Insights From Molecular Profiling of Adult Glioma
Phedias Diamandis and Kenneth D. Aldape

ABSTRACT

The comprehensive molecular profiling of cancer has resulted in new insights into the biology and classification of numerous tumor types. In the case of primary brain tumors that commonly affect adults, an emerging set of disease-defining biomarker sets is reshaping existing diagnostic entities that had previously been defined on the basis of their microscopic appearance. Substantial progress has been made in this regard for common primary brain tumors in adults, especially diffuse gliomas, where large-scale profiling efforts have led to the incorporation of highly prevalent molecular alterations that promote a biologically based classification as an adjunct to the traditional histopathologic approach. The growing awareness that histologically indistinguishable tumors can be divided into more precise and biologically relevant subgroups has demanded a more global routine approach to biomarker assessment. These considerations have begun to intersect with the decreasing costs and availability of genome-wide analysis tools and, thus, incorporation into routine practice. We review how molecular profiling already has led to an evolution in the classification of brain tumors. In addition, we discuss the likely trajectory of incorporation of global molecular profiling platforms into the routine clinical classification of adult brain tumors.

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EVOLUTION OF PROFILING STRATEGIES IN BRAIN TUMORS

Brain and other tumor types have long been recognized to carry a widely variable clinical course despite macroscopic homogeneity. To address this gap, in the mid-1800s, Virchow introduced the concept that disease heterogeneity could be better resolved through the microscopic profiling of disease. This revolutionary idea led Cushing and Bailey to show that classification of brain tumors into morphologic subgroups allowed for better prediction of divergent biologic behavior. Since, this cellular classification approach has remained an essential ingredient of precision medicine, including stratification of patients into appropriate clinical trials and, above all, optimal patient management. As Virchow predicted more than a century ago, submicroscopic profiling of chemical (molecular) differences among brain tumors has improved the ability to resolve and predict the clinical behavior of CNS neoplasms.

Recent technological advancements and the exponential decrease in the cost of genomic sequencing now make the prospect of shifting from a morphologic to molecular profiling–based classification of brain tumors possible. Over the past decade, a multitude of large-scale discovery-driven molecular profiling efforts have uncovered novel biomarkers that allow additional division of microscopically similar tumors into more precise and reproducible clinically distinct subgroups. In addition, they have helped to make once-subjective histologic diagnostic entities clearly defined by objective genomic parameters. Much of these efforts drove the release of a significant update to the WHO classification of CNS tumors in 2016 wherein traditional histologic criteria are supplemented with genomic biomarkers (reference PMID: 27157931). These initial molecular definitions likely represent only the early building blocks of a more comprehensive molecular characterization of CNS tumors. For clinical practice to keep up with these discoveries, we likely will need to see a transition of molecular profiling from a research and discovery tool to a routine diagnostic test. We focus this discussion on the evolution of the classification of diffuse gliomas, the most common of adult primary brain tumors. We also speculate about the implications of widespread molecular profiling on the future of CNS tumor characterization and management.

MOLECULAR REFINEMENT OF THE CLASSIFICATION OF DIFFUSE GLIOMAS

Diffuse gliomas are commonly encountered in neuro-oncology and, as a group, carry a remarkably variable clinical course. Some progress
rapidly, whereas others remain relatively stable for years before transformation. Precise classification is thus essential for appropriate management. Historically, diffuse gliomas have been classified by using a defined set of histologic criteria that focus on cellular morphology (potential cell of origin) and features of malignancy (grade). Morphologically, they are subdivided into tumors that resemble native astrocytes (astrocytoma), oligodendrocytes (oligodendroglioma), or both (oligoastrocytoma). They are then subdivided further on the basis of features of malignancy. Low- and intermediate-grade lesions show nuclear atypia and mitotic activity (WHO grade 2 and 3, respectively). Histologic higher-grade tumors show areas of necrosis and/or microvascular proliferation (WHO grades 3 to 4). This microscopic classification scheme has served neuropathologists well for decades because of the ease and speed of implementation and reasonable effectiveness at predicting the extremes of clinical behavior. Unfortunately, it suffers from well-documented morphologic and subjective interobserver variability that hinder adequate prediction of the clinical variability of gliomas.3–8

