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### Authors

Chow, Daniel  
Chang, Peter  
Weinberg, Brent D  
et al.

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# Imaging Genetic Heterogeneity in Glioblastoma and Other Glial Tumors: Review of Current Methods and Future Directions

Daniel Chow<sup>1</sup>  
 Peter Chang<sup>2</sup>  
 Brent D. Weinberg<sup>3</sup>  
 Daniela A. Bota<sup>4</sup>  
 Jack Grinband<sup>5</sup>  
 Christopher Filippi<sup>6</sup>

**OBJECTIVE.** The purpose of this review is to summarize advances in the molecular analysis of gliomas, the role genetics plays in MRI features, and how machine-learning approaches can be used to survey the tumoral environment.

**CONCLUSION.** The genetic profile of gliomas influences the course of treatment and clinical outcomes. Though biopsy is the reference standard for determining tumor genetics, it can suffer diagnostic delays due to surgical planning and pathologic assessment. Radiogenomics may allow rapid, low-risk characterization of genetic heterogeneity.

**Keywords:** glioblastoma, machine learning, radiogenomics

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<sup>1</sup>Department of Radiology, University of California, Irvine Medical Center, Douglas Hospital, Rte 140, Rm 0115, Orange, CA 92868. Address correspondence to D. Chow (chowd3@uci.edu).

<sup>2</sup>Department of Radiology, University of California, San Francisco, San Francisco, CA.

<sup>3</sup>Department of Radiology, Emory University School of Medicine, Emory University Hospital, Atlanta, GA.

<sup>4</sup>Department of Neuro-Oncology, University of California, Irvine Medical Center, Orange, CA.

<sup>5</sup>Department of Radiology, College of Physicians and Surgeons, Columbia University, New York, NY.

<sup>6</sup>Department of Radiology, North Shore University Hospital, Manhasset, NY.

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**G**lioblastoma (GBM) is the most common and the most deadly primary brain tumor [1]. The primary course of treatment is maximal surgical resection followed by radiotherapy with concurrent temozolomide therapy [1]. When tumors recur, salvage therapy options include repeat surgical resection, antiangiogenic therapy (bevacizumab), and a variety of investigational therapies, including immunotherapy and other chemotherapeutic agents. Despite aggressive treatment, the median survival time remains only 18–24 months. This limited success of treatment is partially due to intrinsically aggressive tumor behavior but also to the heterogeneity of the disease.

Genetic testing of gliomas has provided substantially more information about the underlying tumors, helping to differentiate subtypes of disease and provide improved prognostic information [2]. In addition, these discoveries in genetic profiling have spurred development of new targeted therapies. Over 140 clinical trials are evaluating personalized and targeted therapies specifically for GBM. These therapies are tailored to exploit genetics-specific therapeutic targets in the hope that individualized therapy can improve patient outcomes [3]. However, an apparent roadblock to these individualized approaches is the growing evidence of genetic heterogeneity within a single patient's GBM. Using single-cell RNA-sequencing, Patel et al. [4] found that GBMs consist of a mixture of cells with variable gene expression profiles. Likewise, using a surgical multisam-

pling approach from 11 patients with GBM, Sottoriva et al. [5] found genome-wide variability across the tumor. These findings suggest that each GBM may reflect multiple unique tumor habitats with corresponding differences in response and resistance to therapy. This degree of variability creates challenges in the identification of appropriate tumor targets and subsequent development and implementation of individualized care. Specifically, standard-of-care biopsy techniques sample only limited portions of a tumor. Although this may be sufficient to identify some differences between dominant genetic makeups of different patients, single specimens are unlikely to reflect the complete tumor microenvironment, which inherently limits evaluation of intratumoral differences within patients.

Because imaging can be used to evaluate an entire tumor, MRI may be a useful platform for evaluating tumoral genetic variability. Specifically, spatial and temporal variations in genetic expression of gliomas result in alterations in the biologic characteristics of tumors that may include changes in apoptosis, cellular proliferation, cellular invasion, and angiogenesis [6]. In turn, these biologic changes manifest heterogeneous imaging features, resulting in varying degrees of enhancement and edema that are detectable at MRI, owing to its superior tissue contrast resolution. For example, gadolinium enhancement on MR images results from the breakdown of the blood-brain barrier and can be used to identify areas of necrosis as a mark-

er of apoptosis. In addition, MRI sequences based on physiologic characteristics such as apparent diffusion coefficient and perfusion have been found to relate to tumoral cellularity and angiogenesis, respectively. Thus, if MRI features of the tumor correlate with genetic characteristics, it may be possible to noninvasively identify tumor genetic features.

Traditional imaging approaches have entailed subjective visual inspection or semi-quantitative metrics within limited ROIs. However, these approaches have yielded sub-optimal results because of difficulty in distilling a complex dataset of over 1 million voxels per MRI sequence into a handful of features or numeric descriptors. Moreover, an a priori subjectively defined feature set may not be optimal for characterizing genetic heterogeneity. Therefore, MRI evaluation of GBMs becomes a big-data challenge for which modern data analysis techniques, such as machine learning, are particularly well suited.

