Review Article

Radiogenomics of adult intracranial gliomas after the 2021 World Health Organisation classification: a review of changes, challenges and opportunities

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Abstract: The classification of diffuse gliomas has undergone substantial changes over the last decade, starting with the 2016 World Health Organisation (WHO) classification, which introduced the importance of molecular markers for glioma diagnosis, in particular, isocitrate dehydrogenase (IDH) status and 1p/19-codeletion. This has spurred research into the correlation of imaging features with the key molecular markers, known as "radiogenomics" or "imaging genomics". Radiogenomics has a variety of possible benefits, including supplementing immunohistochemistry to refine the histological diagnosis and overcoming some of the limitations of the histological assessment. The recent 2021 WHO classification has introduced a variety of changes and continues the trend of increasing the importance of molecular markers in the diagnosis. Key changes include a formal distinction between adult- and paediatric-type diffuse gliomas, the addition of new diagnostic entities, refinements to the nomenclature for IDH-mutant (IDH^{mut}) and IDH-wildtype (IDH^{wt}) gliomas, a shift to grading within tumour types, and the addition of molecular markers as a determinant of tumour grade in addition to phenotype. These changes provide both challenges and opportunities for the field of radiogenomics, which are discussed in this review. This includes implications for the interpretation of research performed prior to the 2021 classification, based on the shift to first classifying gliomas based on genotype ahead of grade, as well as opportunities for future research and priorities for clinical integration.

Keywords: Radiogenomics; imaging genomics; magnetic resonance imaging (MRI); glioma; glioblastoma

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Introduction

Diffuse gliomas are the most common primary intracranial malignant neoplasm and over the past decade have undergone repeated and substantial changes to their definition and classification. Understanding these changes and the current classification is not only crucial to accurately communicating with all members of the treating team, but also in interpreting existing and emerging literature.

Pre-2016 classification

Diagnosis and grading of diffuse gliomas have historically been based solely on histological assessment (1). The histological phenotype was based on distinction as either an astrocytic or oligodendroglial tumour, with mixed tumours demonstrating a combination of both cell types being labelled as an oligoastrocytoma (1). Diffuse gliomas have long been graded along a continuum according to the World Health Organisation (WHO) Classification of Central Nervous System (CNS) Tumours, as grade II, grade III (previously known as anaplastic), or grade IV (previously known as glioblastoma) (1). The designation of a grade III tumour indicated more prominent mitotic activity, with grade IV tumours demonstrating the additional features of microvascular proliferation and/or necrosis (1). A higher grade is associated with shorter survival (1,2).

Key changes in the 2016 WHO classification

The identification of distinct genetic changes with prognostic and therapeutic relevance led to the addition of molecular features to the diagnosis of intracranial gliomas in the 2016 update to the WHO classification (1) (henceforth "WHO 2016"). Tumours were first divided according to isocitrate dehydrogenase (IDH) mutation status [as IDH-mutant (IDH^{mut}) or IDH-wildtype (IDH^{wt})], with histological grade II or III IDH^{mut} tumours further divided based on the presence or absence of 1p/19q-codeletion (combined loss of the short arm of chromosome 1 and the long arm of chromosome 19) (1).

The addition of molecular features in WHO 2016 spurred research into the correlation of imaging features, most commonly using magnetic resonance imaging (MRI), with the key molecular markers. This field is known as "radiogenomics" or "imaging genomics". A variety of imaging features have been investigated, with varying ability to predict tumour genotype, as well as differences across tumour grades (in particular, grade II–III *vs.* grade IV) (3). For example, the T2-fluid-attenuated inversion recovery (FLAIR) mismatch sign (*Figure 1*), is strongly predictive of an IDH^{mut}, 1p/19q-intact status in a histological grade II–III glioma (4-7), and is the most specific conventional radiogenomic feature across all diffuse glioma types and grades (3). Earlier studies into conventional MRI features have been followed by studies into advanced MRI techniques, and subsequently by research into predicting genotype using artificial intelligence (AI) techniques, including radiomics (8) and deep learning (9).

