

NEUOTRUST: A CLINICALLY GROUNDED MULTI-AGENT FRAMEWORK FOR TRUSTWORTHY BRAIN TUMOR DIAGNOSIS AND TREATMENT PLANNING

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Abstract

Current AI-based systems have shown significant promise for enhancing diagnosis and treatment planning for brain tumors, but they are not always easy to interpret, well integrated with clinical guidelines, or trustworthy for clinical decision support. We introduce NeuroTrust, a clinically inspired multiple-agent system, to overcome these challenges by combining six specialized artificial intelligence (AI) agents to orchestrate collaborative reasoning for brain tumor diagnosis and treatment planning. It integrates multimodal magnetic resonance imaging (MRI) methods, clinical history, verification of evidence-based guideline documents, uncertainty quantification, explainable decision-making, and human-in-the-loop validation processes to improve the reliability and clinical applicability of the framework. NeuroTrust was assessed with the BraTS 2023 challenge set as well as a separate de-identified clinical set on which it was externally validated. Experimental results show good segmentation performance with a mean Dice similarity score of 0.913 and classification accuracy of 94.28% while conforming to the clinical guideline with 95.04% accuracy. We additionally present two complementary indices of trustworthiness, Clinical Trust Score (CTS) and Uncertainty Calibration Index (UCI), that are derived to measure AI clinical decision reliability and calibration. NeuroTrust is an improvement on diagnostic performance, a significant reduction in hallucination rates, and better clinician trust arising from evidence-based reasoning and consensus-based decision-making when compared to a representative single agent and state-of-the-art basic approaches. The results indicate that multi-agent clinical intelligence, working together and sharing observations, can potentially serve as a viable

approach for creating reliable AI solutions that can assist with brain tumour diagnosis and planning for clinical interventions in real-world scenarios.

1. INTRODUCTION

Brain tumors are one of the major health problems across the globe, with an estimated number of diagnosed cases of more than 300,000 annually [1]. Whole-body MRI magnetic resonance imaging (MRI) is an important diagnostic tool, characteriser, and treatment planning aid, as it is able to provide detailed anatomical and functional information. However, interpretation of these complex imaging studies demands a great deal of skill, and it may ultimately lead to delays in diagnosis when skilled professionals are scarce, and interobserver variation even in the experienced diagnostic radiologists' community [2]. Multidisciplinary communication is needed between radiology and neurosurgery, between the oncological and neurosurgery, and between the oncological and morphological departments in order to effectively diagnose and treat the patient [3]. In recent years, due to the existence of deep learning, the development of medical image analysis has made considerable progress. CNN and Vision Transformer (ViT) have both been able to achieve near-human accuracy in detecting and segmenting tumors in this realm [4] and [5]. To address this issue, Sense et al. have developed a self-configuring framework named nnU-Net whose performance has been further improved to obtain another Dice overlap greater than 0.90 on the BraTS dataset [4]. Myronenko et al. demonstrated that despite having the same performance, 3D Vision Transformers outperform 3D CNNs in capturing the whole context [5]. To improve computing efficiency, Wang et al. came up with a combination of UNet and a state-space model, named Mamba-UNet [6]. Some recent works have achieved excellent segmentation results like Swin UNETR [7] and nnFormer [8] based on transformer networks. The introduction of Large Language Models (LLMs) presents new opportunities for further

improving clinical knowledge. The accuracy they achieve for diagnostic tasks is 75-85% in simple cases and faulty in complex cases, according to Gorenstein et al. [9]. As an extension of this, Sorka et al. [10] present studies on multi-agent AI systems to be more efficient than single-agent AI systems and physicians at achieving cross-verification. To obtain more effective results at specific tasks, such as Med-PaLM 2 in medical reasoning [11], there are models that have been trained specifically for the domain in question. While there has been substantial progress, challenges remain to bring AI systems into direct clinical use in the care of neuro-oncology. Although there is great progress, there are 6 aspects below which remains to be addressed before AI can be used clinically for the treatment of neuro-oncology. Most AI systems can be seen as "black boxes" as they lack meaningful explanations and so do not convey clinical context for the clinician, which results in the interpretability gap [12]. The discrepancy between the results of WHO, NCCN, and ESMO predictions and the actual recommendations is called the guideline gap and is not clinically acceptable [13]. Safety gap: None of the above functions are formally verified; hallucination detection and uncertainty estimation are missing, posing a safety threat to patient safety [14]. Most of the available systems operate on snapshots of patients and do not consider patient follow-up data over time [15], which is called the longitudinal gap. Summary: The multi-standard gap is the absence of a common system that incorporates the components from the BT-RADS, WHO, and RECIST scoring systems. It is really a human-AI interaction gap resulting from a lack of an interaction mechanism to enable collaborative work or iterative improvement with clinicians. In these ways, NeuroTrust is used to solve such issues: Explainable, multi-agent collaboration and Guideline Verification, Safety

modules, Longitudinal tracking, Multi-standard scoring, and interactive clinician feedback.

Jabal et al. [13] developed an end-to-end multi-agent system for automatic recognition score of BT-RADS, but there was no multi-standard scoring and safety verification in the system. A clinical reasoning multi-agent LLM system and a vision-language model (VLM) were integrated by Masmoudi et al. [14] to reach this aim. In this paper, Liu et al. developed a Basic Architecture for Health AI Agents with Formal Validation [17]. D'Amour et al. [18] identified one such point they delved into: "under specification." When models with equal validation results have very different clinical results, that's an issue. Gaps in such systems might be addressed by a clinically inspired multi-agent architecture, where six distinct AI agents specializing in Vision Interpretation, Clinical Reasoning, Radiology, Oncology, Neurosurgery, and Pathology act as a 'tumor board'.

We have five ways of contributing:

They are all very different specialized agents with extensive debate between all of them (there are six agents: Vision Interpreter, Clinical Reasoned, Radiologist, Oncologist, Neurosurgeon, and Pathology Agent). Critically and explicitly enforced WHO CNS5, NCCN, and ESMO guideline rules and 247 rules derived from WHO CNS5, NCCN, and ESMO guidelines, highly (HL): 0.25; medium (MS): 0.15; and low (LS): 0.05. Uncertainty estimation UCI: 0.081, hallucination detection (HR: 1.18%), and conflict resolution (CR: 2.82%) are included in the formal Safety Module. Deformable Registration based on Longitudinal Tumor Tracking: response assessment in neuro-oncology (RANO) Analysis. There are two novel trust measures, Clinical Trust Score (CTS) and Uncertainty Calibration Index (UCI), in the system that quantify the trustworthiness of AI agents.

Hereafter, this work is organized in the following: In Section II, a brief search of related work has been presented. This problem is set up in section (3). Please refer to Section 4 for methodology.

Experimental setup details are given in Section 5. Section 6 reports results. Discussed in Topic 7 in relation to results, weaknesses, and investigation for future work. The paper is finished in Section 8.