Machine learning is a subfield of artificial intelligence in which machines are trained to perform tasks such as pattern recognition without explicit programming [7]. Previous approaches have entailed human-designed feature extraction (e.g., volume of enhancement or edema) and textural analysis approaches for distinguishing tumor features, which has improved the accuracy of diagnostic imaging techniques. However, evolving techniques are shifting toward end-to-end machine learning with neural networks, which can combine both feature selection and classification into one algorithm [8, 9]. Because the machine is able to learn, the image features critical for solving a classification problem do not have to be defined a priori. Given sufficient training data, the machine determines the optimal feature set and the relative importance of each feature, allowing it to use combinations of features to classify images. Thus, machine learning may be a fitting approach to transforming MR images of gliomas into genetic categories.

The purpose of this review is to summarize advances in the molecular analysis of GBMs and its implications for diagnosis and outcome, development of MRI techniques for tissue genetic characterization (radiogenomics), and results from novel machine-learning approaches to objectively survey the tumor environment in its entirety.

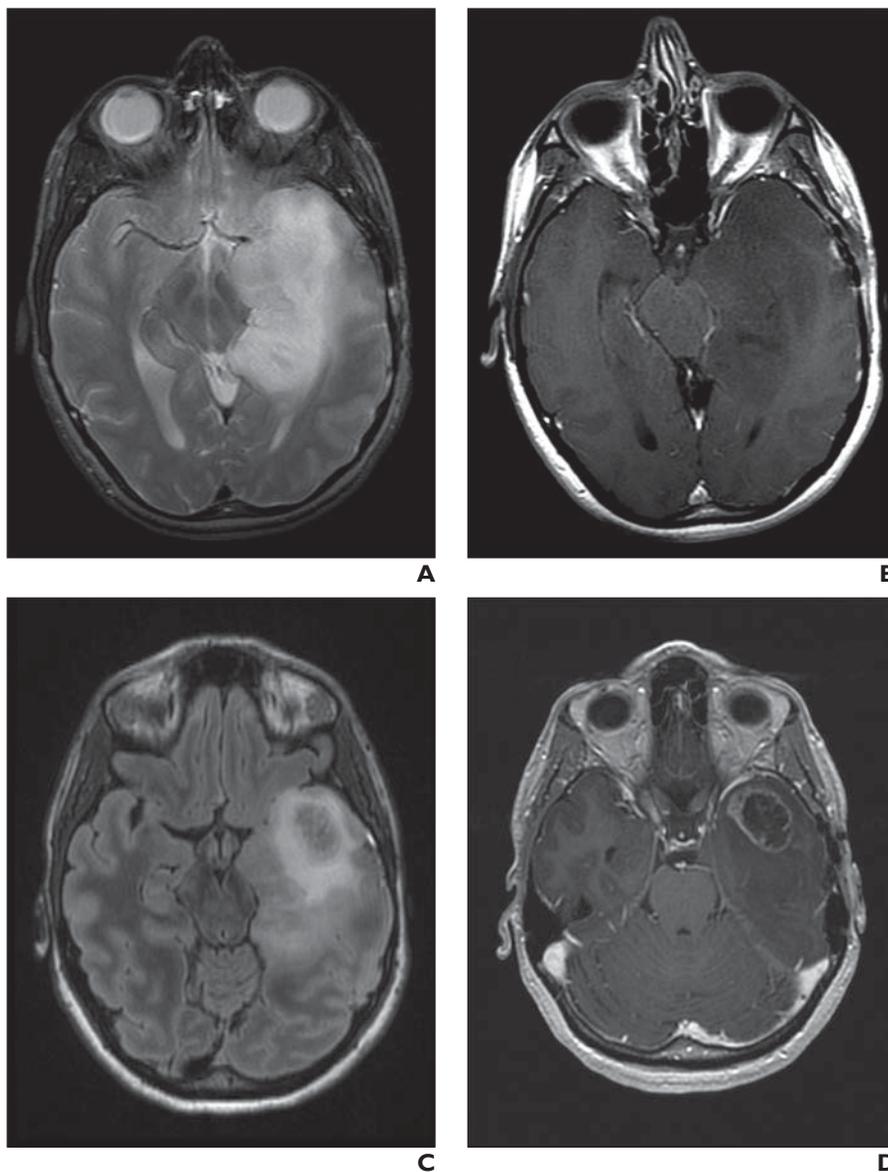
### Genetics of Gliomas

Understanding of CNS tumors at the genetic and molecular levels has increased

considerably. Applications of immunohistochemistry to detect specific mutations have been combined with genome-wide sequencing to yield specific information about the genetic makeup of each tumor. The effects have been wide-ranging, changing the way tumors are diagnosed and providing better information to guide therapy selection and assess prognosis. However, understanding of these tumor features is incomplete, despite

ongoing efforts to convert the information into clinically useful tools and treatments.

