

UCSF

UC San Francisco Electronic Theses and Dissertations

Title

Predicting Meningioma Genetics from multi-sequence Magnetic Resonance Imaging using Machine Learning

Permalink

<https://escholarship.org/uc/item/48v201hx>

Author

Bhalerao, Radhika

Publication Date

2024

Peer reviewed|Thesis/dissertation

Predicting Meningioma Genetics from multi-sequence Magnetic Resonance Imaging using Machine Learning

by
Radhika Bhalerao

THESIS
Submitted in partial satisfaction of the requirements for degree of
MASTER OF SCIENCE

in
Biomedical Imaging

in the
GRADUATE DIVISION
of the
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Approved:

DocuSigned by:

Andreas Rauschecker

Andreas Rauschecker

704B2305CFB3407...

Chair

DocuSigned by:

Yang Yang

Yang Yang

DocuSigned by:

Leo Sugrue

Leo Sugrue

DocuSigned by:

Adam Yala

Adam Yala

34415202AD984C5...

Committee Members

DEDICATION AND ACKNOWLEDGEMENTS

Foremost, I would like to thank my mentor, Dr. Andreas Rauschecker. I am sincerely grateful for your guiding hand in my project and my growth in the field. Your advice and encouragement have sparked excitement in me for pursuing a future in research and confidence in my ability to succeed in doing so.

I would also like to acknowledge Dr. Leo Sugrue, Dr. Yang Yang, and Dr. Adam Yala, members of my advisory committee, who took the time to understand my research interests and for their valuable guidance. I would also like to thank Harshita Kukreja for helping with the experiments related to large language models. My classmates have been a constant wellspring of comfort and joy through this program, and I feel so lucky to have spent the past year alongside them. I am consistently inspired by their tenacity and creativity. I look forward to hearing about all the amazing success they find in their futures. Last but not least, I could not have completed this thesis without the support and love of my mom and dad.

PREDICTING MENINGIOMA GENETICS FROM MULTI-SEQUENCE MAGNETIC RESONANCE IMAGING USING MACHINE LEARNING

Radhika Bhalerao

ABSTRACT

Meningiomas, the most prevalent primary central nervous system tumors, present a significant challenge in neuro-oncology due to their variable clinical behaviors and recurrence rates (1). While magnetic resonance imaging (MRI) remains the primary diagnostic tool, recent advancements in our understanding of meningioma genetics have highlighted the critical role of molecular profiles in determining tumor behavior and treatment outcomes (2). This thesis presents a comprehensive exploration of the intersection between imaging features, genetic biomarkers, and artificial intelligence in meningioma management, with the overarching goal of enhancing diagnostic accuracy, treatment planning, and prognostication.

The work is structured in four interconnected chapters, each addressing a crucial aspect of this multifaceted challenge:

Chapter 1 introduces a novel, large-scale dataset comprising 3,101 pre-processed, multi-sequence MR images along with corresponding genetic and demographic data from patients with histopathological confirmed intracranial meningiomas. This dataset serves as the foundation for subsequent analyses and model development, offering researchers an unprecedented resource to investigate imaging-genetic correlations in meningiomas.

Building upon this dataset, Chapter 2 presents the development of a machine learning model designed to predict genetic mutation status in meningiomas using preoperative multi-sequence MRI. By combining radiomics features, convolutional neural network

(CNN) outputs, and clinically informed features, this approach demonstrates the potential for non-invasive assessment of genetic biomarkers, which could significantly impact clinical decision-making, especially in settings where extensive genetic testing is not readily available.

Chapter 3 addresses a fundamental challenge in medical imaging AI: accurate identification of MRI sequences. Recognizing the limitations of existing methods, this chapter proposes an innovative approach using large language models (LLMs) to parse MRI metadata for sequence identification. This method offers improved robustness to human errors in metadata entry and better generalization across institutions, potentially streamlining the preparation of large, multi-center datasets for AI model training.

Finally, Chapter 4 provides a comprehensive discussion of the findings, their implications for clinical practice and research, and future directions for advancing the field of meningioma management through integrated imaging and genetic approaches.

Throughout this thesis, we demonstrate the potential of combining advanced imaging techniques, genetic profiling, and artificial intelligence to enhance our understanding and management of meningiomas. By bridging the gap between radiological features and underlying genetic alterations, we aim to pave the way for more personalized and effective treatment strategies, ultimately improving outcomes for patients with these complex tumors.