Formal molecular testing is—appropriately—considered the gold standard, but is not universally available. Additionally, it has some limitations, and these vary depending on the specific diagnostic test. IDH immunohistochemistry is only able to identify *R132H* mutations in the *IDH1* gene, and cannot detect other clinically-relevant IDH mutations, including other *IDH1* mutations or any *IDH2* mutations (together referred to as "non-canonical" mutations). Fortunately, the *R132H-IDH1* mutation accounts for the majority of all *IDH* mutations (10), but some *IDH* mutations will not be detected if using immunohistochemistry alone. This accounts for the recommendation of following negative immunohistochemistry with IDH sequencing for patients with a higher likelihood of a non-canonical mutation (being higher in younger patients and in grade II–III tumours compared to grade IV) (10,11). 1p/19q testing can also produce false positive or negative results; for example, fluorescence in situ hybridisation (FISH) can be falsely positive in the setting of partial-arm rather than whole-arm deletion (12). Even sequencing can produce false negative results if there are few tumour cells within the sample (10). These issues highlight just one aspect of the potential value of radiogenomics even when molecular testing is performed (13).

Key changes in the 2021 WHO classification

A growing understanding of the molecular basis of intracranial tumours led to a variety of important changes in the 2021 WHO classification (henceforth "WHO 2021"), including several changes relevant to diffuse gliomas occurring in adults (2). One important change was the distinction between "adult-type diffuse gliomas" and "paediatric-type diffuse gliomas", reflecting differences in the underlying tumour genetics based on patient demographics (2). The paediatric group is further divided

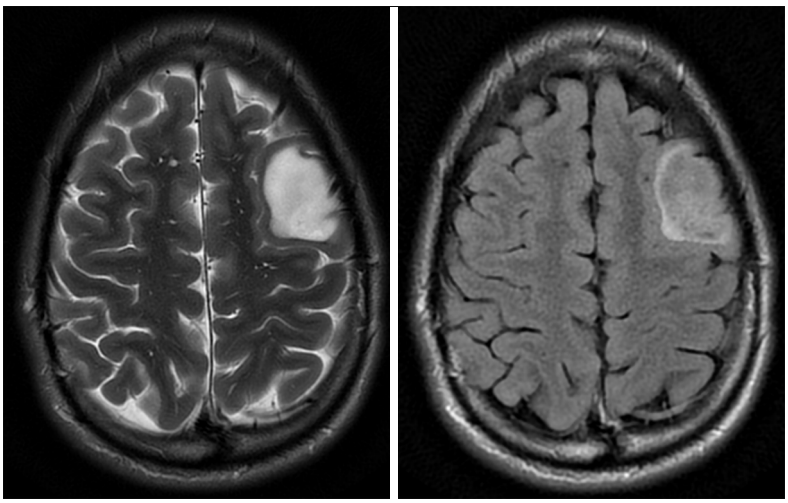

Figure 1 Axial T2 (left) and FLAIR (right) images of a left frontal glioma demonstrating the T2-FLAIR mismatch sign, characteristic of an IDH^{mut} astrocytoma (1p/19q-non-codeleted). The signal is substantially lower on the FLAIR sequence compared to T2. FLAIR, fluid-attenuated inversion recovery; IDH^{mut}, IDH-mutant; IDH, isocitrate dehydrogenase.

into "high-grade" and "low-grade", both containing four entities (2). In all groups, the use of molecular status for determining the type of glioma has been expanded (2). A new addition in WHO 2021, however, is that molecular status now also influences tumour grade in adult-type diffuse gliomas (2). A seemingly trivial change which, however, is a useful clue when reading the literature or pathology reports as to which classification was used, is that tumour grades are now denoted using Hindu-Arabic numerals rather than Roman numerals (2).