Genetic and molecular analysis of tumors has had dramatic impact on the diagnosis of glial tumors, including GBM. In 2016, new World Health Organization guidelines for the diagnosis of glial tumors were published in which considerable emphasis was placed on the use of genetic information for tumor classification [10]. Perhaps the most important



**Fig. 1**—33-year-old woman with low-grade glioma.

**A and B**, Axial FLAIR (**A**) and contrast-enhanced T1-weighted (**B**) MR images show expansile low-grade glioma of left medial temporal lobe without marked enhancement.

**C and D**, FLAIR (**C**) and contrast-enhanced T1-weighted (**D**) MR images 2 years after **A** and **B** show avidly enhancing mass. Biopsy of enhancing portion revealed glioblastoma (GBM), isocitrate dehydrogenase mutant, O-6-methylguanine-DNA-methyltransferase promoter methylated, no epidermal growth factor receptor amplification or mutation, phosphatase and tensin homolog wild-type. Biopsy findings were consistent with secondary GBM with somewhat favorable prognosis. Considerable tumor heterogeneity is present with enhancing region of high-grade tumor within much larger region of likely lower-grade disease.

## Imaging Genetic Heterogeneity in Glial Tumors

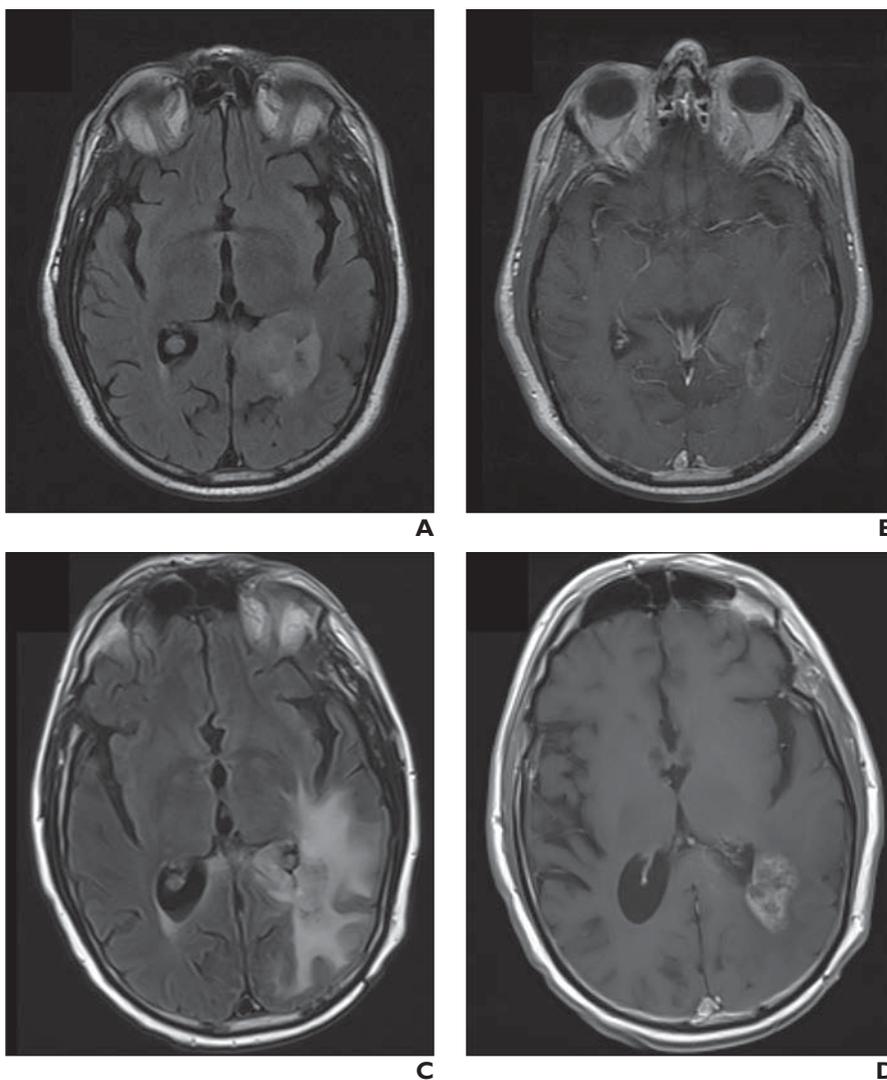
change has been in the classification of low-grade astrocytomas and oligodendrogliomas, both of which are characterized by mutations of isocitrate dehydrogenase (IDH) 1 or 2. Oligodendrogliomas are frequently IDH mutated but are also defined by loss of portions of chromosomes 1 and 19 (1p/19q codeletion) [11]. On the other hand, astrocytomas most commonly have mutations of  $\alpha$ -thalassemia/mental retardation X-linked protein (ATRAX), a protein involved in chromatin remodeling and telomere maintenance, and tumor protein P53 (*TP53*), a tumor suppressor gene [12]. The oligoastrocytoma diagnosis is now discouraged, and these tumors are further characterized by their genetic makeup. Other low-grade tumors, including pilocytic astrocytoma, ganglioglioma, pleomorphic xanthoastrocytoma, and subependymal giant cell tumors, have been clustered into a group of tumors associated with mutations in *BRAF*, a tumor suppressor gene in the mitogen-activated protein kinase pathway [13, 14]. Incorporating genetic information into tumor diagnosis is touted as a way to increase the specificity of tumor diagnosis. This may make it easier to identify imaging features associated with a specific diagnosis and to find and test new therapies by reducing the number of miscategorized tumors, thus reducing the amount of noise within the underlying results.