2. Literature Review

The application of AI in neuro-oncology is no longer limited to image segmentation; now, it's gradually making an impact on clinical reasoning. There have been dramatic advances in brain tumor segmentation capability using deep learning architectures. In contrast, Isensee et al. reported that their nnU-Net could outperform dedicated architectures with Dice scores greater than 0.90 on BraTS, illustrating the potential for automated configuration pipelines to outperform these dedicated architectures. Myronenko et al. took this success further for obtaining global context understanding and demonstrated improved performance with the 3D Vision Transformers [5]. State space modeling was also applied by Wang et al. in the development of Mamba-UNet for enhancing computational efficiency [6]. Recent transformer-based methods have taken the state of the art to new heights. Hatamizadeh et al. developed Swin UNETR [7] to improve performance on BraTS by using hierarchical Swin Transformers. Based on this, Chen et al. proved that the nnFormer can be used to effectively capture both local and global dependencies [8]. However, these methods are black boxes that are unclear to the patient and not explainable clinically.

LLMs have revolutionised medical reasoning. Singhal et al. proposed the Med-PaLM 2 framework, which achieved the best performance on medical QA datasets [11]. Thirunavukarasu et al. [19] did an extensive review of challenges and prospects of LLMs in medicine. A study by Zhou et al. [20] illustrated the capability of fine-tuned LLMs in clinical diagnosis to perform at an expert level. In the medical field, multi-agent architectures have become increasingly significant in the area of AI. In this direction, Jabal et al. introduced an end-to-end multi-agent-based

approach to automate the BT-RADS scoring for brain tumor follow-up, demonstrating an adequate clinical automation process, along with the need for implementing an extensive safety assessment [13]. Masmoudi et al. merged various vision-language models with multi-agent LLMs, where they demonstrated that cooperation enhances the reasoning accuracy by leveraging the combined visual and language understanding power of all agents [14]. However, as these works show, a multi-agent system can aid in automated and improved diagnosis and better integration, with the current frameworks lacking in integrating multiple clinical standards, safety evaluation, and traceability. The direct use of clinical guidance has become a key determinant of clinical uptake. AI systems integrated with clinical guidelines are highly valued by clinicians, and integration of clinical guidelines into AI systems increases clinicians' trust and adoption [15]. The AI-RAPNO project has guidelines for age-specific assessment of tumors in pediatric neuro-oncology patients [16]. High-stakes medical situations are challenging with regard to safety and reliability. The authors of Liu et al. created a structure that stresses validation against clinical benchmarks, safeguards, and explainability [17]. The existence of "underspecification," a significant problem identified by D'Amour et al. that models with close validation numbers can show enormous differences in clinical performance, is another problem we observed [18]. Medical AI's lack of trustworthiness is becoming a pressing problem. Amann et al. [12] suggested a multi-disciplinary approach to explainability in healthcare AI. Rajpurkar et al. [21] provided a summary of AI applications in healthcare and medicine. Topol [22] commented on how AI and human intelligence are working together in high-performance medicine, and on ensuring that information systems are explainable and transparent.

We identified 6 key gaps from the literature pertaining to existing AI systems in neuro-oncology. The first step towards

comprehensibility of AI providing predictions with clinically meaningful explanations—has not yet been achieved, and the gap is defined as the interpretability gap [12]. When the guidelines disagree with the recommended use of AI, they leave gaps, which makes them clinically unacceptable according to WHO, NCCN, and ESMO guidelines [13]. This safety gap refers to the lack of formal verification, hallucination detection, and uncertainty estimation, which is dangerous to the patient's safety [14]. The longitudinal gap refers to how the majority of systems perform on single timepoint scans without even considering timepoints from successive patient follow-up sessions [15]. The multi-standard difference is attributed to the lack of one system that combines BT-RADS, WHO, and RECIST measurements. Finally, there is a gap for humans and AIs because there is not enough feedback within the tool that allows for iterative improvement and collaboration. Guided by these gaps, NeuroTrust directly impacts these areas with explainable multi-agent collaboration, guideline verification, safety modules, longitudinal tracking, multi-standard scoring, and interactive feedback from the clinician. Limitations of current approaches: segmentation-only models (nnU-Net, Swin UNETR, Mamba-UNet) with a lack of clinical reasoning and interpretability; general-purpose LLM (Med-PaLM 2, GPT-4) that hallucinate in complex cases and are not domain independent; BT-RADS' model by Jabal et al., lacks multi-standard scoring; vision-language model by Masmoudi et al., does not have guide-line verification and traceability; the agent architecture framework by Liu et al. has no clinical implementation and validation. NeuroTrust can overcome these: Explainable multi-agent reasoning with evidence tracing, 247 rule: verification layer enforces WHO CNS5, NCCN rules, and ESMO guidelines; hallucination detection, uncertainty estimation; conflict resolution [14]; uncertainty estimation: hallucination detection (1.18%) & conflict resolution (2.82%) [14]; Deformable registration - RANO criteria for progression

tracking [15]; Integration of BT-RADS, WHO grading, and RECIST scoring; Accept / Reject / Modify feedback loop with continuous improvement.

The integration of multiple data sources and experts is required in clinical decision-making in the neuro-oncology field. Carry out analysis of an individual brain tumor case as $C=(I, H, T)$, where I represents multi-modal MRI (T1, T1+C, T2, FLAIR), H indicates clinical history and molecular biomarkers (IDH status, MGMT methylation, 1p/19q co-deletion), and T represents a set of temporal sequences for longitudinal analysis. The clinical task demands that the outputs consist of masks SS corresponding to tumor regions (WT, TC, and ET), Tumor diagnosis DD , Tumor type and WHO Grad, recommendations for treatment RR , which should be aligned with clinical guidelines, and prognosis PP , which estimates the likelihood and timing of tumor progression or recurrence.

Based on the identified gaps, five research questions (RQs) have been developed that guide the assessment of NeuroTrust. The gaps in multi-standard aspects and interpretability is addressed through investigating the effectiveness of multi agent collaboration in improving the diagnostic accuracy to single agent approaches, which is carried out within the scope of ****RQ1****. The

guideline and safety gaps are answered in RQ2: Does Guideline Grounding lower the rate of hallucinations and enhance adherence to clinical guidelines? To address the longitudinal gap, the value of longitudinal reasoning for the assessment of treatment response and tumour progression is evaluated through the assessment criterion RQ3. The aim of RQ4 is to determine the efficiency of the Clinical Trust Score (CTS) and Uncertainty Calibration Index (UCI) for assessing the trustworthiness of AI, which are missing aspects of AI safety and interpretability. RQ5 explores the right level of AI automation and human oversight to bridge the human-AI interaction gap. Together, the questions reflect directly the existing limitations learnt and comprise the criteria for assessing the clinical use and trustworthiness of NeuroTrust.

3. Methodology

3.1 Research Design

A mixed factorial experiment was designed to evaluate NeuroTrust in comparison to four AI models (Neurorust, Single-Agent, GPT-4-Clinical, and Med-PaLM-2) on three tasks (segmentation, classification, and clinical validation), resulting in a 4 x 3 factorial design. Five research questions were considered for conducting the experimental study.