TABLE OF CONTENTS

CHAPTER 1: A MENINGIOMA MULTI-SEQUENCE MRI AND GENE PANEL DATASET.....	1
1.1 Background.....	1
1.2 Methods.....	2
CHAPTER 2: PREDICTING MENINGIOMA GENOMICS FROM MULTI-SEQUENCE MRI.....	5
2.1 Background.....	5
2.2 Methods.....	7
2.3 Results.....	9
CHAPTER 3: BRAIN MRI SEQUENCE IDENTIFICATION USING LARGE LANGUAGE MODELS.....	11
3.1. Background	11
3.2 Methods	12
3.3 Results.....	13
CHAPTER 4: CONCLUSION AND DISCUSSION.....	15
REFERENCES.....	18

LIST OF FIGURES

FIGURE 1: Demographic Information of the Meningioma Radiogenomic Dataset.....	3
FIGURE 2: ROC curves for the most frequent gene mutations.....	9
FIGURE 3: Confusion matrix results from LLM classifier	13
FIGURE 4: Workflow of LLM modality classifier	14

LIST OF TABLES

TABLE 1: Gene mutation frequency and AUC, sensitivity, specificity metrics	10
---	----

CHAPTER 1: A MENINGIOMA MULTI-SEQUENCE MRI AND GENE PANEL DATASET

Background

Meningiomas are slow growing tumors that form in the meninges, one of the three membranes that surround the brain and the spinal cord. Meningiomas are the most common primary central nervous system (CNS) tumor and are the only brain tumors more common in women and elderly patients. Most (80%) meningiomas are fifth edition CNS World Health Organization (WHO) grade I tumors and can recur with previous studies showing a recurrence rate of up to 47% with long term follow-up (3). Higher grade meningiomas with WHO grades 2 and 3 are associated with higher morbidity and recurrence rates despite optimal management. In 2021, WHO revised meningioma grading criteria to incorporate histopathological criteria and molecular profiles. The presence of TERT promoter mutations and CDKN2A/CDKN2B deletions indicate a grade 3 meningioma with increased recurrence risk (2). While the molecular landscape of meningiomas is evolving, MRI is the primary imaging modality for current diagnosis and treatment planning for meningiomas. As such, there is a need for improved understanding of the connection between imaging and genetic biomarkers, which can help guide patient-specific treatment strategies.

Here we present a clinical multi-sequence MRI and gene panel retrospective dataset which includes 3,101 pre-processed, multi-sequence MR images, demographic data, and the genetic profile of meningiomas. The purpose of this dataset is to facilitate exploration of the relationship between imaging and genetic biomarkers in intracranial meningiomas.

Further predictive algorithms developed using this data will allow for assessment from baseline imaging identification of possible gene expressions, which can help guide treatment especially in care centers where such extensive gene paneling is not accessible. This chapter describes the data collection and processing for the meningioma dataset.

Methods

Study Population

The study population consisted of adult patients diagnosed with intracranial meningioma of any CNS WHO grade or subtype confirmed with histopathology. The participants were identified through deidentified data from the cBio portal and Information Commons at University of California San Francisco medical center. If patients had received UCSF500 gene panel testing and were confirmed with meningioma diagnosis, corresponding imaging from Imaging Commons deidentified database was obtained (**Figure 1**).

