG. Databases including PubMed, Google Scholar, Google Search, and preprint repositories (like arXiv) were consulted. This evaluation specifically focused on deep learning experiments utilizing IDH as label input and based on digital pathology. Studies that evaluated IDH status using glioma pictures from outside sources (such as MRI) were excluded. The selection criteria are manuscripts written in English. The evaluation criteria of the study were AUC value and accuracy.

3. Result

About 15 papers, in total, met the retrieval requirements (Fig. 1 shows the selection criteria, and Table 1 summarizes the studies that were chosen). We first provide a summary of each work in this review, after which we address the limitations of the study and its future directions. We categorize the various deep learning frameworks utilized in this study into 3 groups (multi-instance learning (MIL), ResNet, and other framework). We provide a detailed explanation of why combining the same architecture with various deep learning models results in varying prediction performance of IDH state.

3.1. WSI exploration of IDH gliomas using a multiple instance learning framework

Saldanha et al[13] investigated the deep learning-based prediction of histological genetic alterations for clinically relevant oncogenes and tumor suppressor genes in 7 tumor types directly from hematoxylin and eosin (H&E)-stained WSI using 2 large datasets (TCGA, CPTAC). In glioblastoma (GBM), the AUC of IDH1 was 0.84 ± 0.06. The model architecture consisted of self-supervised learning (SSL) and an attention-based MIL model (attMIL), where SSL was used to extract WSI features and attMIL was utilized for patient-level predictions. The model demonstrated superior performance when benchmarked against 3 other models, ImageNet + attMIL, ImageNet + avgPool, and SSL + avgPool. In contrast to previous studies, this research provides separate attention heatmaps and classifications, producing interpretable spatial predictions that challenge the deep learning "black box" labeling. Additionally, the study incorporated a robust external validation cohort to minimize the risk of overfitting.

Fang et al[20] proposed a fully automated Kanto called Multi-Beholder that utilizes H&E-stained WSIs with slide-level labels