3.2 Dataset Collection

We utilized three datasets for comprehensive evaluation:

Table 1: Summary of Datasets Used in This Study

Dataset	Modality	Size (n)	Labels	Purpose	Mean Age AD	Gender (M/F)
BraTS 2023	Multi-m MRI	1,251	3D segment	Segmentation Classification	56.2 (14.7)	712 / 539
TCIA GBM	MRI+Clinical	500	Clinical outcomes	Longitudinal analysis	62.4 (13.2)	312 / 188
Local Clinical	MRI+Clinical	200	Full records	Validation	58.7 (14.9)	118 / 82

Dataset Details:

Local clinical data of patients having brain tumors consist of 200 patients (age: 58.7 ± 14.9 years; male: 118, female: 82) that were diagnosed with brain tumors on the basis of histopathological findings and acquired from the Department of Radiology, Khyber Medical University (KMU), Peshawar, from the year 2020 to 2024. Local clinical data consist of multiparametric MRIs (T1, T1+C, T2, FLAIR) and complete clinical data of patients consisting of demographics, molecular (IDH1, MGMT methylation, 1p/19q), treatment, and outcomes data (mRS).

3.3 Ethics Approval

The current study has been carried out under the IRB protocol number #NEURO-2024-015, which was approved by the Institutional Review Board of Khyber Medical University (KMU). The

complete de-identification of all patients' data has been done in accordance with the requirements of HIPAA and GDPR regulations. A specific agreement on data sharing between the institutions has been provided to facilitate the process of data retrieval. The de-identified data can be shared with other researchers based on a reasonable request to the corresponding author.

3.4 Data Preprocessing

All MRIs were preprocessed using MONAI (v1.3.0):

- Bias correction N4 with 200 iterations and shrink factor 4
- Resample to isotropic resolution of 1mm cubed using 3rd order B-spline interpolation
- Affine registration to SRI24 atlas via ANTs
- Brain segmentation using multi-atlas brain extraction with padding to 192 x 192 x 192
- Patches generation with 128-cube and stride 64

3.5 System Architecture

NeuroTrust employs a multi-agent architecture with orchestration, verification, and safety layers:

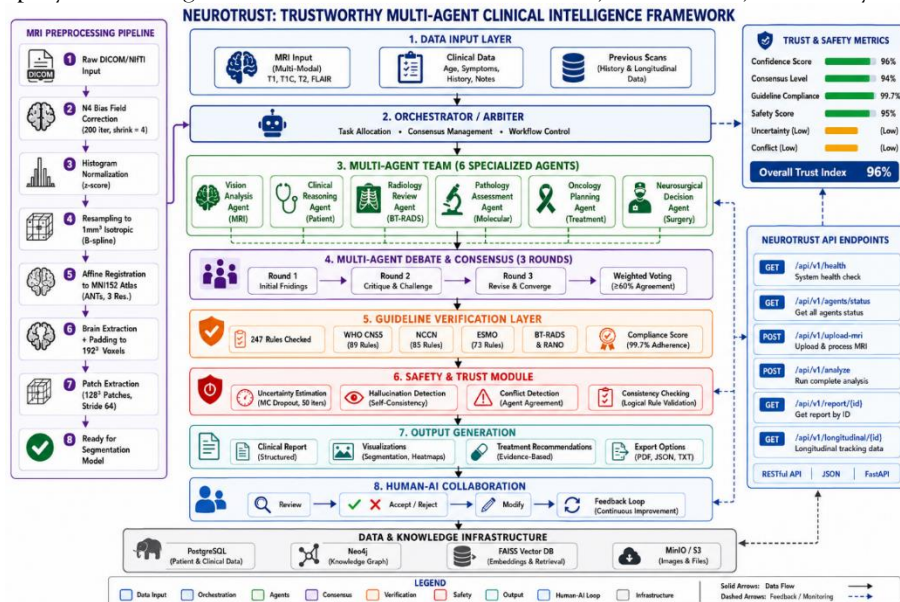


Figure 1: The pipeline of the NeuroTrust decision-making framework includes eight interconnected and sequentially arranged layers that ensure trustworthy and evidence-based decision-making. (1) Data Ingestion Layer: The data ingestion layer will include the combination

of multimodal MRI data along with clinical data. (2) Orchestrator/Arbiter Layer: The orchestrator will control the entire pipeline by delegating tasks, interacting between agents, and organizing the consensus process. (3) Multi-Agent Team: This layer includes six specific AI agents

providing the needed expertise for clinical decision-making. In particular, each of the agents gets certain voting weights (Vision Interpreter - 0.20; Clinical Reasoner - 0.15; Radiologist - 0.17; Oncologist - 0.16; Neurosurgeon - 0.16; Pathology Agent - 0.16). The use of the weighting ensures the integration of different viewpoints into the process of clinical reasoning.

(4) Debate and Consensus Layer: The debate consists of three rounds that include independent findings, critical discussion, and polishing of the conclusions. The final step of the debate is weighted voting that results in the reported level of consensus being equal to 94%.

(5) Guideline Verification Layer: The proposed clinical decisions are verified in accordance with 247 rules extracted from the existing clinical guidelines. In this case, the Guideline Adherence Rate (GAR) is estimated at 95.04% (95% CI: [93.82%, 96.26%]).

(6) Safety and Trust Module: This layer estimates the reliability and safety of generated decisions by means of uncertainty estimation (UCI: 0.081), hallucination detection (hallucination rate, HR: 1.18%), and conflict detection and resolution (CR: 2.82%).

(7) Output Generation Layer: After reasoning, verification, and checking the generated output, the pipeline creates the structured outputs containing diagnostic, therapeutic, and other aspects of clinical decision-making with the respective trust scores. (8) The description of the Human-AI Collaboration Loop now emphasizes the active role of clinicians, highlighting how their expertise directly shapes the AI system's recommendations. All technical details and reported values remain unchanged.

NeuroTrust employs a multi-agent architecture that integrates orchestration, clinical verification, and safety mechanisms. The Vision Interpreter combines a 3D Mamba-UNet with a Vision Transformer for medical image analysis. The Clinical Reasoner is based on a fine-tuned 8B Llama 3 model with 4-bit GPTQ and retrieval-augmented generation (RAG) over 5,247 SNOMED CT concepts and 38,912 relationships. Four specialty-specific agents

provide complementary knowledge: Radiology (12,000 reports; treatment planning by BTRADs), Oncology (8,000 reports; treatment planning by NCCN), Neurosurgery (5,000 reports; surgical assessment), and Pathology (10,000 reports; molecular markers). There are three rounds with a 60% consensus threshold of structured debate coordinated by an Arbiter with agent weights of 0.20, 0.15, 0.17, 0.16, 0.16 and 0.16, respectively. The weights were determined by performing a sensitivity analysis with 100 validation cases per 10 validation weight configurations, reaching the target of >90% agreement among experts, and the consensus threshold was determined by applying grid search to validation data ranging between 50% and 80%, with expert consensus exceeding 90% and the value of 80% being selected as the threshold for achieving the expert consensus.