Imaging Data

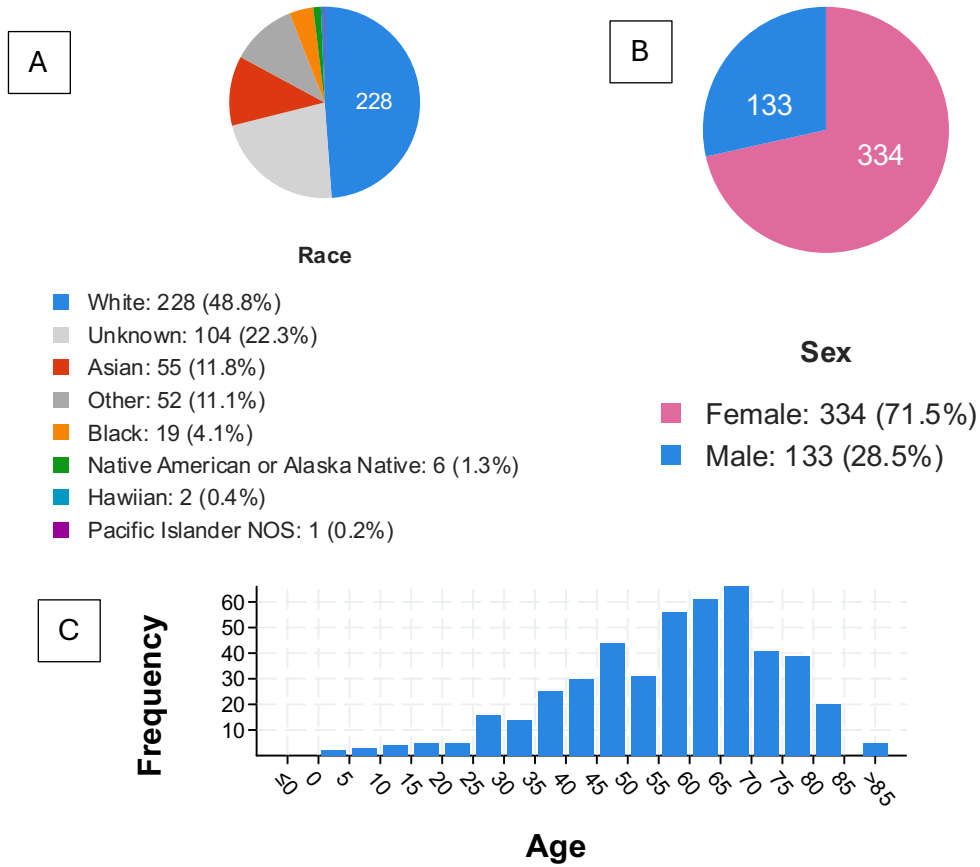


FIGURE 1: Demographic Information of the Meningioma Radiogenomic Dataset

The imaging data included pre-operative and pre-treatment multi-sequence MR images of the brain including pre-contrast T1-weighted, post-contrast T1-weighted, T2-weighted, T2-weighted fluid attenuated inversion recovery (FLAIR), Gradient Echo (GRE), Diffusion-weighted imaging (DWI), and Average diffusion coefficient (ADC) sequences. Using clinical notes and manual validation of images, only the pre-surgical scans were retained. Imaging parameters were variable between different acquisitions.

Image Processing

All data were converted to NIfTI format using dcm2niix v2.0. All sequences were registered to the anatomical space of the T1-weighted image using automated nonlinear registration tools and manually verified. Resampled coregistered data were skull stripped and segmented using an in-house meningioma segmentation pipeline. All images also underwent coil bias correction and intensity normalization.

Genetic Data

UCSF500 gene panel results were obtained from the cBio portal. All sample types were from the primary sample type. Presence of whether the mutated gene is present were recorded as a matrix of binary values, 0 for not present, 1 for present.

Demographic Data

Demographic data was obtained using the cBio portal. The age range of patients spanned from 2 to 85 years and 71.5% of the cohort was female, 28.5% male. Ethnicity, race, and survival status were also included.

CHAPTER 2 : PREDICTING MENINGIOMA GENOMICS FROM MULTI-SEQUENCE MRI

Background

Meningioma is the most common type of central nervous system tumor and high grade meningiomas have increased risk of returning after treatment. Surgery, radiation, or observation are the three treatment methods and for high grade meningiomas, often radiation plus surgery combined is often inadequate (3). Genomic understanding of meningiomas has been shown to identify genetic biomarkers that predict tumor behavior and prognosis. These genetic drivers may also provide therapeutic targets for drug therapy (4). However, widespread and extensive tumor genetic testing is limited due to cost and need for biopsy (5). In cases where biopsy is not possible, meningioma treatment is based of imaging alone. Therefore, there is a need to understand how clinically relevant meningioma biomarkers can be inferred based off preoperative baseline MRI.

Previous studies in other types of brain tumors, such as glioblastoma, have shown that image features extracted from image segmentations through radiomics or convolutional neural networks (CNNs) or a combination of these features lead to successful oncologic inference tasks (6). Most prior work has focused on using features from segmentations or single slices, not preserving the location of a tumor in the whole brain as a feature.

However, studies in underlying tumor genetics shows that tumor locations correlate with underlying mutations (7). Convexity meningiomas usually harbor NF2 and SMARCB1 mutations. Brain convexity harbors more Grades 2 and 3 meningiomas than skull base. Skull base meningiomas harbor mutations in AKT1, KLF4, TRAF7, SMO, PIK3CA, and POLR2A genes. Spinal cord meningiomas often harbor SMARCE1 mutations. Locations of