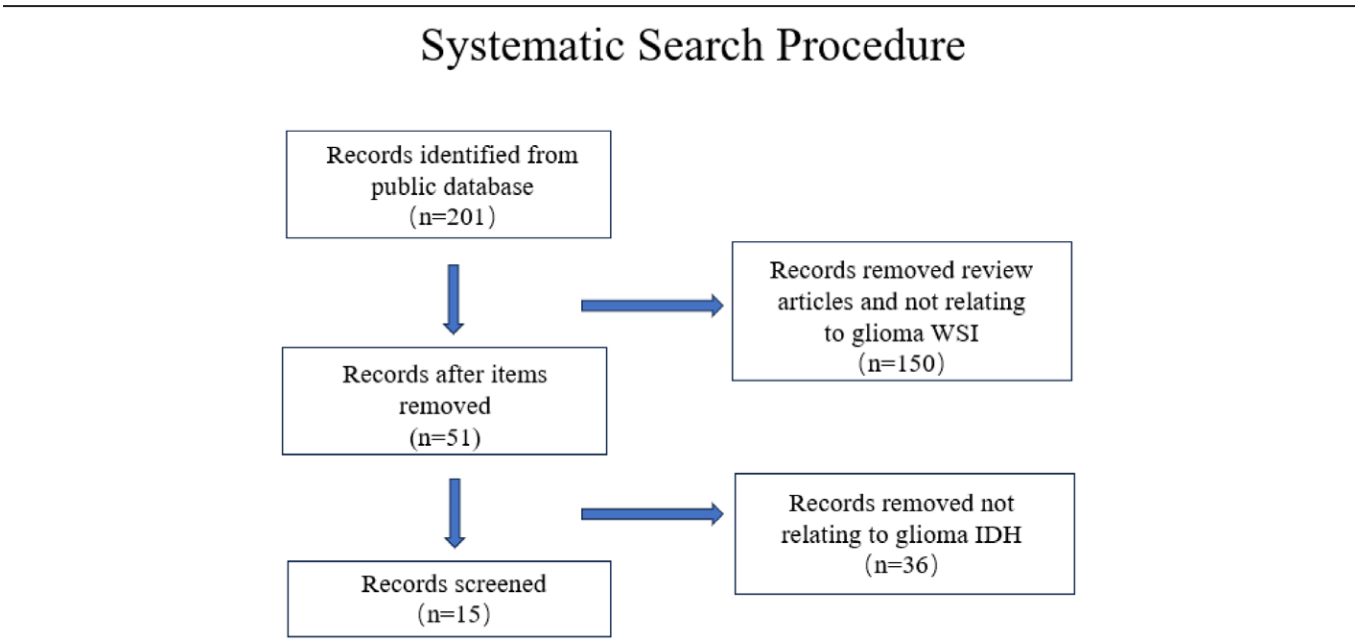

Figure 1. Overview of the systematic literature search according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Table 1

A summary of the studies using deep learning-based on WSI to predict glioma IDH. Provides a list of several analytical research together with the datasets, data sources, model performance, CNN architecture, and the presence of external validation for each study.

Study	Source of data	Patients	Performance	CNN	Validation
Saldanha et al (2023)[13]	TCGA CPTAC	TCGA (n = 397) CPTAC (n = 96)	AUC (0.84 ± 0.06)	SSL + attMIL	Yes
Rathore et al (2019)[14]	TCGA	TCGA (n = 663)	AUC (0.86)	ResNet	No
Cui et al (2020)[15]	TCGA	TCGA (n = 1121)	AUC (0.84)	MIL-based CNN (customised architecture)	No
Deng et al (2023)[16]	TCGA	TCGA (n = 613)	AUC (0.7737)	CS-MIL	No
Loeffler et al (2022)[17]	TCGA	TCGA (n = 680)	AUC (0.764)	DenseNet	No
Wang et al (2023)[18]	TCGA	TCGA (n = 940)	AUC (86.4)	HMT-MIL (Customised architecture)	No
Faust et al (2022)[19]	University of Toronto	University of Toronto (n = 47)	Accuracy (99.3%)	VGG19	No
Fang et al (2023)[20]	TCGA Xiangya Hospital	TCGA (n = 844) Xiangya (n = 116)	AUC (0.827 ± 0.0465)	Multi-Beholder (Customised architecture)	Yes
Li et al (2023)[21]	TCGA The First Hospital of Harbin Medical University	TCGA (n = 879) The First Hospital of Harbin Medical University (n = 326)	AUC (0.960)	ViT-WS (Customised architecture)	Yes
Liu et al (2020)[9]	TCGA Yeditepe University	TCGA (n = 200) Yeditepe University (n = 66)	AUC (0.920)	ResNet50	Yes
Despotovic et al (2023)[22]	National Center of Pathology	National Center of Pathology (n = 28)	Accuracy (96.39)	ResNet50 + ViT-B/16	No
Pei et al (2021)[23]	CPM-RadPath 2020	CPM-RadPath 2020 (n = 221)	Accuracy (80%)	3DCNN	No
Jiang et al (2021)[24]	TCGA	TCGA (n = 296)	AUC (0.689)	ResNet18	No
Pei et al (2021)[23]	TCGA	TCGA (n = 549)	Accuracy (84.32%)	ResNet	No
Wang et al (2023)[18]	FAHZZU HPPH XHCMU	FAHZZU (n = 1991) HPPH (n = 305) XHCMU (n = 328)	AUC (0.935–0.984)	ResNet50	Yes