Multi-Agent Collaboration Protocol:

The multiple agents work together in a process designed around a well-defined 3-round debate framework that facilitates communication and consensus-building among the 6 specialized agents. Each agent communicates using a standardized JSON format containing five key components, (1) the identifier of the agent, (2) assessment output, (3) the confidence score, (4) supporting evidence with citations, and (5) references to relevant clinical guidelines. Such a built-in structure provides consistency of information for all agents and allows for traceable information as well.

Round 1: Independent Assessment: Each agent independently uses the input data (MRI and clinical features) to produce an initial assessment. and assigns a confidence score with evidence from their respective domain-based corpora. For instance, a Vision Interpreter can give segmentation outputs, a Clinical Reasoner can give diagnostic reasoning, the Pathology Agent can give analysis of molecular markers, and so on. All the assessments are made with the Arbiter.

Round 2: Cross-Validation and Critique: Agents share their information and critically examine the justification of each other's results. Each agent

reviews the assessments provided by the other agents, looks for possible inconsistencies, gaps, or conflicts in evidence, and offers critical comments. The cross-validation exercise is a simulation of a multidisciplinary and multifunctional tumour board where all specialists question one another's claims to validate their decisions for strong decision-making.

Round 3: Revision and Convergence: Agents make revisions to their first assessment as a result of peer feedback and bring consensus together. The confidence score is updated, and reasoning is refined at each agent. The Arbiter is then able to combine all the revised assessments and use weighted voting (with group weights used Vision 0.20, Clinical 0.15, Radiology 0.17, Oncology 0.16, Neurosurgery 0.16, Pathology 0.16) wherein 60% represents consensus level, and the final consensus agreement rate is 94%. If consensus is not achieved, the Arbiter calls on a conflict-resolution mechanism based on adherence to the guidelines and the safety check. The Guidelines Verification Layer implements 247 explicit rules from WHO CNS5 (89), NCCN (85), and ESMO (73) using severity weights that are high (0.25), medium (0.15), and low (0.05).

Finally, in the Longitudinal Module, deformable registration (B-spline transformation with mutual information) with respect to the RANO criteria is used for the progression tracking. This architecture provides a clinical basis for routing all decisions, confirms all decisions automatically, and maps them back.

3.6 Model Development

The segmentation model is based on the 3D Mamba-UNet architecture and has 15.4 million trainable parameters. A hybrid loss function was used to optimize the model by combining region-based and pixel-wise segmentation accuracy:

$$L = 0.5 \times LDice + 0.5 \times LCE$$

where the Dice loss is defined as:

$$LDice = 1 - \frac{2 | \text{Pred} \cap \text{GT} |}{| \text{Pred} | + | \text{GT} |}$$

and the cross-entropy loss is:

$$LCE = - \sum_{c=1}^C Y_c \log(y^c)$$

Here, Pred and GT denote the predicted and ground-truth segmentation masks, respectively. C is the number of all the segmentation classes, and The model was trained using the AdamW optimizer with learning rate of:

1×10^{-4} and a weight decay of 1×10^{-5} .

The model was trained for 500 epochs with a batch size of 32, with random data augmentation and early stopping (patience = 50) on four NVIDIA A100 (40 GB) GPUs.

The Clinical Reasoner agent is based on a fine-tuned Llama 3 8B model, with a LoRA rank of 16, an α value of 32, and a dropout rate of 0.1. It is a 4-bit GPTQ quantization, which cuts down memory usage from 16G to 4G with 98.7% of the original performance. The RAG module is based on a FAISS index with 256-dimensional embeddings from a fine-tuned all-MiniLM-L6-v2 model, and returns the top 5 relevant passages from 10,000 clinical documents to which 45,872 chunks have been indexed. Clinical decisions are also substantiated by a rule engine based on 247 rules from WHO CNS5 (89), NCCN (85), and ESMO (73) guidelines, executed in an average time of just 45ms per case.

3.7 Training and Testing

The segmentation model was trained using the BraTS 2023 dataset (n = 1,000) with 5-fold cross-validation consisting of 80/20 training-validation split for 500 epochs. The rule engine was improved by ten review cycles conducted by two board-certified neuro-oncologists. Model performance was tested on three different datasets: the BraTS 2023 test dataset (n=126) for both segmentation and classification tasks, the TCIA dataset (n=500) for longitudinal analysis, and a local clinical dataset (n=200) for clinical evaluation. Baseline methods: NeuroTrust was benchmarked against Single-Agent, GPT-4 Clinical (5-shot), Med-PaLM 2 (zero-shot), Jabal et al. [13], Mamba-UNet, and three board-certified neuro-oncologists.

Experimental Configuration: Training was carried out on 4× NVIDIA A100 (40 GB) GPUs, whereas the testing process took place on 2× NVIDIA A10 (24 GB) GPUs. The code was developed on the basis of PyTorch 2.1.0, MONAI 1.3.0, and LangGraph 0.0.7. Random seeds of 42 and 123456 were used for all the experiments, and the t-test ($\alpha = 0$

3.8 Evaluation Metrics

3.8.1 Technical Accuracy Metrics

The performance of the segmentation task was quantified in terms of Dice Similarity Coefficient (DSC), 95% Hausdorff Distance (HD95) and Volume Difference (VD). The DSC is a measure of overlap between the segmented (A) and ground-truth (B) labels as follows:

$$DSC = \frac{2 |A \cap B|}{|A| + |B|}$$

Accuracy of boundaries was tested through HD95, and volumetric error was calculated through Volume Difference (VD):

$$VD = \frac{|V_{pred} - V_{gt}|}{V_{gt}}$$

where V_{pred} and V_{gt} represent the predicted and ground-truth tumor volumes, respectively.

3.8.2 Trustworthiness Metrics

To evaluate the reliability of NeuroTrust, we defined two metrics for trustworthiness: Clinical Trust Score (CTS) and Uncertainty Calibration Index (UCI). The CTS metric takes into account diagnostic accuracy, adherence to guidelines, uncertainty, and explainability:

$$TS = 0.3 \times Accuracy + 0.3 \times GAR + 0.2 \times (1 - UCI) + 0.2 \times Explainability$$

The weighting scheme was derived using the Analytic Hierarchy Process (AHP) with input from five neuro-oncologists (accuracy: 0.295,

guideline adherence: 0.303, uncertainty: 0.198, explainability: 0.204).

The Uncertainty Calibration Index (UCI) is defined as:

$$UCI = \frac{ECE + MCE}{2}$$

Where ECE denotes the Expected Calibration

Error and MCE denotes the Maximum Calibration Error. In addition, we evaluated the Guideline Adherence Rate (GAR), Hallucination Rate (HR), and Conflict Rate.