Grade 3 meningiomas are highlighted in the right inset of panel (B). Grade 1 (benign) meningiomas commonly occur in the parasagittal and posterior fossa with alterations in chromosome 22 and variation in the second allele of neurofibromatosis 2 (NF2). Genetic alterations in AKT1, PIK3CA, SMO, TRAF7, KLF4, and SMARCB1 also take place in Grade 1 meningiomas in the presence or absence of NF2 mutations depending on the gene. Grade 2 (atypical) meningiomas tend to exist in the brain convexity and spine and can have a loss of a copy of chromosomes 1, 10, or 14 in addition to genetic alterations in NF2 and SMARCEL. Grade 3 (malignant or anaplastic) meningiomas are characterized by the absence of chromosome 9p and genetic alterations of NF2, BAP1, LDH229, CDKN2 A/B, and pTERT. BAP1 mutations are frequent rhabdoid meningioma subtype, rhabdoid meningiomas with BAP1 mutations are more aggressive compared to rhabdoid meningiomas devoid of these mutations (7). Therefore, there is a need for anatomical MRI images in meningioma assessment, specifically the location of the tumor to the whole brain as a clinically relevant feature in machine learning models.

TERT promoter mutations are associated with more aggressive behavior and increased cellular proliferation in meningiomas. Tumors with TERT promoter mutations tend to have higher cellularity and a higher proliferation rate, which can contribute to the restricted diffusion pattern observed on DWI. Shin et. al explored this relationship in a small cohort study with surgically confirmed grade II meningiomas. ADC 10th percentile was found to be an independent predictor of TERT promoter mutation status (3). As such, other modalities of imaging such as DWI or ADC might infer critical information about meningioma genetics.

The goal of this study is to build a clinically relevant, interpretable, and efficient machine learning model that can predict genetic mutation status of a meningioma from preoperative multi-sequence MR imaging. Our method leverages not only the strength of predefined radiomics features and learned CNN features in a 3D space, but features based on clinical knowledge to provide improved prediction performance and interpretability. This model was trained on the large (n=443) patient cohort (See Chapter 1) of surgically confirmed meningioma patients who underwent a 500 cancer gene mutation panel test.

Methods

Image Preprocessing and Radiomics Feature Extraction

As the different MRI sequences were acquired with different number of slices, the middle 3 slices for each sequence were acquired. ADC values were computed using segmentations and PyRadiomics 2.2.0 command line tools with default extraction parameters. Tumor location was identified using MNI atlas based registration on the post-contrast T1 images.

Network Architecture

A CNN classifier was constructed using TensorFlow 2.4. The CNN limb consisted of a 3D multiscale deep convolutional autoencoder with 1, 1, 2, and 2 bottleneck residual blocks per level, respectively, and a max-pool down-sampling layer (pool size = [2, 2, 2]) between each level. Bottleneck blocks included leaky ReLU activation, batch normalization, and 40% feature dropout. The number of features per layer was set at 32 for the top level and doubled after each pooling step. This yielded one logit output for each gene of interest which were converted to a probability using the sigmoid logistic function. A threshold of $P \geq 0.5$ was used to determine a positive result.

Network Inputs and Training

The neural network training protocol employed a k-fold cross-validation methodology (k=5) with a data partition ratio of 0.8:0.2 for the training and test sets, respectively. Distinct convolutional neural networks were constructed and trained for each genetic biomarker under investigation. The CNN architecture's input layer was designed to accommodate three-dimensional tensors of dimensions $96 \times 96 \times 18$ voxels where the slices from each sequence modality were stacked together. To enhance model generalization and mitigate overfitting, data augmentation techniques were implemented. These included stochastic dimension permutations and random rotations within the range of $\pm 0-90$ degrees along each orthogonal axis. The training data sampling strategy ensured class balance within each batch, with an equal representation of positive and negative cases. Network parameter initialization utilized the Glorot (Xavier) method to optimize initial weight distributions. The training regimen consisted of 40 epochs with a fixed batch size of 10 samples. Notably, neither validation-based early stopping nor interim model evaluation were incorporated into the training pipeline. The objective function for optimization was defined as the binary cross-entropy loss between the model's predictive output and the ground truth genetic biomarker status. Parameter optimization was conducted using the Adam algorithm, a variant of stochastic gradient descent that adapts learning rates based on first and second moments of the gradients.

Network Performance Evaluation

Genetic biomarker prediction was evaluated using receiver operating characteristic (ROC) analysis as well as several different scalar metrics for the ROC best point: sensitivity,

specificity, accuracy, precision. Statistically significant differences between ROC curves were assessed using DeLong's method with a threshold of $P < .05$.

Results

ROC curves for each genetic mutation were generated and a summary of the evaluation metrics are included in the table below for brevity included the top 9 most prevalent genes

(Figure 2)(Table 1).