Adult-type diffuse gliomas

The diagnosis of adult-type diffuse gliomas according to WHO 2021 is broadly similar, but with three important changes, as well as some subtle changes to the nomenclature (2). Firstly, IDH^{mut} and IDH^{wt} gliomas are more explicitly separated (2). As a result, the diagnosis of a glioblastoma (WHO grade 4) is reserved for IDH^{wt} tumours, and can no longer be applied to an IDH^{mut} tumour, now referred to as astrocytoma IDH^{mut}, grade 4 (2). Secondly, the diagnosis of "glioblastoma, IDH-wildtype" can now also be made based on the identification of at least one of three characteristic molecular changes—epidermal growth factor receptor (*EGFR*) amplification, combined whole chromosome 7 gain and whole chromosome 10 loss (+7/–10), and telomerase reverse transcriptase (*TERT*) promoter mutation—even if the histological findings of microvascular proliferation and necrosis are absent (2,14). Histological grade 2–3 IDH^{wt} gliomas without either necrosis or microvascular proliferation and lacking any of these three molecular features, and also without any other mutations which would indicate a paediatric-type diffuse glioma, do not fulfill the criteria for any of the specific diagnoses in WHO 2021 and are hence labelled IDH^{wt} not elsewhere classified (NEC) (2). It is also important to consider the possibility of a glioneuronal or neuronal tumour, ependymal tumour or a circumscribed astrocytic glioma in such cases, and radiogenomics may provide some guidance here. Thirdly, similar to the aforementioned change in the diagnosis of IDH^{wt} gliomas, the identification of cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) homozygous deletion upgrades an IDH^{mut} astrocytoma (without 1p/19q-codeletion) to grade 4 (2).

Paediatric-type diffuse gliomas

Adult- and paediatric-type diffuse gliomas have been explicitly separated in WHO 2021. However, paediatric-type diffuse gliomas may also occur in adults, especially young adults. For example, many cases of "diffuse midline glioma, H3 K27-altered" have been reported in young adults (15,16), and cases have even been reported in patients over 60 years of age (17,18). Paediatric-type diffuse gliomas are IDH^{wt} by definition (2), thus some of the entities are a consideration in adult patients with an IDH^{wt} glioma, in

particular H3 K27-altered and H3 G34-mutant gliomas (which demonstrate different changes in the H3 histone). These tumours are WHO CNS grade 4 by definition, but can demonstrate lower grade histological features (16,19,20), highlighting the importance of molecular testing, and in turn a potential role for radiogenomics. Identification of such molecular changes, even in adults, will become particularly important if there is success in targeting them therapeutically (21).

Challenges for radiogenomics post-WHO 2021

A watch-and-wait strategy for tumours with less aggressive MRI appearances has fallen out of favour since the identification of molecular markers with prognostic significance, and at least biopsy is recommended at diagnosis (22). Prior to WHO 2021, radiogenomics could provide some reassurance, by identifying features suggesting a favourable molecular profile, in particular the presence of an IDH mutation (13). We expect that the addition of new molecular markers in WHO 2021 will further decrease clinicians' comfort with employing a conservative approach. For example, knowledge of *CDKN2A/B* status is important even if a histologically low-grade tumour is known to be an IDH^{mut} astrocytoma based on molecular testing, due to the worse survival associated with the presence of homozygous deletion (2), and thus far there has been little research into predicting *CDKN2A/B* status using radiogenomics (23). Growing interest in more aggressive resection of the non-contrast-enhancing tumour component (24-28) may further accelerate the trend towards earlier surgery.

WHO 2021 has led to changes to how we consider and diagnose adult gliomas, which will affect how the findings of previous studies can be interpreted and translated into clinical practice. Firstly, many studies have focused on either grade 2–3 or grade 4 gliomas—distinguished based on the traditional histologic criteria—but now it may be more appropriate to consider grade 2–4 tumours together. Indeed, some tumours within the grade 2–3 cohorts would now be considered grade 4 based on the presence of the additional molecular markers discussed above (2). Inevitably, the accuracy of radiogenomics in a grade 2–4 cohort will be lower than in cohorts matched more closely to histological grade. It is worthwhile noting that some tumours classified as IDH^{wt} would now instead be classified as one of the paediatric-type diffuse glioma entities, though such tumours would constitute a small minority of tumours, thus this may not have significantly affected results.