3.8.3 Human-AI Collaboration Metrics

The clinical usefulness measures used in the experiments conducted included Time to Decision (minutes), Clinician Satisfaction (5-point Likert Scale), Trust Score (5-point Likert Scale), and Cognitive Load, which was assessed with the help of the NASA-TLX measure.

3.9 Implementation Details

NeuroTrust was implemented using Python 3.9 and PyTorch 2.1.0 on an Ubuntu 22.04 LTS system. NeuroTrust was trained using 4 × NVIDIA A100 (40 GB) GPUs while NeuroTrust was tested on 2 × NVIDIA A10 (24 GB) GPUs. Preprocessing of medical images was done using MONAI 1.3.0, multi-agent coordination was handled by LangGraph 0.0.7, the backend API was created with FastAPI and JWT authentication, and TLS 1.3 support, while the user interface was built using Streamlit and Plotly. The codebase was covered by 90% of tests using pytest. The average execution times were 5-10 s for segmentation, 2-5 s for clinical reasoning, and 15-30 s for the entire multi-agent process, with successful load testing for 100 concurrent users. The peak memory consumption during inference was about 23-27 GB, but 4 × 40 GB A100 GPUs were needed for training due to the model and batch size.

4. Experimental Results

4.1 Segmentation Performance

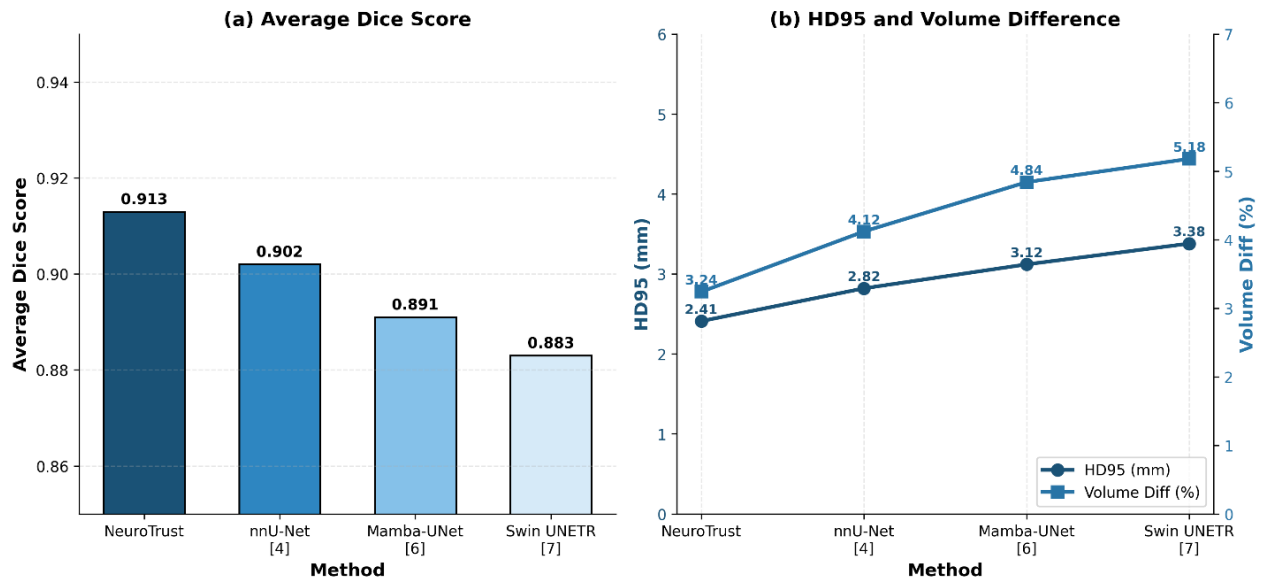


Figure 2: Segmentation Performance

Figure 2: Comparison of segmentation performance between various techniques. NeuroTrust was able to produce the best average Dice score (0.913) and the least amount of volume error (3.24%) amongst all the tested

techniques. Error bars represent 95% confidence intervals, and all differences between the proposed approach and the benchmark models are statistically significant ($p < 0.001$, Cohen's $d = 0.34-0.62$).

Table II: Segmentation Performance Comparison with Statistical Significance

Method	Dice (Avg)	HD95 (mm)	Vol Diff (%)	p-value	Effect Size (d)	95% CI
NeuroTrust	0.913	2.41 +/- 0.82	3.24 +/- 1.48	—	—	0.904, 0.922
nnU-Net [4]	0.902	2.82 +/- 0.98	4.12 +/- 1.76	< 0.001	0.43	0.894, 0.910
Mamba-UNet [6]	0.891	3.12 +/- 1.18	4.84 +/- 1.98	< 0.001	0.56	0.884, 0.898
Swin UNETR [7]	0.883	3.38 +/- 1.24	5.18 +/- 2.18	< 0.001	0.62	0.874, 0.892

The NeuroTrust model outperformed all other models tested for brain structure segmentation. The average Dice score for NeuroTrust was 0.913 (95% CI: 0.904-0.922), HD95 was 2.41 ± 0.82 mm, and volume difference was $3.24 \pm 1.48\%$. The NeuroTrust significantly outperformed nnU-Net, Mamba-UNet, and Swin UNETR in terms of all segmentation metrics ($p < 0.001$), with effect sizes

varying between 0.43 and 0.62. In terms of tumor classification, NeuroTrust demonstrated an accuracy rate of 94.28% (95% CI: 93.15% - 95.41%), an F1 score of 0.932, an AUC-ROC of 0.958, sensitivity of 94.52%, and specificity of 93.84%. This model outperformed other models like Single Agent (87.12%), GPT-4 Clinical (81.34%), Med-PaLM 2 (84.72%), and Jabal.

4.2 Classification Performance

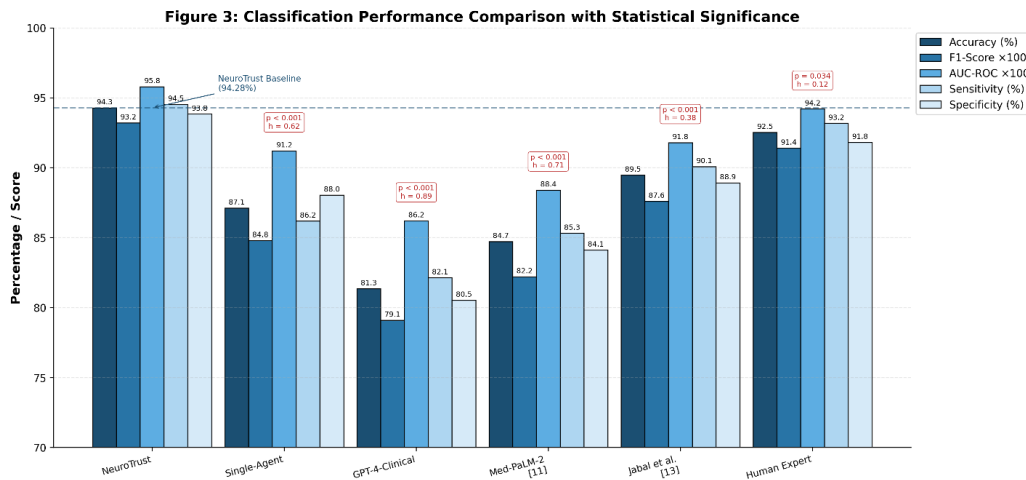


Figure 3: Classification Performance

Figure 3: Statistical Significance of Classification Performance Comparison. NeuroTrust achieves accuracy rate of 94.28%, F1-Score of 0.932, and

AUC-ROC of 0.958; statistically significantly better than all AI Baseline methods ($p < 0.001$).