Early genomic analysis of gliomas more recently has begun to define genetic differences between microscopically indistinguishable gliomas. For example, glioblastomas with mutations in the tumor suppressor gene TP53 tend to occur in younger adults, arise from documented lower-grade lesions (secondary glioblastomas), and have a longer interval of survival. Conversely, de novo glioblastomas (primary glioblastoma), which arise more abruptly in patients without a previous clinical history, enrich for chromosome arm 10q loss (a region that encompasses the PTEN tumor suppressor gene) and carry genomic gains in the region that contains EGFR on chromosome arm 7p.9–11 Similarly, within tumors with an oligodendrogliial morphology, codeletion of chromosome arms 1p and 19q (1p/19q codeletion) is a strong predictor of prolonged survival and chemosensitivity to procarbazine, lomustine, and vincristine.12,13 These early findings are proof of concept that, as Virchow predicted, molecular analysis can further subclassify microscopically similar lesions.

Since, large-scale genomic efforts that systematically profile brain tumors have found additional clinically relevant molecular biomarkers that more objectively differentiate among these three distinct groups. In glioblastomas, genomic profiling has identified novel mutations in the isocitrate dehydrogenase genes (IDH1/2) to be strong predictors of secondary glioblastomas and good prognosticators among histologically indistinguishable glioblastomas.14,15 Similarly, multiplatform molecular profiling efforts that included a survey of genomic, methylation, and transcriptional differences in lower-grade gliomas revealed numerous molecularly defined subgroups of which three robust, reproducible, and nonoverlapping prognostic classes were consistently identified.3,16 These groups could be defined on the basis of a binary pattern of mutations in IDH1/2 and TP53 and the assessment of 1p/19q codeletion status. Routine assessment of this small group of biomarkers have been repeatedly shown to predict survival more accurately than traditional histologic assessment.3 For example, IDH wild-type anaplastic astrocytomas, which are traditionally given a WHO grade 3 designation, have a contradictory inferior prognosis compared with IDH mutated glioblastomas with a WHO grade 4 designation. Similarly, the large clinical variability of oligoastrocytomas is well resolved by reclassification of these tumors into glioma subgroups defined solely on the basis of IDH mutation and 1p/19q codeletion status. The superior prognostic power of these molecular markers has since prompted an updated 2016 WHO diffuse glioma diagnostic classification scheme. In addition to a traditional morphologic description of cell lineage (astrocytic, oligodendrogliial, or both), and grading (WHO grades 2 to 4), glioma entities explicitly include annotations of IDH1/2 mutations and 1p/19q codeletion status (Fig 1).

So far, widespread practical and clinical application of the results of such large-scale profiling efforts has relied on the development of a growing panel of focused and cost-effective molecular surrogate assays. These assays could be triaged and ordered as deemed necessary by the practicing neuropathologist, and in diffuse gliomas, an immunohistochemical stain has largely been used for the most common mutant IDH alleles (eg, IDH1 R132H) and ATRX along with florescent in situ hybridization (FISH) to determine 1p/19q codeletion status. Although these surrogates, when compared with the initial-discovery global profiling efforts, provide cost-effective (approximately $10 to $20 per immunohistochemical stain and $200 to $300 for FISH) and convenient solutions for molecular analysis, they come with significant drawbacks. First, they require diverse expertise in optimization, quality control measures, laborious protocols, and interpretation. The serial nature of testing also results in significant reporting delays. For example, immunohistochemistry for IDH mutation status only detects the most common R132H alteration.17 When negative, this sometimes necessitates the need for more-tailored IDH1/2 polymerase chain reaction (PCR)–based hotspot mutational analysis of exon 4, which is not yet widespread. Similarly, 1p/19q codeletion assessment by FISH can take 1 to 2 weeks to report and often is initiated only after histologic assessment and IDH immunohistochemistry are completed. Furthermore, FISH and PCR-based assessment of 1p/19q codeletion status are prone to false-positive results when whole-arm loss of 1p and 19q, as is most commonly the case, are not assessed. These limitations are significant given the dramatically different prognosis in histologic lower-grade gliomas that lack these aberrations.5