CPTAC = Clinical Proteomic Tumor Analysis Consortium, FAHZZU = First Affiliated Hospital of Zhengzhou University, HPPH = Henan Provincial People's Hospital, TCGA = the Cancer Genome Atlas, XHCMU = Xuanwu Hospital Capital Medical University

to predict the status of 5 common biomarkers of lower grade glioma (LGG), including IDH. The MIL framework treats WSIs as bags and image patches as instances, where the features of all the instances are aggregated to a bag feature, thereby enabling bag-level labels to supervise the whole pipeline. Fang et al[20] train the Multi-Beholder pipeline on the TCGA-LGG dataset with a 10-fold Monte Carlo cross-validation. Applying the Muli-Beholder pipeline on the TCGA-LGG dataset to predict the IDH1/2 mutation status and validate the trained pipeline on the Xiangya external cohort, which achieved an AUC of 0.8247 ± 0.0465, and in other metrics, Multi-Beholder achieved 0.8490 ± 0.0456 for accuracy, F1 score, recall, and precision at 0.5 classification threshold, with values of 0.6053 ± 0.0900, 0.6166 ± 0.0848 and 0.6907 ± 0.173, respectively.

Cui et al[15] introduced a convolutional neural network (CNN) model based on MIL a unique structure. This model incorporates attention after the Fc ReLU activation function to obtain instance-level scores. These instance scores are then aggregated into bag-level scores through a MIL pool. The model associates the benefits of the end-to-end classification capabilities of deep neural networks with MIL by aggregating instance scores into bag-level scores. The model achieves good performance in classifying IDH1 mutations in histopathological images of gliomas with an area under the curve of 0.84.

Deng et al[16] proposed a novel cross-scale MIL algorithm (CS-MIL) that explicitly aggregates inter-scale relationships into a single MIL network for pathology image diagnosis. In addition, the proposed method utilizes cross-scale attention scores to generate importance maps, which enhances the interpretability and comprehensibility of the CS-MIL model. This approach is based on the attention-based "early fusion" paradigm, which learns knowledge holistically from multiple scales, in contrast to the Visual Transformer (ViT), which is based on the inherent hierarchical structure of WSI and uses 2 levels of SSL to learn high-resolution images. In the TCGA-GBMLGG queue, 500 image bags of size 32 were randomly generated for each WSI, and the mean of the bag scores was calculated as the final prediction at the patient level. The IDH status classification prediction achieved better scores in most of the evaluation metrics with an AUC of 0.7737 and an AP of 0.8187.

Wang et al[25] propose a hierarchical multi-task MIL framework to jointly predict histological and molecular markers and design a DCC learning strategy to simulate the interaction between histological and molecular markers for glioma classification. All the WSIs are crop into patches of size 224 × 224 px at 0.5 μm px^{-1}. The HMT-MIL framework extracts information from the N = 2500 patches of each WSI by utilizing the MIL learning paradigm with embedded converters. The model achieves an AUC of 92.0 in predicting IDH mutations and has a visualization experiment based on patch decision scores for readers and physicians to understand its model.

3.2. Prediction of IDH for glioma WSI based on ResNet network architecture

Rathore et al[14]developed a ResNet-based computational method to predict overall survival and molecular subtypes of glioma patients from microscopic images of tissue biopsies reflecting the presence of microvascular proliferation, mitotic activity, nuclear isoforms, and necrosis. The ResNet architecture is used to detect the sub-type of glioma as well as patient survival. The ROIs extracted from histologic images were given as input to the ResNet architecture. Sub-images of live tumors that are free of artifacts and contain descriptive histological features are extracted, which are further used to train and test the deep neural network. The output layers of the network were configured in 2 different ways: a final Cox model layer for

outputting predictions of patient risk, and a final layer with a sigmoid activation function and a binary cross-optimization-entropy loss based on stochastic gradient descent. The c-statistic was estimated to be 0.82 (P-value = 4.8×10^{-5}) between the risk scores of the proposed deep learning model and overall survival, while accuracies of 88% (area under the curve [AUC] = 0.86) were achieved in the detection of IDH mutational status and 1p/19q codeletion. However, it is worth noting that the computational approach in the study relies on manual quality checking of the patches extracted by the software, which is tedious and time-consuming.