Molecular characterization has also been applied to GBMs to improve the quality of diagnosis. Division of adult GBMs into two groups, IDH wild-type and IDH mutant, is the most important clinical distinction. IDH is an enzyme involved in cellular metabolism, and mutations are most frequently seen in GBMs that arise in a preexisting low-grade lesion, known as secondary GBM [15]. IDH mutant GBMs have a better prognosis than IDH wild-type GBMs. Other low-grade glioma markers, including ATRX and TP53, are also frequently seen in secondary GBMs, which comprise approximately 10% of all GBMs and arise in younger patients (median age, 44 years). An example of a secondary GBM is shown in Figure 1. Alternatively, primary GBMs lack IDH mutations and are more likely to have amplification of epidermal growth factor receptor (*EGFR*) and phosphatase and tensin homolog (*PTEN*) tumor suppressor gene and loss of other cyclin-dependent kinases [16]. These tumors have a higher median age (62 years) at diagnosis and a slight male predominance [10]. An example of a primary GBM is shown in Figure 2. A subset of high-grade midline gliomas in pediatric patients has been

separated into a new entity, diffuse midline glioma, H3 K27 M mutant, which exhibits mutations of the gene encoding histone H3, a protein involved in DNA folding, and lacks IDH mutations [17, 18].

Genetic markers also provide prognostic information, which may guide image interpretation and patient care. Initial and follow-up imaging of GBMs should be performed in the context of known genetic abnormalities. Including common genetic abnormalities such as IDH status in the dictated history may assist in oncologic planning. IDH-1

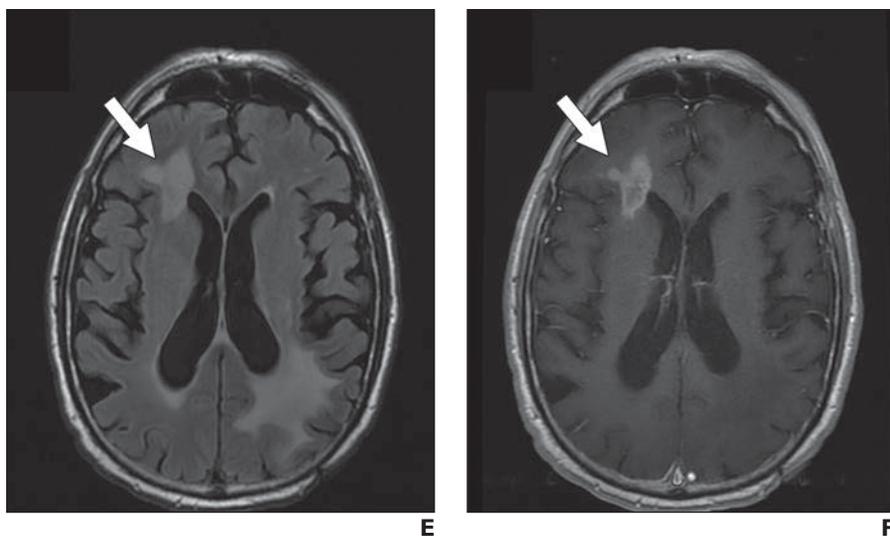
and IDH-2 mutations and ATRX mutation or loss and tumors with 1p19q codeletion have definite associations with prolonged survival [19, 20]. Other abnormalities not yet used in diagnosis decisions can also provide prognostic information. Hypermethylation of O-6-methylguanine-DNA-methyltransferase (MGMT) promoter, an enzyme involved in DNA dealkylation and mediation of DNA damage, is a positive prognostic factor, and is associated with other GBM markers, including IDH mutation, P53 overexpression, and ATRX underexpression [21].



**Fig. 2**—66-year-old man with glioblastoma (GBM).

**A and B**, FLAIR (**A**) and contrast-enhanced T1-weighted (**B**) MR images show left temporal GBM of isocitrate dehydrogenase (IDH) wild-type,  $\alpha$ -thalassemia/mental retardation X-linked (ATRAX) protein retained, O-6-methylguanine-DNA-methyltransferase promoter methylated, phosphatase and tensin homolog (PTEN) loss of function, protein 53 (P53) mutated, and epidermal growth factor receptor (EGFR) amplified. These biopsy results are consistent with primary GBM with largely unfavorable genetic indicators (IDH, PTEN, P53, EGFR). **C and D**, Follow-up FLAIR (**C**) and contrast-enhanced T1-weighted (**D**) MR images 6 months after treatment with concurrent radiotherapy and temozolomide show local control with increasing edema, thought to be largely treatment related.