Of note, the WHO classification scheme focuses primarily on prognostic biomarkers and omits clinically relevant predictive (eg, therapeutically relevant) biomarkers. For example, hypermethylation of the O6-methylguanine–DNA methyltransferase (MGMT) promoter, most commonly assessed by PCR-based methods, is not included in the current classification scheme. This epigenetic alteration is found in 35% to 50% of glioblastomas and predicts a robust response to DNA alkylating agents, such as temozolomide. MGMT promoter methylation status dramatically changes clinical management of glioblastomas, especially in elderly patients. Its omission, however, may be overlooked by inexperienced pathologists at smaller academic centers, which results in inappropriate or delayed treatment. Fortunately, most tertiary centers now routinely assess MGMT methylation status. As the
As we transition to a more personalized era of precision medicine, routine assessment of actionable biomarkers will become...
a priority for clinical neuro-oncology teams. As such, patient-specific molecular characterization and therapeutic target predictions soon will become more important than population-based classification of brain tumors.

MOLECULAR PROFILING AS A ROUTINE CLINICAL TOOL: BEYOND HISTOLOGIC CLASSIFICATION

Molecular profiling efforts have uncovered an additional array of biomarkers that still are not routinely assessed (Table 1). For example, some divide gliomas into five groups that are based on the combination of their status of IDH1/2 mutations, TERT promoter mutations, and 1p/19q codeletions. For simplicity, assessment of TERT promoter mutations are, however, not yet incorporated in the current WHO classification scheme, despite their prognostic role. Similarly, gains of chromosome arm 7p (35% to 40%) and losses on chromosome arms 9p and 10q (75% to 95%) are not routinely assessed in gliomas. These changes have been likely omitted as a result of their overlap with other more indolent glial tumors.

Although they currently have unclear clinical significance, other mutations further divide the current tumor classes into smaller and smaller subgroups. For example, mutations in PTEN (35% to 45%), EGFR (VIII variant), and PDGFR amplifications are heterogeneously found in glioblastomas. Similarly, some IDH mutated and 1p/19q codeleted oligodendrogliomas develop subsequent mutations in CIC, FUBP1, NOTCH1, and TERT promoter in varying frequencies. Although their prognostic value currently may be limited, as treatment regimens diversify in our molecular era, being able to simultaneously monitor these biomarkers may help to reveal specific tumor genotypes that differentially respond to treatment. As additional biomarkers continue to guide prognosis, therapy, and clinical trials, the cost and diagnostic knowledge of surrogate testing panels will quickly outpace the budgetary and quality control capabilities of standard pathology departments.

The decreasing cost and widespread use of genomic technologies has resulted in an economy of scales that has allowed a growing number of international pathology centers to use molecular profiling as a routine tool in the diagnostic work-up of CNS and other tumors, which has provided a more uniform, objective, and precise description of the genomic landscape of gliomas (including noncanonical IDH-mutant gliomas) remain on the differential.

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Table 1. Frequencies of Alteration of Selected Genes in Diffuse Gliomas