Opportunities

Given the recency of WHO 2021, data on the imaging features associated with the new glioma types and molecular markers is limited, providing great opportunity for research in this area. Relatively few studies have reported on correlations between imaging features and the molecular markers added to the diagnosis of adult-type diffuse gliomas—namely *CDKN2A/B* homozygous deletion, *EGFR* amplification, +7/–10 and *TERT* promoter mutation (2). Of note, while some research has correlated imaging with some of the molecular GBM features, fewer studies have examined all three of the molecular GBM features together, which is currently the more important distinction clinically. However, correlating with individual molecular markers remains of value, as each of the three markers (*EGFR* amplication, +7/–10, and *TERT* promotor mutation) could in principle be associated with different appearances, and such differences may provide insight into how these mutations affect tumour biology and behaviour. For example, Mesny *et al.* have found that gyriform infiltration by non-contrast-enhancing tumour is associated with molecular GBM, in particular *TERT* promoter mutation (29), and an analogous appearance of gyriform dissemination along the grey matter had previously been correlated with IDH^{wt} status (30). An ability to predict how a tumour is likely to behave based on its genotype may in turn have therapeutic implications, for example suggesting a location to target with more aggressive surgical resection (31) or stereotactic radiosurgery (32).

An ability to predict or exclude paediatric-type diffuse gliomas has also become more important for adult patients with gliomas. Of this group, there has been the most radiogenomics research into "diffuse midline glioma, H3 K27-altered" (16), and imaging already provides an important role in their diagnosis (*Figure 2*). Firstly, a midline location is necessary for its diagnosis (2,33), thus imaging can prompt appropriate testing. Conversely, a glioma demonstrating H3 K27-alteration but no involvement of midline structures cannot be diagnosed as this entity (2,33). It is worthwhile noting that more disseminated tumours with a component of midline involvement may also harbour this molecular change (18), and such a pattern may not be apparent without close attention to the imaging. Beyond this, however, no features have yet been identified which can confidently suggest or exclude this genotype (16). It

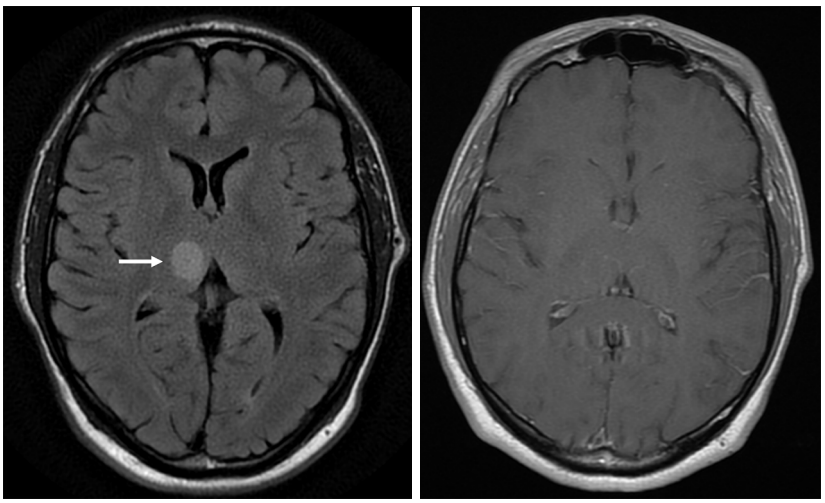

Figure 2 Axial FLAIR (left) and post-contrast T1 (right) images of a right thalamic glioma (arrow) in an adult patient which harboured an H3 K27M mutation. Despite the lack of enhancement and low-grade features on histology, this is now considered a WHO grade 4 tumour. FLAIR, fluid-attenuated inversion recovery; WHO, World Health Organisation.

is worthwhile noting that the change in nomenclature in WHO 2021 from "H3 K27M-mutant" to "H3 K27-altered" reflects an understanding that this pathway may be altered through mechanisms other than H3 K27 mutation (2). In such cases, immunohistochemistry would be falsely negative. Therefore, if immunohistochemistry is negative but imaging predicts a high likelihood of H3 K27-alteration, this may suggest value in sequencing, similar to the ability of the T2-FLAIR mismatch sign to predict a non-canonical IDH mutation despite negative R132H-IDH1 immunohistochemistry (7).