(Fig. 2 continues on next page)



**Fig. 2 (continued)**—66-year-old man with glioblastoma (GBM). **E** and **F**, FLAIR (**E**) and contrast-enhanced T1-weighted (**F**) MR images 12 months after **A** and **B** show aggressive tumor behavior and new distant site of disease progression (arrow) in right frontal lobe.

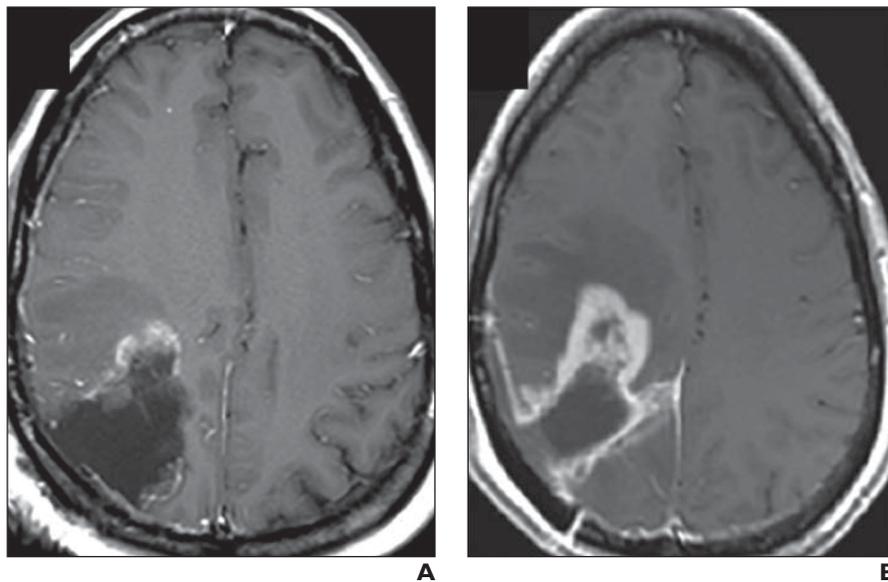
Patients with methylated MGMT promoter have improved survival and better response to radiation with concurrent temozolomide therapy [21, 22]. The methylated MGMT promoter is also associated with high rates of pseudoprogression [23]. For this reason, increases in enhancement within 3 months after completion of radiotherapy in patients with MGMT methylated tumors should be viewed as suspicious for treatment-related effects as opposed to progressive disease (Fig. 3). Mutations in the promoter for telomerase reverse transcriptase (TERT), an enzyme that elongates telomeres, have been found to be associated with a worse prognosis in both IDH mutant and IDH wild-type GBMs [24–26]. Increased amounts of Ki-67, a cellular protein associated with proliferation and present in many tumors, is also associated with a worse prognosis [27, 28].

Several other cellular abnormalities, including TP53, PTEN, EGFR (wild-type amplification or the presence of the EGFRvIII mutation), and platelet-derived growth factor receptor (PDGFR), have had either no or inconsistent effects on patient prognosis.

### Imaging Evaluation of Tumor Genomics

At present, genetic and molecular information about tumors comes solely from pathologic results. However, given the importance of genetic information for diagnosing and treating glioma, numerous attempts are underway to characterize tumors by means of imaging. This effort to classify genetic information based on imaging findings has been

termed radiogenomics. Many studies have evaluated tumor location and size and other imaging features, such as degree of enhancement, type of margins, and diffusion characteristics, in an attempt to classify tumors on the basis of MRI appearance. A review of the literature highlighting commonly cited features, including IDH mutation, 1p19q codeletion, MGMT methylation, and EGFR mutation, is summarized in Table 1.



**Fig. 3**—47-year-old woman with glioblastoma, O-6-methylguanine-DNA-methyltransferase promoter methylated.

**A**, Axial contrast-enhanced T1-weighted MR image obtained immediately after resection shows minimal residual enhancing disease.

**B**, Axial contrast-enhanced T1-weighted MR image 1 month after completion of chemoradiotherapy shows development of thick rim of enhancement around resection cavity that is suspicious for pseudoprogression.

(Fig. 3 continues on next page)