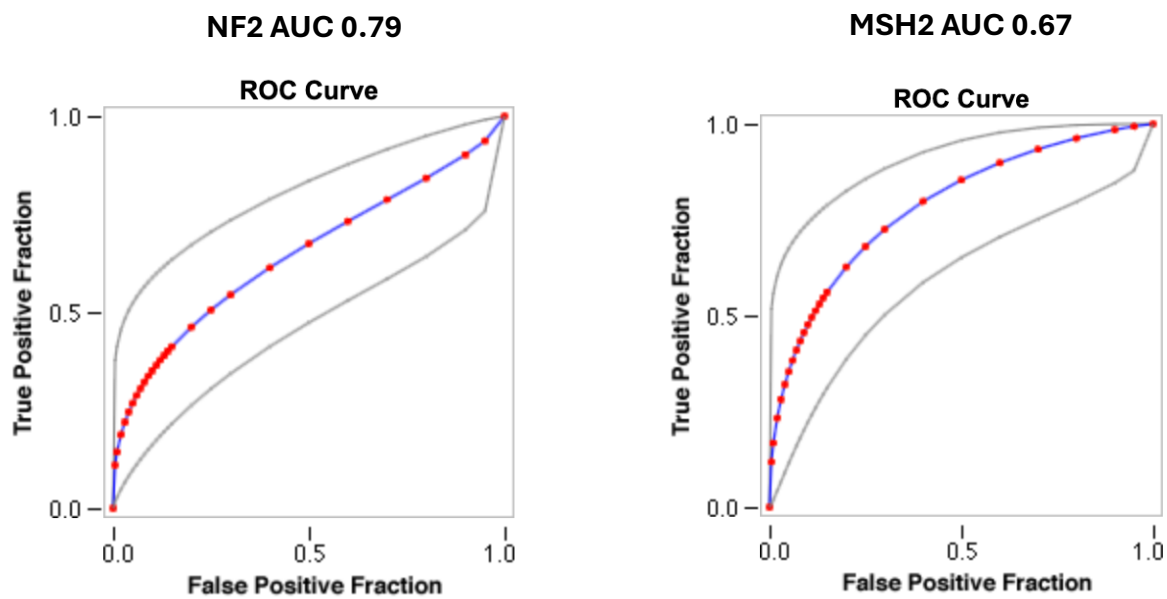


FIGURE 2: ROC curves for the most frequent gene mutations

TABLE 1: Gene mutation frequency and AUC, sensitivity, specificity metrics

Gene	Frequency	AUC	Sensitivity	Specificity
NF2	0.39	0.79	0.75	0.71
MSH2	0.227	0.67	0.87	0.74
TRAF7	0.212	0.63	0.79	0.83
MT-ND5	0.193	0.64	0.75	0.73
TERT	0.176	0.61	0.68	0.65
KIT	0.119	0.59	0.77	0.66
AKT1	0.105	0.59	0.69	0.7
KMT2C	0.097	0.57	0.63	0.66
KMT2D	0.094	0.53	0.68	0.62

The average AUC across all gene prediction was 0.71. Shown in Figure – are the ROC curves for the two most prevalent gene mutations in the dataset NF2 and MSH2. While comparing the frequencies of genes in the dataset to AUC performance, we observed that the lower the frequency of the gene mutation, the lower the AUC was. This indicated class imbalance and future steps of this work will require modifying the model to account for this. In addition, heat maps for which imaging features in different sequences correspond to findings is being currently investigated. This work is a baseline model performance and will be augmented with results from unsupervised learning approaches in future.

CHAPTER 3: BRAIN MRI SEQUENCE IDENTIFICATION USING LARGE LANGUAGE

MODELS

Background

In order to train artificial intelligence-based models to assist medical experts, a large, labeled training dataset is mandatory. However, this is a challenging task due to several reasons. These datasets are often acquired from various medical centers across the world and given the wide set of variations available in radiological imaging, there is a need to sort MRI scans, based on sequence type. Each particular MRI sequence lends different clinical information to a radiologist. MRI file types such as the digital imaging and communications in medicine (DICOM) contain metadata pertaining to the scan in the file headers and contain information such as MRI sequence, magnet strength which are entered manually by technicians at the time of acquisition. This metadata is also transferred to other file formats such as NIFTI as json files. In such scenarios, automatic identification of the MRI sequence from MRI data can prove to be of immense significance in sorting these massive datasets out for training deep learning models. Previous work has focused on using convolutional neural networks to train networks that can identify sequence type as different classes (8). Hard coded logic using regex has also been used in inhouse tools. None of these methods are robust to the human spelling and grammatical mistakes made while entering the DICOM header information. In addition, from clinical and research experience, these models have difficulty generalizing to out of distribution datasets, especially those from other institutions.