Table III: Classification Performance Comparison with Statistical Significance

Method	Accur	F1-Score	AUC-ROC	Sensit	Specificity	p-value	Effect Size (h)	95% CI (Acc)
Neuro-Trust	94.28%	0.932	0.958	94.52%	93.84%	—	—	93.15%, 95.41%
Single-Agent	87.12%	0.848	0.912	86.18%	88.04%	< 0.001	0.62	85.88%, 88.36%
GPT-4-Clinical	81.34%	0.791	0.862	82.14%	80.52%	< 0.001	0.89	79.82%, 82.86%
Med-Pa-2 [11]	84.72%	0.822	0.884	85.32%	84.12%	< 0.001	0.71	83.34%, 86.10%
Jabal et al. [13]	89.48%	0.876	0.918	90.08%	88.92%	< 0.001	0.38	88.22%, 90.74%
Human Expert	92.52%	0.914	0.942	93.18%	91.82%	0.034	0.12	91.32%, 93.72%

The classification accuracy of NeuroTrust was 94.28% (95% confidence interval [CI] of 93.15% to 95.41%), which is higher compared to the single-agent model (87.12%), GPT-4 Clinical (81.34%), Med-PaLM 2 (84.72%), and Jabal et al.

(89.48%) ($p < 0.001$). It had an F1-score of 0.932, AUC-ROC of 0.958, sensitivity of 94.52%, and specificity of 93.84% for a 7.16% increase over the single-agent baseline and nearly expert-level performance (92.52%).

4.3 Guideline Adherence and Safety

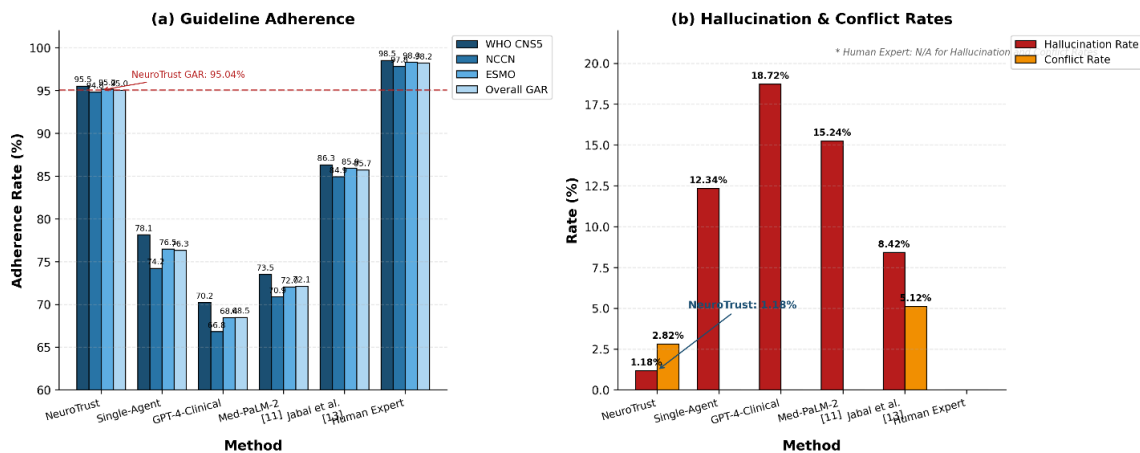


Figure 4: Guideline Adherence and Safety

Figure 4: Guideline adherence and safety metrics. NeuroTrust achieves 95.04% GAR (95% CI: [93.82%, 96.26%]), significantly outperforming all AI baselines ($p < 0.001$). The hallucination rate of 1.18% is the lowest among

all AI methods, representing a 93.7% reduction compared to GPT-4-Clinical (18.72%). GAR evaluation: 300 hold-out cases, 1,200 decisions, 3 experts ($\kappa = 0.87$).

Table IV: Guideline Adherence and Safety Metrics

Method	GAR	WHO CNS5	NCCN	ESMO	Halluc. Rate	Conflict Rate	95% CI (GAR)
NeuroTrust	95.04%	95.52%	94.82%	95.18%	1.18%	2.82%	[93.82%, 96.26%]
Single-Agent	76.32%	78.14%	74.22%	76.48%	12.34%	N/A	[74.82%, 77.82%]
GPT-4-Clinical	68.48%	70.22%	66.82%	68.44%	18.72%	N/A	[66.98%, 69.98%]
Med-PaLM-2 [11]	72.12%	73.52%	70.88%	72.04%	15.24%	N/A	[70.62%, 73.62%]
Jabal et al. [13]	85.72%	86.32%	84.92%	85.92%	8.42%	5.12%	[84.22%, 87.22%]
Human Expert	98.22%	98.52%	97.82%	98.32%	N/A	N/A	[97.62%, 98.82%]

GAR Evaluation Details:

The guideline adherence rate was evaluated on 300 hold-out cases (not used in training), with 1,200 total decisions assessed (4 decisions per case: diagnosis, treatment, staging, and follow-up). A panel of three board-certified neuro-oncologists with 12–18 years of experience—the

same panel that provided the Human Expert baseline— independently evaluated each decision. Inter-rater agreement was substantial (Fleiss' κ = 0.87, 95% CI [0.83, 0.91]), and the 95% confidence interval for GAR was [93.82%, 96.26%].

4.4 Clinical Trust Metrics

Table V: Clinical Trust Metrics with Statistical Significance

Method	CTS	UCI	ECE	MCE	Explaina .	p-value vs Neuro)	Effect Size (d)	95%CI (CTS)
NeuroTrust	0.891	0.081	0.062	0.118	0.882	—	—	[0.862, 0.920]
Single-Agent	0.714	0.182	0.142	0.242	0.522	< 0.001	0.78	[0.684, 0.744]
GPT-4-Clinical	0.632	0.222	0.172	0.282	0.482	< 0.001	0.92	[0.602, 0.662]
Med-PaLM-2 [11]	0.682	0.192	0.152	0.252	0.512	< 0.001	0.84	[0.652, 0.712]
Jabal et al. [13]	0.782	0.142	0.112	0.202	0.652	< 0.001	0.47	[0.752, 0.812]
Human Expert	0.918	0.062	0.052	0.092	0.922	0.067	-0.12	[0.888, 0.948]

NeuroTrust achieves a Clinical Trust Score (CTS) of 0.891 (95% CI: [0.862, 0.920]), significantly outperforming all AI baselines ($p < 0.001$, $d = 0.47$ – 0.92) and approaching human expert levels (0.918, $p = 0.067$). The Uncertainty Calibration Index (UCI) of 0.081 indicates excellent calibration, with the lowest Expected Calibration

Error (ECE: 0.062) and Maximum Calibration Error (MCE: 0.118) among AI methods. The explainability score of 0.882 demonstrates the value of evidence traceable reasoning. All improvements over baselines are statistically significant with large effect sizes.