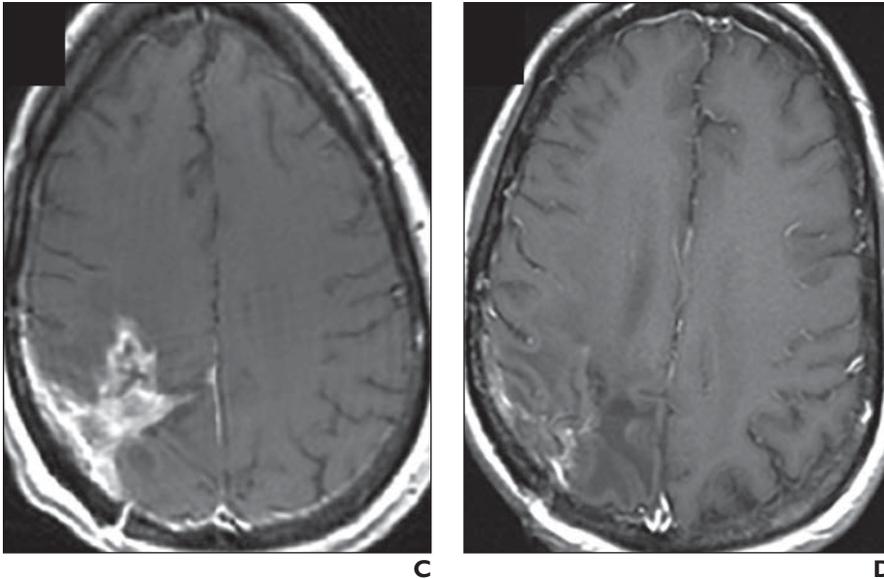
### Isocitrate Dehydrogenase

IDH mutation has been one of the most thoroughly investigated with respect to imaging features. Commonly cited features of tumors with IDH mutations include frontal lobe location [29–32], absent or minimal enhancement [29, 31, 33], small size [29, 34], and well-defined tumor margins [33, 34]. IDH status has been found to correlate with diffusion tensor imaging characteristics, IDH wild-type tumors having lower mean diffusion values [32, 35]. At perfusion imaging, IDH mutants have lower cerebral blood volume than their IDH wild-type counterparts [36, 37]. In summary, IDH mutant tumors have less enhancement, higher mean diffusion values, and less blood flow according to perfusion measures.

### 1p19q Codeletion

Like IDH mutant tumors, 1p19q codeleted tumors are more likely to be found in the frontal cortex [32]. However, other reliable imaging correlates of 1p19q codeletion have not been found. Sonoda et al. [31] found that codeleted tumors are more likely to exhibit contrast enhancement. Xiong et al. [32], however, found the opposite. Tumor margins of 1p19q-codeleted tumors have been argued to be more likely to be poorly circumscribed [38] and alternatively to have equal likelihood of sharp and ill-defined tumor margins [31, 32].

## Imaging Genetic Heterogeneity in Glial Tumors



**Fig. 3 (continued)**—47-year-old woman with glioblastoma, O-6-methylguanine-DNA-methyltransferase promoter methylated. **C** and **D**, Axial contrast-enhanced T1-weighted MR image shows progressively decreased enhancement and collapse of surgical cavity 6 months (**C**) and 18 months (**D**) after completion of chemotherapy, confirming that early enhancement was related to treatment effect.

Similarly, 1p19q-codeleted tumors have been found to have lower mean diffusion values [38, 39] and not to be correlated with diffusion [32, 40].

### O-6-Methylguanine-DNA-Methyltransferase

For MGMT promoter methylation, commonly cited features include frontal lobe location [30, 41] (often colocalization with IDH mutation in this region [41]), presence of an eccentric necrotic cyst [42, 43], and high apparent diffusion coefficient values [44]. By contrast, nonmethylated tumors commonly exhibit either ring enhancement with central necrosis [42, 45], solid enhancement [46], or ill-defined margins [43]. Multifactorial models have confirmed these features and shown modest accuracy in preoperative classification between methylated and unmethylated tumors [46].

### Epidermal Growth Factor Receptor

For EGFR amplification, commonly cited features include left temporal lobe loca-

**TABLE 1: Summary of Qualitative Features Associated With IDH Mutation, 1p19q Codeletion, MGMT Promoter Methylation, and EGFRvIII Mutation**

Reference	Year	Qualitative Finding
<b>IDH mutation</b>		
Metellus et al. [34]	2010	Rare insula; smaller size; rare ill-defined margins
Carrillo et al. [29]	2012	Frontal lobe, less enhancement, smaller size
Qi et al. [33]	2014	Single lobe (frontal); unilateral pattern of growth, well-defined tumor margins, homogeneous signal intensity; less enhancement
Sonoda et al. [31]	2015	Frontal lobe, rare temporal lobe, less enhancement
Paldor et al. [30]	2016	Frontal lobe
<b>1p19q loss of heterogeneity</b>		
Sonoda et al. [31]	2015	Rare temporal lobe, more enhancement
Johnson et al. [38]	2017	Ill defined margins; heterogeneous T1 and T2 signal intensity; lower mean ADC value
<b>MGMT promoter methylation</b>		
Eoli et al. [45]	2007	Rare central necrosis, rare ring enhancement, parietooccipital lobe
Drabycz et al. [42]	2010	Rare ring enhancement; eccentric cyst
Moon et al. [43]	2013	Ill-defined margins; high ADC; low attenuation; eccentric cyst
Romano et al. [44]	2012	High ADC
Ellingson et al. [41]	2013	Left superficial temporal lobe; left frontal lobe (with IDH)
Paldor et al. [30]	2016	Frontal lobe
Kanas et al. [46]	2017	Less edema; rare absence of necrosis; rare solid enhancement
<b>EGFRvIII</b>		
Aghi et al. [48]	2005	Increased edema-enhancing tumor ratio; ill-defined T2 margins
Ellingson et al. [41]	2013	Left temporal lobe
Young et al. [47]	2013	Lower ADC
Gupta et al. [49]	2015	Increased cerebral blood volume, decreased peak signal recovery

Note—IDH = isocitrate dehydrogenase, MGMT = O-6-methylguanine-DNA-methyltransferase, EGFRvIII = epidermal growth factor receptor variant III, ADC = apparent diffusion coefficient.

tion [41] and reduced diffusion values [47]. EGFR-amplified tumors have also been found to have a higher ratio of the T2-hyperintense tissue volume to enhancing volume [48]. MRI perfusion has had some utility in identifying EGFR amplified tumors, which have higher cerebral blood volume [49].