<table>
<thead>
<tr>
<th>Gene</th>
<th>Oligodendroglioma With IDH Mutation and 1p/19q Codeletion</th>
<th>Diffuse Astrocytoma With IDH Mutation and No 1p/19q Codeletion</th>
<th>GBM, IDH Mutant</th>
<th>LGG, IDH Wild Type</th>
<th>GBM, IDH Wild Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH1/2</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TERT promoter mutations</td>
<td>5,16,14,16,17</td>
<td>96</td>
<td>4</td>
<td>26</td>
<td>64-80</td>
</tr>
<tr>
<td>TP53 mutations</td>
<td>17,20,21</td>
<td>94</td>
<td>74-81</td>
<td>23-35</td>
<td>23-35</td>
</tr>
<tr>
<td>ATRX</td>
<td>21,24</td>
<td>86*</td>
<td>71</td>
<td>Very rare</td>
<td>24-35</td>
</tr>
<tr>
<td>EGFR amplification</td>
<td>5,16,15,26,28</td>
<td>0</td>
<td>4</td>
<td>38</td>
<td>35-45</td>
</tr>
<tr>
<td>PTEN mutation</td>
<td>5,17,21,25,26</td>
<td>0</td>
<td>5</td>
<td>35-50</td>
<td>25</td>
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<tr>
<td>CDKN2A deletion (chr 9 loss)</td>
<td>15,25-27</td>
<td>Approx. 40</td>
<td>63</td>
<td>35-50</td>
<td>25</td>
</tr>
<tr>
<td>NFKB1A deletion</td>
<td>25</td>
<td>13</td>
<td>7</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CDKN2A promoter hypermethylation</td>
<td>5,16,29</td>
<td>15-30</td>
<td>15-18</td>
<td>15-18</td>
<td></td>
</tr>
<tr>
<td>LOH 19p</td>
<td>22,25</td>
<td>32-50</td>
<td>3-4</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>LOH 10p</td>
<td>25</td>
<td>63</td>
<td>Approx. 50</td>
<td>Approx. 70</td>
<td></td>
</tr>
<tr>
<td>Chr 10q loss</td>
<td>25</td>
<td>&gt; 60</td>
<td>15-18</td>
<td>15-18</td>
<td></td>
</tr>
<tr>
<td>NFI mutation</td>
<td>15,25</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>PIG3R1 mutation</td>
<td>25</td>
<td>60†</td>
<td>13</td>
<td>12 (350)</td>
<td></td>
</tr>
<tr>
<td>PIG3R2</td>
<td>25,30</td>
<td>4</td>
<td>5-15†</td>
<td>5-15†</td>
<td></td>
</tr>
<tr>
<td>MET amplification</td>
<td>25,30</td>
<td>13</td>
<td>7</td>
<td>7</td>
<td></td>
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<tr>
<td>MD M4 amplification</td>
<td>25,30</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>CDKN4 amp</td>
<td>25</td>
<td>40</td>
<td>25§</td>
<td>8-12</td>
<td></td>
</tr>
<tr>
<td>RB1 (promoter hypermethylation)</td>
<td>25</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1p/19q codeletion</td>
<td>5,16</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MGMT promoter methylation</td>
<td>5,16</td>
<td>20-31</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CIC mutation</td>
<td>5,16</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>FUBP1 mutation</td>
<td>5,16</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviations: Approx., approximately; chr, chromosome; GBM, glioblastoma; LGG, lower-grade glioma; LOH, loss of heterozygosity.
*Mutations, 79%; deletions, 3%; gene fusions, 2%; multiple, 2%.
†Increased expression.
‡Overexpressed in > 60%.
§Deletion.
diffuse gliomas and other brain tumors. Perhaps the most common approach incorporates targeted exomic sequencing of a select panel of actionable tumor genes and an array-based platform to assess genome-wide copy number changes. Most targeted panels consist of 300 to 500 genes known to be mutated and act as molecular drivers of carcinogenesis.35 These gene panels are assessed by massively parallel sequencing strategies; comprehensively identify actionable deletions, fusions, and single nucleotide variants in the genome from small amounts of input (50 to 70 ng of material); and include mutations in IDH1/2 not captured by immunohistochemistry. These panels are supplemented with high-resolution array-based technologies, such as comparative genomic hybridization and methylation profiling, to effectively assess chromosomal copy number changes (eg, whole-arm 1p and 19q status). Methylation profiling also has the benefit of assessing MGMT promoter methylation status. In addition to not suffering from the described limitation of current surrogate biomarkers, these panels offer a vast amount of additional information necessary for the practice of precision and personalized medicine. For example, these global molecular profiling efforts offer improved sensitivity and specificity of the current classification scheme. IDH wild-type diffuse astrocytoma remains a diagnosis of exclusion in the current classification scheme and may be mistaken for other astrocytic lesions with favorable prognoses. The use of routine molecular profiling platforms that simultaneously capture other informative biomarkers, such as chromosome arm 7 amplification and chromosome arm 10 loss, can help to resolve difficult cases of undifferentiated brain tumors more definitively.

Unbiased profiling of the whole spectrum of mutations and genetic changes known to occur in cancer may also yield unanticipated information with clinical relevance. For example, although rare in gliomas, mutations such as BRAF V600E, offer alternative precise and targeted therapeutic alternatives compared with current nonspecific therapies.34 Of note, such global profiling efforts identified an NAB2-STAT6 fusion product in a glioblastoma, a molecular alteration previously identified in and associated with solitary fibrous tumor/hemangiopericytoma.33