In this chapter we propose the use of large language models (LLMs) in parsing MRI metadata to help in identifying sequences in an efficient and interpretable manner. Our hypothesis is that LLMs will be able to understand grammatical mistakes and identify sequence type quickly while being able to give explanation as to why the sequence type was chosen.

Methods

From the radiogenomic and imaging meningioma dataset described in Chapter 1, 48 MRI sequences were randomly selected and manually labeled. The associated json file containing DICOM metadata was extracted for each sequence. The contents of this file served as input to the prompt to the LLM (**Figure 4**). We utilized UCSF Versa, an AI platform that allows researchers to work with LLM API with PHI compliant data from companies such as OpenAI. We used GPT-4 for this preliminary test.

Results

The following diagram shows the workflow of applying the LLM without any fine tuning (Figure 4). The sensitivity and specificity for each modality as well as the confusion matrix of results is shown below. For sequences classified ADC, DWI, FLAIR, and T2 the sensitivity was 100%, specificity was 100%. For GRE, the sensitivity was 0.98% and specificity was 100%. For T1 pre-contrast images, the sensitivity was 100% and specificity was 0.89%. For T1 post-contrast, the sensitivity was 0.97% and specificity was 0.83%.

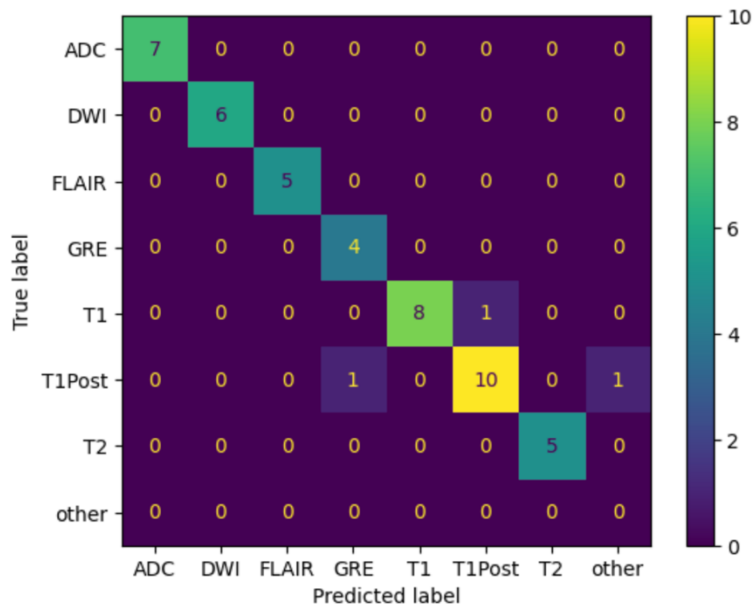


FIGURE 3: Confusion matrix results from LLM classifier

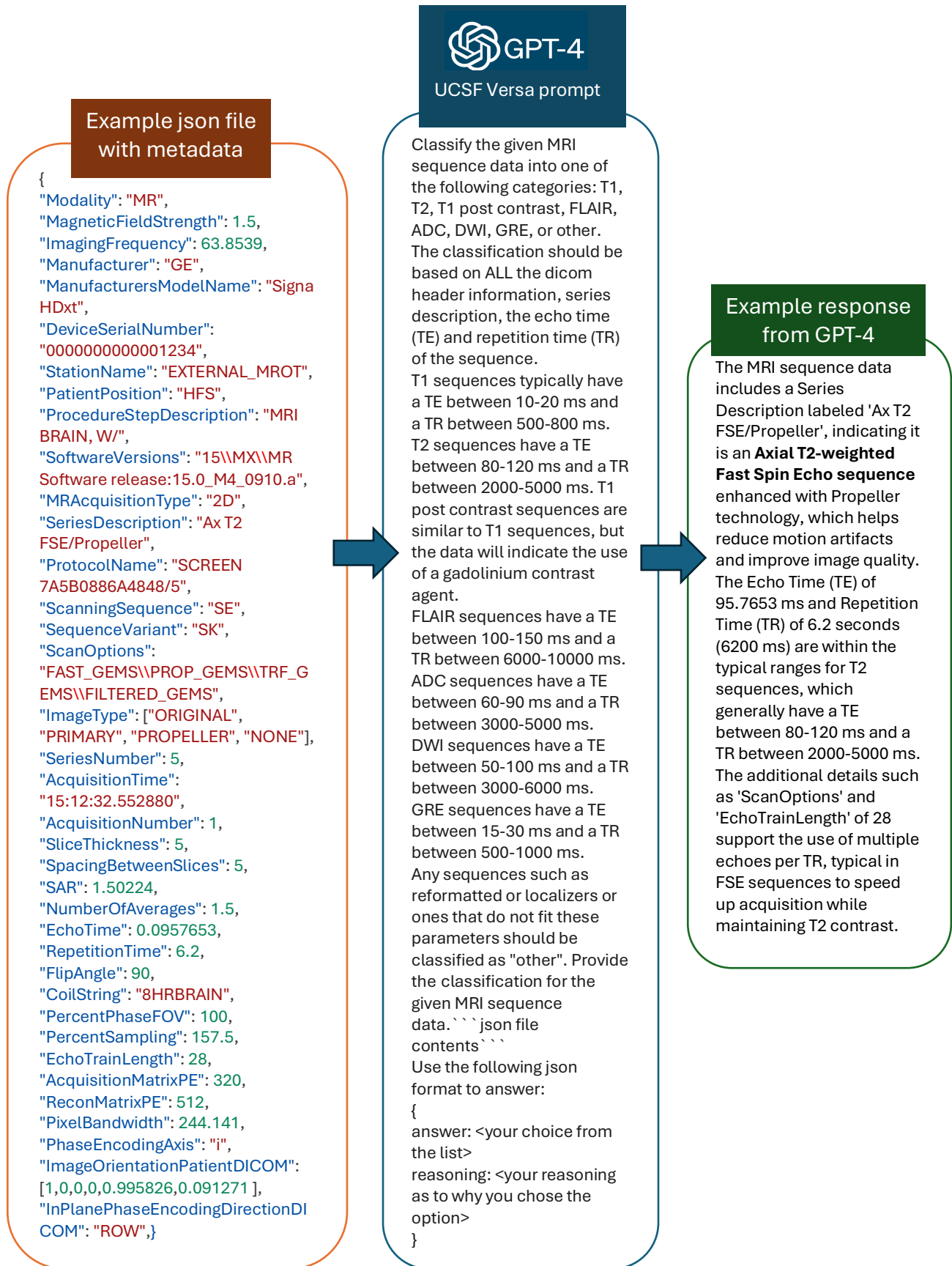


Figure 4: Workflow of LLM modality classifier

CHAPTER 4: CONCLUSION AND DISCUSSION

This thesis has explored the intricate relationship between imaging features, genetic biomarkers, and artificial intelligence in the context of meningioma management. Through a series of interconnected studies, we have demonstrated the potential for significant advancements in diagnosis, treatment planning, and prognostication of these common intracranial tumors.

The development of a large-scale, multi-sequence MRI dataset with corresponding genetic and demographic data (Chapter 1) represents a significant contribution to the field. This resource enables researchers to conduct more comprehensive studies on imaging-genetic correlations in meningiomas, potentially leading to new insights into tumor biology and behavior.