Liu et al[9] proposed a deep learning-based histopathology image classification model, which was enhanced by a data augmentation method based on generative adversarial networks (GAN). The original deep learning had an accuracy of 0.794 and an AUC of 0.920 in predicting the IDH status, and after data augmentation by GAN, the prediction accuracy of the IDH mutation status was improved to 0.853 with an AUC of 0.927. In this study, a TCGA cohort of 921 patients was used for training and testing in ResNet50, and the GAN-generated images were fed into ResNet50, which is a very deep convolutional neural network with multilayer convolution and nonlinear activation functions to extract and represent histopathology image features efficiently.

Despotovic et al[22]proposed a semi-supervised learning method (ResNet50 + ViT-B/16) to accomplish computer-aided classification of diffuse gliomas by comprehensively comparing various transfer learning strategies and deep learning architectures. They divided the WSI-extracted regions of interests into 512 × 512 tiles. They performed image enhancement on all extracted tiles in the training dataset by flipping and rotating them by 90°, 180°, and 270°, and the accuracy obtained for prediction of the IDH state by ResNet50 + ViT-B/16 was 96.93%.

Jiang et al[24]used ResNet18 as a backbone to develop and validate their model on 296 patients from The Cancer Genome Atlas (TCGA) database. Patches of size 224 × 224 pixels and without overlap were extracted from the WSI, and the ResNet18 convolutional neural network transformed each patch into a 512 × 1 vector, average pooling was performed at the patient level, and the vector was then continued to be outputted through a 2-layer fully connected network model, with a concordance (C-) index for predicting prognosis of 0.715 (95% CI: 0.569, 0.830), and the area under the curve for predicting IDH mutations was 0.667 (0.532, 0.784).

Pei et al[26] used the over-segmentation technique to select ROIs. They sorted hyperpixels based on average intensity, firstly segmented cell nuclei in H&E using UNet, and then used ResNet to classify glioma patients, corresponded molecular information with cytoarchitectural features, and investigated the effect of cytoarchitectural features on distinguishing IDH mutations, and the results showed that the effect of cytoarchitectural features on distinguishing IDH mutations was not significant, and the results showed that between cytoarchitecture and IDH type the potential correlation between cellular structure and IDH type. The study obtained an accuracy of 84.32% in IDH classification.

Wang et al[18]proposed an integrated diagnostic model for automatic classification of unannotated standard diffuse glioma WSI. This model uses trained ResNet50 for feature extraction, whereas the extracted features (patches) are later utilized for K-mean clustering to classify these patches into K clusters, and automatic selection of patch clusters contributing more to the integrated classification task is achieved through patch clustering, patch selection, patch-level classification, and patient-level classification, avoiding the need for manual annotation. The AUC value of this model in predicting IDH status is AUC (0.935–0.984).

3.3. Other model architectures predict IDH

Loeffler et al[17]manually outlined tumor tissue in H&E-stained sections from 23 patients with different tumor types (including gliomas), the tumor regions within WSI were tessellated into tiles of 256 × 256 μm^2 at 0.5 μm px^{-1}., a convolutional neural network (DenseNet) was trained in an end-to-end manner, the network was trained at the patient level using a triple cross-validation approach, and each image block was trained to aggregate at the patient level by simple majority voting, enabling the detection of clinically relevant genetic changes directly from histological images. The predicted AUC value for the status of IDH1 in gliomas was 0.764.

Faust et al[19] combined different computer vision tools, including scale-invariant feature transformation (sIFT) and deep learning, to efficiently pair them and integrate H&E and IHC information, with an emphasis on the utility and automation of spatial patterns of diffuse gliomas. They used migration learning to optimize the VGG19 CNN, fine-tuning an existing ImageNet-based weight matrix. This approach led to the development of a histomorphometric molecular classifier with 99.3% accuracy in predicting IDH status.