Despite these significant advantages, important practical considerations have affected early widespread adoption of these technologies. Cost is still an important factor. As a result, many centers are still reluctant to perform IDH1/2 immunohistochemistry (approximately $10 to $20 per tumor sample), 1p/19q FISH testing (approximately $300), and IDH sequencing ($100 per case) in gliomas where these mutations are likely to be extremely rare (eg, in elderly patients). Routine adoption of more global testing, such as exomic sequencing (approximately $500 to $800 per case), and methylation profiling (approximately $500 per case), which costs an order of magnitude more, thus is likely to remain largely restricted to a small group of tertiary academic medical centers. Similarly, the 3 to 6 week turnaround time of many of these more global tests currently require make the integration of this information into the current clinical decision making time frame more difficult. Finally, most global molecular tests still require a relatively large amount of tissue compared with the single to 200 cells needed for immunohistochemical and in situ–based molecular testing. As such, pathology departments, to their disappointment, may find an increase in rather than consolidation of the large number of more-focused molecular tests they currently maintain. Until the clinical and cost-effectiveness of the more-unfocused profiling approach is proven, histomorphologic triaging of focused molecular tests (immunohistochemistry, PCR, and FISH) will be the most widespread method encountered clinically.

Even in the molecular era, interobserver variability limits the reproducibility and consistent classification of disease through biomarkers to a small panel with binary readouts (eg, positive, negative). Significant advances in artificial intelligence, machine learning, and bioinformatics analysis now allow for more-complex patterns of subtle molecular changes to be analyzed.

Surveys of more modest, but biologically relevant, changes in a set of genes (molecular signatures) allow for sufficient statistical power to yield new, highly reproducible, and clinically significant biomarkers that could not be previously resolved through linear single gene analysis.35 For example, highly sophisticated machine learning tools, including random forest classifiers,36 now allow accurate subclassification of tumors with clinically relevant turnaround times without the aid of knowing histologic grouping. DNA methylation profiles also have shown utility in subclassifying tumors that are histologically homogenous into clinically relevant subgroups.35-41 In gliomas, these profiles provide accurate tumor classification with turnaround times of < 2 weeks and concurrently function as a readout for DNA copy number and IDH mutational and MGMT hypermethylation status.

The falling cost of global genomic analysis and advances in machine learning algorithms have now shifted many research efforts to integrated multiphase-based profiling efforts. As these studies uncover finer and finer layers of molecular detail that cannot be converted into binary biomarkers, they will eventually demand incorporation into diagnostic practice and may eventually include a simultaneous survey of the genomic; methylation; transcriptional; and, eventually, proteomic landscape of cancer. For example, transcriptional profiling of glioblastomas has uncovered four transcriptional subtypes (proneural, classic, mesenchymal, and neural).35,42 Some correlate with known other prognostic alterations. Proneural glioblastomas, for example, are enriched for IDH mutations, MGMT promoter hypermethylation, and amplifications of PDGFRA. Although the other transcriptionomic subgroups have characteristic genomic correlates (eg, NF1 mutations in mesenchymal glioblastomas), they currently offer no clear prognostic significance.42 Routine definition of these groups should not be omitted, though. Their continual evaluation and reporting may eventually reveal effective subgroup-specific treatment regimens that would have been overlooked. Furthermore, global profiling efforts may provide unanticipated biomarkers in the tumor microenvironment, such as assessment of intratumoral leukocyte content and mutational burden and PD-L1 expression for immunotherapies.43 Although these biomarkers may provide no prognostic significance to the patient, they may offer significant predictors of biologic response to dramatically different, but highly specific therapeutic strategies.

Although routine molecular profiling appears to be a daunting task, it may significantly simplify the workflow of pathology departments by reducing the need for a large panel of specialized and
highly context-specific tests. Furthermore, by creating a uniform platform, smaller pathology departments can take advantage of streamlined informatics and analytic tools that process and interpret raw genomic data.44