#### Overall Observations

Overall, attempts to classify tumors on the basis of their MRI appearance have had mixed results. Noninvasive determination of IDH mutation status has had the greatest success. Repeatable results have shown that IDH mutant tumors have less enhancement, higher mean diffusion values, and less blood flow on perfusion measurement. Awareness of these imaging features is particularly important because IDH mutation is the genetic abnormality most strongly associated with improved prognosis. Noninvasive classification of other markers, including 1p19q, MGMT, EGFR, and others, has been less reproducible for multiple reasons. Significant overlap of MRI features between different mutations can prevent accurate classification. Different mutations are also not independent: several mutations, such as IDH, MGMT, and P53, often occur in tandem and share imaging properties. Some inconsistency may also reflect intratumor heterogeneity whereby different portions of the tumor have different genetic characteristics and image features.

Novel advanced imaging techniques, such as amino acid PET [50], have shown promise in supplementing MRI by showing elevated tumor metabolism. Currently, the use of PET is limited owing to the costs and time necessary to obtain the scans. However, PET/MRI systems that allow simultaneous multimodal imaging are increasing in popularity, and their use may further improve tissue classification of glioma subregions [51]. With improving techniques and an increasing number of patients, minimally invasive categorization of tumors is expected to become more accurate and clinically useful.

#### Machine-Learning Approaches

Because each patient typically has a large amount of available MRI data, advanced data analysis techniques such as machine learning may be especially promising for glioma radiogenomics. The use of machine learning has several potential advantages over visual inspection by human experts, including objective quantitative evaluation and the ability to detect subtle voxel-level patterns. Ap-

plying machine-learning techniques to GBM assessment has several key considerations, including feature selection, classifier type, and accuracy assessment.

#### Feature Selection

Just as a human summarizes an image with a few key succinct descriptors (e.g., ring enhancement, ill-defined margins), a machine-learning algorithm attempts to do the same with a matrix of voxels. These numeric descriptors can be roughly classified into semantic features, first-order statistical metrics, and second-order statistical metrics. Semantic features require a human to manually score a particular image with a predefined feature set, such as the VASARI system [52].

First-order statistics include various metrics that can be derived from voxel intensities within the ROI, such as mean, median, minimum, maximum, and percentiles, and descriptors of histogram shape, such as kurtosis or skewness [53]. Kickingeder et al. [54] found that analysis of first-order features of GBMs could identify imaging signatures predictive of survival, which had better performance than previous survival nomograms. Although simple to calculate, these first-order statistics do not retain any information regarding the spatial distribution of voxels, and instead depend only on absolute signal intensities.

By contrast to first-order statistics, second-order statistical measures attempt to capture both the spatial distribution and signal intensities of the ROI [55]. These second-order methods may be particularly important in the evaluation of heterogeneous diseases, such as GBM, in which imaging features may vary substantially in different regions of the tumor. Although many methods and equations have been described, common algorithms include those based on textures (including those derived from gray-level cooccurrence matrices, including Haralick features), wavelets, or fractals [56, 57].

#### Classifier Types

After each tumor image has been converted into numeric descriptors, a method must be chosen to leverage this information to predict one of multiple potential classes. In certain cases, even very simple models, such as basic logistic and linear regression, can be effective [58]. However, if nonindependent, nonlinear relationships can be expected between the various chosen features, a more complex model is required. Although

many such machine-learning classifiers exist, the most popular include random forests, support vector machines, k-nearest neighbor clustering, and neural networks [59]. In general, these techniques are modeled by an underlying finite number of adjustable parameters. As a given set of features is passed through the model, these adjustable parameters convert the input descriptors into a predicted output class. Starting with randomly initialized parameters, a series of iterative updates are performed until an accurate mapping between numeric features and correct class is achieved, thus training the machine-learning model [60].

#### Convolutional Neural Networks

There has been a gradual paradigm shift toward end-to-end machine learning through the use of convolutional neural networks (CNN). These models are capable of automatically identifying patterns in complex imaging datasets, thus combining both feature selection and classification into one algorithm and removing the need for direct human interaction during the training process. In the computer vision field, advances in CNNs have led to algorithms for achieving human accuracy in identification of everyday entities, such as cats and dogs, whose appearance had previously been impossible to model with rigid mathematic formulas [61]. Thus far, the primary limitation of CNNs in the medical domain has been the need for large datasets to train state-of-the-art algorithms (14 M+ in the ImageNet database) compared with what is typically available in radiologic databases (hundreds or thousands of cases). Nonetheless, early use of CNNs has yielded promising results in the detection of pulmonary nodules [62], colon cancer [63], and cerebral microbleeds [64]. As large multiinstitutional databases are compiled, the use of CNNs will likely result in important advances in noninvasive characterization of tumor radiogenomics.