Li et al[21] developed an end-to-end deep learning architecture based on the visual transformer (ViT), ViT-WSI accompanied by weakly supervised learning as well as a gradient attribution analysis program, which can learn from the H&E WSI and labels extracted purely from electronic health records, complete the task of classifying glioma subtypes without the supervision of additional pathologists, and accurately predict 3 glioma molecular markers (IDH1 mutation, p53 mutation, and MGMT

Table 2

Four deep learning frameworks are reviewed with their benefits and drawbacks for categorizing medical images.

Model	Advantages	Disadvantages
ResNet	Deal with the vanishing gradients problem. Excellent for complicated jobs and vast amounts of data. High capacity for learning and generalization. Measurement effectiveness	The cost of computing resources is quite high. High training data requirements. Small datasets are susceptible to overfitting.
Multiple Instance Learning	Handle labels that are inaccurate or incomplete. Ideal for jobs involving categorization and targeting. Lessen the work involved in labelling.	Both the training approach and the associated loss functions are intricate. Data must be tagged at the packet level.
VGG	Structured simply and clearly. Learning is easily transferred. Ideal for datasets of a modest size.	Computing resources are large and easy to overfit. Not suitable for fine-grained feature learning.
DenseNet	Dense connections alleviate the problem of vanishing gradients. Parameter sharing. Ideal for small datasets. Efficient information transfer.	High computational complexity. Large memory requirements. Model of a relatively large size.

methylation), at the slide level, on the combined cohort of the in-house data and TCGA, ViT-WSI achieved accuracy scores of 0.8127 (ROC–AUC = 0.8637), 0.6609 (ROC–AUC = 0.6763), and 0.6906 (ROC–AUC = 0.6981), respectively for the 3 tasks.

Pei et al[23] fused whole slide images (WSI) and multimodal magnetic resonance images (mMRI) to predict IDH status and identify glioma subtypes with 80% identification accuracy, and the fused accuracy was better than the prediction results of medical images considering only 1 type.

4. Summarizing the lessons learned

The majority of the research was retrospective, most used the TCGA database, just 5 were externally evaluated, and the majority were single-center investigations.

4.1. Types of DL architectures

ResNet has demonstrated strong performance in medical image classification tasks, as evidenced by 6 studies incorporating ResNet. MIL is gaining attention, and it is noteworthy that researchers often integrate MIL when combining various deep learning models. In this review, 5 studies utilize multi-instance learning, alongside VGG and DenseNet architectures. A detailed comparison of the pros and cons of these 4 deep learning architectures is presented in Table 2. Although each model has its own unique architecture and design principles, most of the approaches mentioned above utilize convolutional layers, pooling layers, activation functions, and regularization techniques (e.g., dropout and batch normalization) for model optimization. Additionally, the use of pretrained models and migration learning is becoming increasingly popular, allowing for the use of knowledge learned from large datasets (e.g., ImageNet) to improve the performance of their models on smaller specialized datasets, as utilized by Despotovic et al in their model construction.

4.2. Performance

Performance metrics are a consistent component across all the research studies, with the majority including metrics such as AUC, accuracy, sensitivity, and specificity. AUC values predominantly fell between 0.76 and 0.96, with a concentration between 0.8 and 0.9. DL training strategies included the hold-out strategy, the leave-one-out method, and the partition of the dataset (e.g., 80%/20% training/testing) with cross-validation. Most research utilized five- or tenfold cross-validation for performance evaluation; however, others used a single hold-out strategy, and some did not use cross-validation at all. Cross-validation is essential to avoid unintentional data skewing that results from dividing data for training and testing. Performance might vary based on the training methodology employed. Given that metrics can be influenced by factors such as overfitting, small sample sizes, and research reporting bias, a cautious evaluation of these metrics is essential. While high-performance metrics of DL algorithms are crucial for their adoption in clinical applications, strong indicators alone are insufficient. The widespread clinical implementation of deep learning algorithms requires additional measures, including heatmaps and experiential validation, to establish credibility.