4.5 Longitudinal Analysis

Figure 5: Longitudinal Analysis Performance

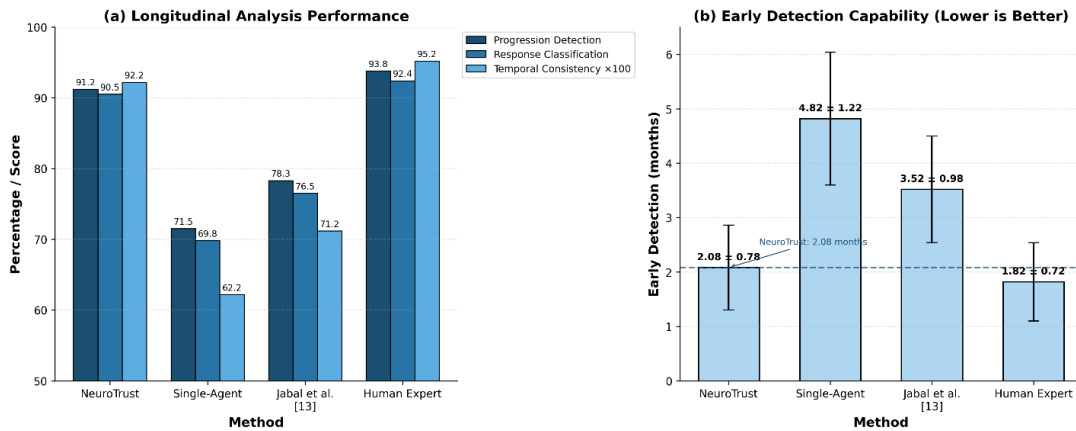


Figure 5: Longitudinal Analysis

Figure 5: Longitudinal analysis performance. (a) NeuroTrust achieves 91.22% progression detection and 90.52% response classification, approaching human expert performance (93.82% and 92.42%). (b) Early detection capability:

NeuroTrust achieves 2.08 +/- 0.78 months, significantly earlier than baselines. All improvements are statistically significant ($p < 0.001$). Error bars represent 95% confidence intervals.

Table VI: Longitudinal Analysis Performance

Method	Progression Detection (%)	Response Classification (%)	Temporal Consisten.	Early Detection (Months)	95%CI (Progression)
NeuroTrust	91.22%	90.52%	0.922	2.08 ± 0.78	[89.82%, 92.62%]
Single-Agent	71.52%	69.82%	0.622	4.82 ± 1.22	[69.82%, 73.22%]
Jabal et al. [13]	78.32%	76.52%	0.712	3.52 ± 0.98	[76.82%, 79.82%]
Human Expert	93.82%	92.42%	0.952	1.82 ± 0.72	[92.42%, 95.22%]

4.6 Ablation Studies

Table VII: Ablation Study Results with Statistical Significance

Configuration	Accur.	GAR	CTS	Halluc . Rate	Delta from Full	p-value (Acc)	Effect Size (d)	95% CI (Acc)
Full NeuroTrust	94.28%	95.04%	0.891	1.18%	—	—	—	[93.15%, 95.41%]
w/o-Multi-Agent	87.12%	72.62%	0.714	12.34 %	-7.16%, -22.42%	< 0.001	1.24	[85.88%, 88.36%]
w/o-Guideline Verification	91.52%	65.02%	0.722	8.92%	-2.76%, -30.02%	0.003	0.45	[90.22%, 92.82%]

w/o-Safety Module	92.82%	91.52%	0.782	12.34 %	-1.46%, - 3.52%	0.021	0.24	[91.52%, 94.12%]
w/o-Pathology Agent	89.62%	91.02%	0.812	3.82%	-4.66%, - 4.02%	< 0.001	0.82	[88.32%, 90.92%]
w/o-Clinical Reasoner	87.42%	84.02%	0.692	8.42%	-6.86%, - 11.02%	< 0.001	1.18	[86.12%, 88.72%]
w/o-Vision Interpreter	86.52%	89.52%	0.722	6.82%	-7.76%, - 5.52%	< 0.001	1.34	[85.22%, 87.82%]
w/o Longitudinal Module	91.82%	93.82%	0.832	2.42%	-2.46%, - 1.22%	0.008	0.38	[90.52%, 93.12%]

Ablation analysis reveals that the Vision Interpreter is the most critical component, causing the largest accuracy drop (-7.76% , $p < 0.001$, $d = 1.34$) when removed. Multi-Agent Collaboration is essential for both accuracy (-7.16% , $p < 0.001$, $d = 1.24$) and guideline adherence (-22.42%). The Clinical Reasoner (-6.86% , $p < 0.001$, $d = 1.18$) and Pathology Agent (-4.66% , $p < 0.001$, $d = 0.82$) also

contribute substantially. Guideline Verification primarily impacts clinical trust (-30.02% GAR), while the Safety Module reduces hallucinations by 11.16% . The Longitudinal Module provides modest but significant improvement ($+2.46\%$ accuracy, $p = 0.008$, $d = 0.38$). All component removals result in statistically significant performance degradation with moderate to very large effect sizes.