Our machine learning model for predicting genetic mutation status from preoperative MRI (Chapter 2) demonstrates the feasibility of non-invasive genetic assessment. With an average AUC of 0.71 across all gene predictions, this approach shows promise for clinical application, particularly in settings where genetic testing is limited by cost or accessibility. This could lead to more informed treatment decisions and personalized management strategies.

The use of large language models (LLMs) for MRI sequence identification (Chapter 3) addresses a critical challenge in medical imaging AI. By leveraging the natural language understanding capabilities of LLMs, we've shown potential for more robust and generalizable sequence identification, which could streamline the preparation of multi-institutional datasets for AI model training.

Limitations and Challenges

While our work presents significant advancements, several limitations should be acknowledged:

1. The dataset, although large, is from a single institution, which may limit generalizability.
2. The genetic prediction model's performance, while promising, still leaves room for improvement. Data imbalance needs to be addressed in future models. In addition, by excluding patients who have not received biopsy, the findings of the model are limited to patients whose meningiomas can be safely resected.
3. The LLM approach to sequence identification, while innovative, requires further validation on larger and more diverse datasets.

Future Directions

Building on the foundation laid by this thesis, several avenues for future research emerge:

Expanding the dataset to include images and genetic data from multiple institutions would enhance the generalizability of our findings and models. Incorporating data from advanced MRI techniques such as perfusion imaging, spectroscopy, or radiomics could potentially improve the accuracy of genetic prediction models. Conducting longitudinal studies to correlate imaging features, genetic profiles, and long-term patient outcomes could provide valuable insights into tumor progression and treatment response.

In conclusion, this thesis represents a significant step forward in the integration of imaging, genetics, and artificial intelligence for meningioma management. By bridging these diverse fields, we have opened new possibilities for personalized medicine in neuro-oncology. As we continue to refine these approaches and expand their applications, the potential for

improving patient care and outcomes becomes increasingly tangible. The future of meningioma management lies in the synergistic application of advanced imaging, genetic profiling, and artificial intelligence, paving the way for more precise, effective, and personalized treatment strategies.