4.3. Current challenges and future directions

In order for deep learning models to train, they need a lot of high-quality data, yet medical datasets are frequently tiny and uneven. There aren't many publicly available data sets, and the majority of the research in this study made use of open-access publically available datasets like CPM-RadPath 2020 and TCGA. Due to the time and money restrictions associated with data collecting, these public databases do not always contain matching molecular data and hence do not provide researchers with high-quality data. Furthermore, only 3 studies in this review combined TCGA and local data to hardly constitute a multicenter study, and the time and effort of the researcher during data collection was severely taxed. A smaller number of studies used their own local hospital datasets for their research work. Obtaining private medical records from a single institution can make them less generalizable since they might not be representative of certain racial or ethnic subgroups. The majority of recent studies on the histologic pictures of glioma pathology have demonstrated encouraging advancements in the field thanks to the availability of data gathered by several organizations.[27] At the moment, every institution has a tendency to gather and examine data independently, while some studies have integrated data from several organizations. The collecting of more extensive and varied medical imaging data can be facilitated by data exchange and collaboration between healthcare institutions. In order to expand the training dataset, a generator network is trained to generate synthetic data that resembles real medical images. A discriminator network is trained to distinguish between real and synthetic images, resulting in the generation of more realistic synthetic images. At the moment, GANs are being used to generate synthetic medical images.

Sometimes deep learning models are thought of as "black boxes" that are difficult to comprehend. This is especially problematic when diagnosing medical photos since understanding the logic behind a diagnosis is crucial. The aim of recent work has been to develop methods that may be used to describe the decision-making process of deep learning models. Examples of these methods include the use of attention processes and the creation of heatmaps to highlight important regions of the WSI picture. While methods for explaining the decision-making process of deep learning models have been developed, the explainability of these models remains restricted. This might make applying the concept to real-world scenarios challenging. To this end, Begoli et al recommend developing and using systematic and practical approaches of uncertainty measurement in artificial intelligence (AI) models.[28] Artifacts, model misspecifications, intrinsic biases in the data, the accuracy and completeness of the data, and the data selection process can all contribute to a model's level of uncertainty. A systematic framework for improving models and increasing confidence in AI-assisted clinical decision-making will eventually be provided by research on assessing uncertainty in data-driven prediction models.

5. Conclusions

AI has the potential to revolutionize molecular screening and diagnosis of gliomas, helping pathologists diagnose gliomas more efficiently and accurately, ultimately leading to better outcomes for patients. However there are certain obstacles that have prevented widespread use in clinical practice thus far. practice thus far. Large, varied, and thoroughly documented images that are easily accessible for research are required. Deep learning results need to be interpretable and generalizable. Future research directions should focus on incorporating other clinical data, exploring different histologies, and incorporating various types of medical images into the models. These efforts aim to enhance diagnostic accuracy and enable the realization of personalized medicine in the field of glioma diagnosis.

Anticipating forward, prevention rather than therapy may prove to be the most attractive application of AI in cancer care. As a consequence of ground-breaking research, the community has already developed a portfolio of cancer risk factors. Many methods of collecting patient data are now feasible because

of technological advancements. Apart from electronic health records and genetic testing, wearable technology sensors, like those found on smartphones, also collect an enormous amount of patient data. These data can improve the accuracy of diagnoses by allowing AI to recognize physiological and environmental conditions. They may be in favor of highly customized methods for the prophylaxis and management of each patient's sickness. AI systems may have the capability to remotely monitor cancer patients and alert physicians when intervention is necessary. In the near future, personalized recommendations for early intervention and risk factor management may be provided by AI algorithms that accurately assess a person's cancer risk in almost real-time by taking into account lifestyle, environmental, genetic, and health-related factors.

Author Contributions

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