EMERGING METHODOLOGIES: SINGLE CELL SEQUENCING

An appreciation that human cancers are in fact complex mixtures of cells with distinct cells of origin, phenotypes, genotypes, and epigenetic states is growing. In this regard, our current bulk profiling models do not adequately capture this heterogeneous tumor composition in patients. Prior microarray and next-generation sequencing work on bulk tumor samples yield data that are, in essence, representative of the average cellular composition of the tumor mass. Population-based methods for classification and analysis have provided important biologic insights but do not recapitulate the diversity present in an individual tumor between both the neoplastic component and the microenvironmental nonneoplastic elements. Several studies have pointed to this emerging area of interest to elucidate the biology of brain tumors, and initial work has focused on gliomas. One study performed single cell sequencing on five glioblastoma samples.45 The authors typed the bulk tumors on the basis of transcriptional subtype (proneural, classic, mesenchymal, and neural) and found that all five tumors contained a mixture of individual cells that correspond to each of the four glioblastoma subtypes. Individual cells showed a predominance of subtype in each tumor, but the heterogeneity was striking. An additional finding linked a stemness signature to proneural status. In a second study, this group profiled six IDH-mutant oligodendrogliomas and found a rare subpopulation of cells with an expression signature suggestive of neural stem cells that also overexpress genes associated with proliferation.46 The findings are consistent with a model in which cancer stem cells are primarily responsible for self-renewal in oligodendroglioma. In a third study, single cell profiling was performed on a set of IDH-mutant gliomas.47 Because this method can identify and distinguish tumor cells from nonneoplastic populations, a direct comparison of the neoplastic elements of astrocytomas versus oligodendrogliomas could be made. Notably few genes could be identified that differed between neoplastic cells of these two histologies. More striking were the differences in the microenvironment where macrophase-specific gene overexpression was observed in the astrocytomas and neuron-specific genes predominated in oligodendrogliomas. Higher-grade astrocytomas had a greater proportion of resident macrophages/microglia, which also implicates this cell population in this histology. The findings suggest that the biology of astrocytoma and oligodendroglioma tumor cells are more similar than might have been expected. Furthermore, microenvironmental influences may play an important role in the distinct clinical behavior of these entities. Overall, these studies indicate the power and potential of single cell analysis to elucidate the complex biology of gliomas.

Although profiling that uses nucleic acid–based platforms (eg, DNA mutation, copy number epigenetics, RNA-based platforms) have been helpful in describing the biology of gliomas, a need exists for an increased understanding of the proteomic landscape of these tumors. Reverse phase protein arrays (RPPAs) in 203 IDH wild-type glioblastomas from The Cancer Genome Atlas data set could provide important biologic and clinical information.48 These focused RPPA-based antibody panels are encouraging and suggest that additional protein-based biomarkers exist and await discovery. The outcomes of proteogenomic studies in gliomas may become a valuable addition to current genomic-based molecular profiling efforts.49-51 Additional areas of interest include the exploration of liquid biopsy specimens, including the evaluation of circulating tumor cells in glioblastomas.52 The detection of circulating nucleic acids in gliomas through identification of tumor-specific mutations has proven to be challenging,53 but this area of investigation is rapidly changing, and methodologies are likely to be developed to detect circulating blood nucleic acids from gliomas.54 CSF may also prove to be a valuable resource to detect and monitor disease in a manner that is less invasive than a brain biopsy.55

CHALLENGES

Much has been learned through profiling of adult brain tumors, especially the diffuse gliomas. Unbiased approaches and the integration of multiple genomic platforms have led to an understanding of the central role of IDH mutation status to distinguish two major types of gliomas that, although similar under the microscope, display distinct biologies. With respect to clinical implementation, the decreasing cost and accessibility of genomic technologies will make routine molecular profiling a realistic goal for most academic centers over the next decade. The wealth of information and novel technologies that have become available will increasingly become accessible for possible clinical use, which has become apparent with the WHO update for classification for CNS tumors where specific molecular changes have become integral to the definition of specific diagnostic entities. Future goals will include molecular characterization that is based on specific molecular alterations that will provide pathologists with tools to classify tumors biologically and clinicians with the ability to select drugs with actionable targets more rationally for specific patients. Much more work will be required to reach these goals given the therapeutic resistance inherent in higher-grade gliomas, especially glioblastomas. The reason for the failure of our current precision therapies could be that many of the mutations that are being targeted are important for tumor initiation but perhaps are subsequently overridden by secondary pathways and mechanisms of late tumor progression. An additional problem is intratumoral heterogeneity such that particular clones of cells vulnerable to that pathway may be targeted, but clones whose growth is independent of that pathway remain resistant. Overall, a coordinated approach toward tumor profiling matched with carefully designed biomarker-driven clinical trials will be most helpful to identifying biologic brain tumor classes enriched for sensitivity to specific therapeutic regimens.
Disclosures provided by the authors are available with this article at jco.org.

REFERENCES

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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