REFERENCES

1. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016-2020. *Neuro Oncol.* 2023 Oct 4;25(12 Suppl 2):iv1-iv99. doi: 10.1093/neuonc/noad149. PMID: 37793125; PMCID: PMC10550277.
2. Meningiomas. AANS. (n.d.). *Meningiomas*. AANS. (2024, April 8). <https://www.aans.org/patients/conditions-treatments/meningiomas/>
3. Haddad, Alexander F et al. "WHO Grade I Meningioma Recurrence: Identifying High Risk Patients Using Histopathological Features and the MIB-1 Index." *Frontiers in oncology* vol. 10 1522. 28 Aug. 2020, doi:10.3389/fonc.2020.01522
4. Ilah Shin, Yae Won Park, Sung Soo Ahn, Seok-Gu Kang, Jong Hee Chang, Se Hoon Kim, Seung-Koo Lee, Clinical and diffusion parameters may noninvasively predict TERT promoter mutation status in grade II meningiomas, *Journal of Neuroradiology*, Volume 49, Issue 1, 2022, Pages 59-65, ISSN 0150-9861, <https://doi.org/10.1016/j.neurad.2021.02.007>.
5. Dusic EJ, Theorin T, Wang C, Swisher EM, Bowen DJ; EDGE Study Team. Barriers, interventions, and recommendations: Improving the genetic testing landscape. *Front Digit Health.* 2022 Nov 1;4:961128. doi: 10.3389/fdgth.2022.961128. PMID: 36386046; PMCID: PMC9665160.
6. <https://genomics.ucsf.edu/UCSF500>

7. Calabrese E, Rudie JD, Rauschecker AM, Villanueva-Meyer JE, Clarke JL, Solomon DA, Cha S. Combining radiomics and deep convolutional neural network features from preoperative MRI for predicting clinically relevant genetic biomarkers in glioblastoma. *Neurooncol Adv.* 2022 Apr 22;4(1):vdac060. doi: 10.1093/noajnl/vdac060. PMID: 35611269; PMCID: PMC9122791.
8. Kalchev E. Insights Into Meningioma Visibility on Arterial Spin Labeling MRI: Location Outweighs Size. *Cureus.* 2023 Jun 10;15(6):e40204. doi: 10.7759/cureus.40204. PMID: 37304385; PMCID: PMC10257063.
9. Mahmutoglu, Mustafa & Jayachandran Preetha, Chandrakanth & Meredig, Hagen & Tonn, Joerg & Weller, Michael & Wick, Wolfgang & Bendszus, Martin & Brugnara, Gianluca & Vollmuth, Philipp. (2023). Deep Learning-based Identification of Brain MRI Sequences Using a Model Trained on Large Multicentric Study Cohorts. *Radiology: Artificial Intelligence.* 6. 10.1148/ryai.230095.
10. Grist, J. T., Miller, J. J., Zaccagna, F., McLean, M. A., Riemer, F., Matys, T., Tyler, D. J., Laustsen, C., Coles, A. J., & Gallagher, F. A. (2020). Hyperpolarized ¹³C MRI: A novel approach for probing cerebral metabolism in health and neurological disease. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*, 40(6), 1137–1147.
<https://doi.org/10.1177/0271678X20909045>
11. Domingues, P., González-Tablas, M., Otero, Á., Pascual, D., Ruiz, L., Miranda, D., Sousa, P., Gonçalves, J. M., Lopes, M. C., Orfao, A., & Taberner, M. D. (2015). Genetic/molecular alterations of meningiomas and the signaling pathways

targeted. *Oncotarget*, 6(13), 10671–10688.

<https://doi.org/10.18632/oncotarget.3870>

Publishing Agreement

It is the policy of the University to encourage open access and broad distribution of all theses, dissertations, and manuscripts. The Graduate Division will facilitate the distribution of UCSF theses, dissertations, and manuscripts to the UCSF Library for open access and distribution. UCSF will make such theses, dissertations, and manuscripts accessible to the public and will take reasonable steps to preserve these works in perpetuity.

I hereby grant the non-exclusive, perpetual right to The Regents of the University of California to reproduce, publicly display, distribute, preserve, and publish copies of my thesis, dissertation, or manuscript in any form or media, now existing or later derived, including access online for teaching, research, and public service purposes.

DocuSigned by:

Radhika Bhaleerao

12E69B381BA644A...

Author Signature

8/28/2024

Date