Paediatric-type diffuse gliomas are a particular consideration for histological grade 2–3 tumours classified as IDH^{wt} NEC (i.e., lacking *EGFR* amplification, +7/–10 changes and *TERT* promoter mutation). Currently, it is unclear whether additional genetic testing (e.g., for an H3 G34 mutation) is warranted, and if so, whether this is dependent on patient age (for example, having limited value above 40 years of age). This is analogous to recommendations in WHO 2016 that negative IDH immunohistochemistry be followed by IDH sequencing in patients with grade 4 gliomas who are under 55 years of age, based on a relatively higher likelihood of a non-canonical IDH mutation (11). In a young adult patient with an IDH^{wt} glioma, imaging may be able to identify features suggestive of a paediatric-type diffuse glioma, thus prompting further genetic testing, or alternatively the lack of such features would provide reassurance than further genetic testing is unlikely to change the integrated diagnosis. This highlights that future radiogenomics research into the small proportion of histological grade 2–3 adults gliomas which are IDH^{wt} NEC would be valuable in order to more appropriately target additional molecular testing.

The flexibility of radiogenomics is an important strength when it comes to investigating associations between imaging features and new molecular markers (13). Once an imaging dataset has been curated, new radiogenomic associations can be readily investigated simply by adding new molecular information. This is particularly the case for AI techniques, but also applies to conventional MRI assessment. In addition to the newer molecular markers, important factors to consider and incorporate into radiogenomics research post-WHO 2021 include patient age, midline *vs.* non-midline location and considering 2–4 tumours together. A good example of such an evolution relates to the T2-FLAIR mismatch sign, which has only been validated in histological grade 2–3 gliomas (3). Patel *et al.* recently noted that a similar appearance predicts an IDH mutation in grade 4 tumours, though the percentage of mismatch is typical lower than usually seen in grade 2–3 tumours (34). Subsequently, in grade 2–3 gliomas, it has been shown that considering the T2-FLAIR mismatch sign to be positive with a smaller percentage of mismatch (25% rather than 50%) allows improved sensitivity, whilst maintaining high specificity (35). This suggests that the T2-FLAIR mismatch sign, considering a lower percentage of mismatch than

usually seen in grade 2–3 gliomas, may be able to be adapted to a broader cohort of grade 2–4 adult gliomas (35).

The WHO 2021 criteria have inevitably been developed by experts from well-resourced institutions with access to modern technology, providing ready access to the techniques which allow optimal diagnosis. Such access is far from universal, however, leading critics to question the benefit of WHO 2021 for low- and middle-income countries (36). In such settings, glioma characterisation may remain largely based on IDH and *ATRX* immunohistochemistry (37), with or without techniques such as FISH for 1p/19q testing. This can be supplemented by H3 K27M immunohistochemistry for gliomas in midline locations (22). Therefore, in centres where sequencing of all gliomas is not routine, radiogenomics research based on WHO 2016 may continue to be relevant. Indeed, some important aspects of molecular assessment, and hence radiogenomics, are unchanged by WHO 2021. For example, radiogenomics research into predicting O^6-methylguanine-DNA-methyltransferase (MGMT) methylation status continues (38,39), though this lies beyond the scope of this review.