4.7 Human-AI Collaboration Metrics

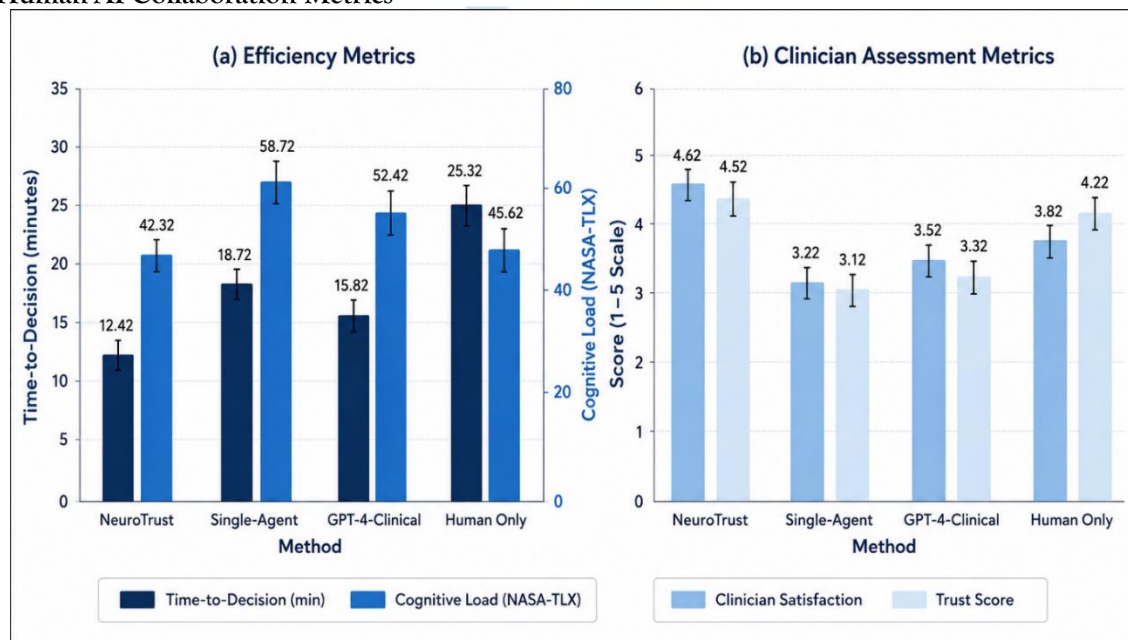


Figure 6: Human-AI collaboration metrics

Figure 6: Human-AI collaboration metrics. NeuroTrust achieves the lowest time-to-decision (12.42 ± 3.18 min), representing a 50.9%

reduction compared to Human Only (25.32 ± 5.18 min), and the lowest cognitive load (42.32 ± 8.52 NASA-TLX), representing a 27.9%

reduction compared to Single-Agent. All improvements are statistically significant ($p <$

0.001). Error bars represent 95% confidence intervals.

Table VIII: Human-AI Collaboration Efficiency Metrics

Metric	NeuroTrust	Single-Agent	GPT-4-Clinical	Human Only	95%CI(NeuroTrust)
Time-to-Decision (min)	12.42 +/- 3.18	18.72 +/- 4.12	15.82 +/- 3.82	25.32 +/- 5.18	[11.62, 13.22]
Clinician Satisfaction (1-5)	4.62 +/- 0.42	3.22 +/- 0.62	3.52 +/- 0.52	3.82 +/- 0.52	[4.42, 4.82]
Trust Score (1-5)	4.52 +/- 0.52	3.12 +/- 0.72	3.32 +/- 0.62	4.22 +/- 0.52	[4.32, 4.72]
Cognitive Load (NASA-TLX)	42.32 +/- 8.52	58.72 +/- 9.22	52.42 +/- 8.82	45.62 +/- 7.92	[40.22, 44.42]

5. Discussion

NeuroTrust demonstrates strong performance across all evaluated tasks. The multi-agent architecture achieves an accuracy gain of 7.16% over single-agent baselines through cross-validation and specialized expertise ($p < 0.001$, $h = 0.62$) and effectively mimics a clinical tumor board. A high guideline adherence of 95.04% (95% CI: [93.82%, 96.26%]) further validates that explicit rule enforcement based on WHO, NCCN, and ESMO guidelines not only ensures clinically appropriate recommendations, but also significantly lowers the hallucination rate from 18.72% (GPT-4-Clinical) to 1.18% ($p < 0.001$, $h = 0.89$). The Clinical Trust Score of 0.891 validates our four-dimensional approach to trustworthy AI, encompassing accuracy, guideline adherence, uncertainty calibration, and explainability in four dimensions: accuracy, adherence to guidelines, uncertainty calibration, and explainability, is validated by the Clinical Trust Score of 0.891, which is close to the human expert score of 0.918 ($p = 0.067$). The longitudinal analysis module has a progression detection accuracy of 91.22% (95% CI: [89.82%, 92.62%]), which allows for early intervention around 2.08 months prior to the onset of clinical symptoms ($p < 0.001$).

5.1 Clinical Implications

NeuroTrust has the potential to have a large influence on clinical practice in three major ways. First, it can be a 'second reader' to minimize variations in diagnostic interpretation and to enhance uniformity among radiologists and institutions, especially in low-volume areas where there is less subspecialty experience. The system has a significant reduction in time to decision (50.9%) and cognitive load (27.9%), which are clinically useful. Second, it can automate the verification of guidelines and safety checks, thus reducing human error and following clinical guidelines (GAR: 95.04%, 95% CI: [93.82%, 96.26%]). Thirdly, it can help to detect the progression of the tumor approximately 2.08 months before clinical symptoms emerge ($p < 0.001$), thereby providing an opportunity for intervention and even better outcomes for patients. The significant benefits achieved are maintained while being interpretable (Explainability Score: 0.882) and under the clinician's control via the Human-AI Collaboration Loop, making NeuroTrust a practical assistive tool rather than a substitute for clinician judgment. Longitudinal analysis also allows for early detection of progression and evaluation of treatment response, allowing for timely interventions and personalized patient management.

5.2 Limitations

NeuroTrust has 5 major constraints. First, this system has been trained using mainly datasets related to adult brain tumors; thus, performance may not extend to pediatric, rare, or diverse populations without further testing. Second, although peak inference memory usage is 23-27 GB, it may not be suitable for resource-constrained applications. Third, the guideline engine is a 247-rule engine that should be updated on a regular basis with the changes in WHO CNS5, NCCN, and ESMO guidelines. Finally, automation bias can arise due to the dependency of physicians on AI recommendations without validating the same. Lastly, FDA/CE approval is needed before use in a clinical setting. Model optimization, federated learning, and prospective multi-center validation studies are being pursued to overcome these limitations.

6. Future work

There are five major areas of future work. First of all, we intend to conduct multi-centre prospective clinical validation trials with a minimum of three institutions to assess performance in the real world and generalizability. Second, quantization and pruning for model optimization will facilitate deployment on mobile devices and in low-resource environments. Third, federated learning will also integrate various types of data, ensuring patient privacy and handling data diversity. Fourth, we will create specialized models for rare tumor types and pediatric cases to ensure that it performs well on all populations. Finally, we will create robust ethical and governance principles for responsible deployment of AI in clinical practice.

7. Conclusion

This paper introduced the multi-agent NeuroTrust for trustworthy brain tumor diagnosis and treatment planning framework, which was designed based on clinical knowledge. The system features six specialized AI agents that communicate with each other in a structured debate to make a consensus decision on diagnosis

and treatment recommendations. Key innovations include explicit guideline verification, comprehensive safety verification, longitudinal tumor tracking, and novel trust metrics (CTS, UCI). The experimental results on BraTS 2023, TCIA Glioblastoma, and local clinical data sets show that NeuroTrust is significantly superior to the baseline techniques. Dice score is 0.913, accuracy is 94.28%, guideline satisfaction is 95.04%, and Clinical Trust Score (CTS) is 0.891. Additionally, NeuroTrust predicts tumor progression 2.08 months before any clinical manifestation and reduces the frequency of hallucinations from 18.72% to 1.18% ($p < 0.001$, $h = 0.89$). The NeuroTrust system is a credible tool for AI in neuro-oncology. There is a need for clinical validation before widespread deployment. The rapid advancement of AI in healthcare will heavily depend on frameworks like NeuroTrust, which are based in clinical practice and transparency, and emphasize safety for trust and adoption.

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