#### Accuracy Assessment

The most important consideration in evaluation of a machine-learning experiment is the method of assessing algorithm accuracy. Often in the testing of a large number of potential features, a few numeric descriptors meet the threshold for statistical significance between two target classes. However,  $p$  values are often more a reflection of the underlying power (sample size) of an experiment and may or may not relate to the clinical significance of the identified difference in features. As a

## Imaging Genetic Heterogeneity in Glial Tumors

**TABLE 2: Summary of Machine Learning Techniques for Prediction of IDH Mutation, 1p19q Codeletion, MGMT Promoter Methylation, and EGFRvIII Mutation**

Reference	Year	Features	Classifier	Modalities <sup>a</sup>	Accuracy	Sensitivity	Specificity	AUC
IDH mutation								
Yu et al. [65]	2016	FOS, SOS		T2	0.80	0.83	0.74	
Zhang et al. [66]	2017	FOS, SOS	Random forest	T1, T2, ADC	0.89			
Zhang et al. [67]	2017	SOS	Support vector machine	MRI <sup>b</sup>		0.822	0.850	
Zhou et al. [68]	2017	SOS	Logistic regression	MRI <sup>b</sup>				0.86
1p19q loss of heterogeneity								
Fellah et al. [40]	2013	FOS	Random forest	MR spectroscopy, DWI, PWI	0.60			
Zhou et al. [68]	2017	SOS	Logistic regression	MRI <sup>b</sup>				0.96
MGMT promoter methylation								
Levner et al. [70]	2009	SOS	Neural network	MRI <sup>b</sup>	0.877			
Drabycz et al. [42]	2010	Semantic, SOS		T2	0.71			
Korfiatis et al. [71]	2016	SOS	Support vector machine, random forest	T2		0.803	0.813	
Kanas et al. [46]	2017	Semantic, volumetric	k-Nearest neighbor	MRI <sup>b</sup>	0.702			
EGFRvIII								
Kickingereeder et al. [72]	2016	FOS		MRI <sup>b</sup> , DWI, PWI, SWI	0.63			

Note—IDH = isocitrate dehydrogenase, MGMT = 0-6-methylguanine-DNA-methyltransferase, EGFRvIII = epidermal growth factor receptor variant III, FOS = first-order statistics, SOS = second-order statistics, T2 = T2-weighted MRI, ADC = apparent diffusion coefficient, PWI = perfusion-weighted MRI.

<sup>a</sup>Imaging approaches used to train and create the specified machine-learning algorithm.

<sup>b</sup>Conventional MRI.

result, it is critical not only to prove that a difference in features exists but also to assess the sensitivity, specificity, and accuracy of the features to predict a given endpoint.

A summary of machine-learning techniques for prediction of IDH mutation, 1p19q codeletion, MGMT promoter methylation, and EGFR mutation is presented in Table 2. In general, identification of IDH mutation has been the most successful. Several approaches have yielded accuracies over 80% [65–69]. The other molecular alterations tend to have more mixed results. In addition to the foregoing technical considerations for algorithm design, it is also important to carefully choose the diagnostic modalities used as model inputs. Although most studies to date have focused on conventional MRI, as advanced imaging modalities become more popular (e.g., perfusion-weighted MRI, MR spectroscopy), the addition of complementary information should certainly improve the diagnostic accuracy of future machine-learning algorithms.

Machine-learning approaches have limitations that should be considered. First, the development of algorithms requires datasets that are large, organized, well-classified, and ac-

curate. Differences in image acquisition and data storage between institutions and difficulties in sharing data can be obstacles to collecting enough data to obtain useful models. Disseminating standard imaging methods and data collection can address this issue. Second, limited reference standard data, such as biopsy samples, can thwart efforts to address tumor heterogeneity. Biopsy samples often cover only a limited area of a tumor, and the exact biopsy site may not be known. More extensive sampling during surgical biopsy and correlating this with imaging at the exact site of biopsy may mitigate these problems. Despite limitations, machine learning remains a powerful tool that can contribute to noninvasive tumor diagnosis and classification.

### Conclusion

Advances in genetic profiling of gliomas have improved classification and available prognostic information, which can be incorporated into routine image interpretation. Furthermore, although radiogenomics holds promise for individualized therapy, interpatient and intratumor genetic heterogeneity has made the development and testing of new treatments an ongoing challenge. MRI is

uniquely poised to facilitate noninvasive tumor genetic classification owing to its superior tissue contrast resolution and sensitivity to a variety of physiologic processes, such as diffusion and perfusion. Continued advances will likely further shape the diagnosis, treatment, and ongoing assessment of glial tumors as these imaging techniques are leveraged with machine learning approaches.

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