Ultimately, the potential role of radiogenomics will depend substantially on the processes and availability of molecular testing, which vary substantially between countries and institutions. Assuming comprehensive sequencing is not routinely performed for all gliomas, radiogenomics has greatest potential value when it suggests discrepancy with, or refinement to, a diagnosis based on immunohistochemistry. This allows limited sequencing resources to be directed towards patients with the highest likelihood of this changing the diagnosis and potentially also their subsequent treatment (13). Possible examples include a midline location as an indicator of possible H3 K27-alteration; features (such as T2-FLAIR mismatch) suggesting an IDH mutation despite negative *R132H-IDH1* immunohistochemistry; an imaging phenotype discordant with 1p/19q results; or features suggesting a molecular glioblastoma (when IDH^{wt}) or *CDKN2A/B* homozygous deletion (when IDH^{mut}). *Figure 3* outlines the diagnosis of diffuse gliomas in adults, including where molecular testing is important for classification or grading, and therefore where radiogenomics may play a role. Of note, in contrast to WHO 2016 (1), the key first step in classification is IDH status, rather than histologic grade.

AI has the potential to provide a similar role to a more comprehensive sequencing panel, by predicting a variety of molecular markers simultaneously. However, a challenge is that much of the existing literature has examined a single genetic marker, and the accuracy for predicting the overall genotype based on a combination of markers will be lower (8). This is compounded by the addition of new markers in WHO 2021. Additionally, current technology generally only provides the most likely result for each marker or overall genotype, rather than the definitive diagnosis which is obtained through sequencing. This highlights a limitation of AI radiogenomics techniques as they stand currently, namely that the level of confidence is often unknown (40,41). Understanding the likelihood of a particular genotype is important for determining whether confirmatory sequencing is warranted, for example if the likelihood lies above or below a certain threshold. It would also be valuable to have an algorithm into which demographic data and initial molecular testing results can be inputted. This is analogous to the prediction of IDH mutation, which will vary depending on patient age, histological grade and the results of *R132H-IDH1* immunohistochemistry (42). Further challenges with AI include reproducibility, given the inherent risk of over-fitting, and lack of transparency, due to the "black box" nature of most AI algorithms (9). Key strategies for improving translation of AI methods include obtaining multi-centre datasets, performing external validation, improving explainable AI methodologies and prospectively evaluating the incorporation of these techniques into clinical practice (8,9,43,44).

Beyond radiogenomics

Our discussion has focused on the ways in which imaging features can predict genotype. However, it is important to recognise that, based on current standard-of-care treatment options, genotype largely provides a prediction of prognosis, but may not substantially alter treatment. Fortunately, imaging features identified through conventional assessment or AI techniques also have the potential to provide additional prognostic information which is complementary to the genotype (45). Such analyses are particularly well suited to AI, given the multitude of features which can be combined.

The role of predictive imaging features will also evolve or grow as the new treatment options become available. Different imaging phenotypes may vary in their response to different agents, for example based on their pattern of growth or infiltration. An understanding of these differential responses may in turn facilitate selection of the optimal therapy. If such novel therapies, including agents currently undergoing evaluation, target specific molecular changes,

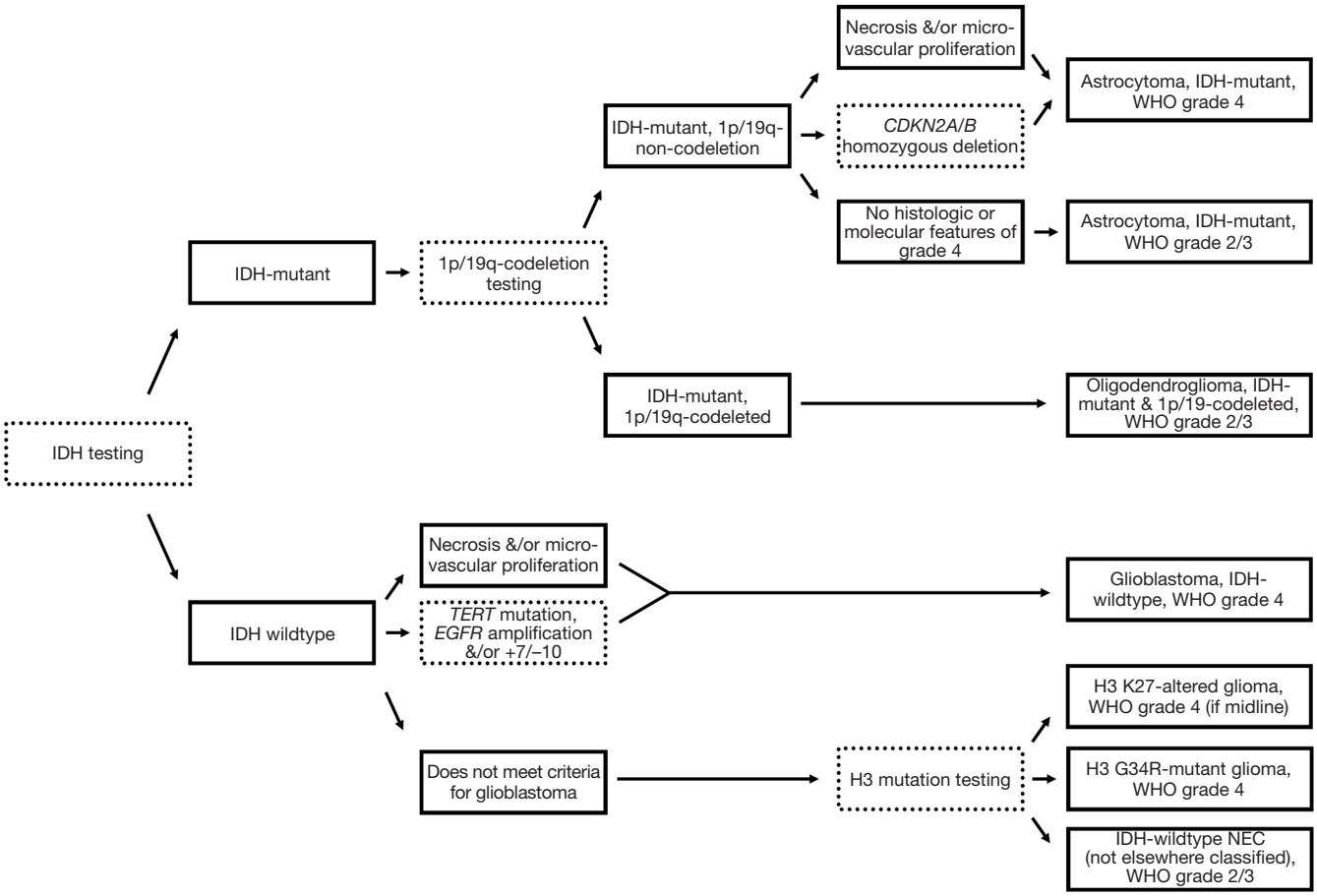

Figure 3 Outline of the diagnosis of diffuse gliomas in adults, including where molecular testing is important for classification or grading (dotted boxes), and therefore where radiogenomics may play a role. The WHO diagnoses are presented in bold. Distinction between grade 2 and 3 tumours is determined by histologic features. IDH, isocitrate dehydrogenase; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; WHO, World Health Organisation; TERT, telomerase reverse transcriptase; EGFR, epidermal growth factor receptor; NEC, not elsewhere classified.

definitive genetic testing may nevertheless be necessary. However, it is possible that imaging phenotypes associated with better response to a particular treatment could occur through a variety of different molecular mechanisms rather than a single genetic mutation, providing another role which is complementary to molecular testing.

Conclusions

WHO 2021 has led to important changes to the diagnosis of adult intracranial gliomas, with an expansion of the importance of molecular assessment for optimal diagnosis. These changes will affect how radiogenomics can be incorporated into clinical practice. Some aspects of radiogenomics will become less important in centres with convenient access to comprehensive genetic assessment, but will remain relevant in the many centres without such access. In addition, there are a variety of new opportunities for research and clinical integration, with a growing role for AI. Furthermore, it is important to expand the role of predictive imaging features beyond just the prediction of genotype, aiming to provide prognostic and therapeutic information which is complementary to that obtained through comprehensive molecular assessment.

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Footnote

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