Integrated Molecular-Morphologic Meningioma Classification: A Multicenter Retrospective Analysis, Retrospectively and Prospectively Validated

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PURPOSE Meningiomas are the most frequent primary intracranial tumors. Patient outcome varies widely from benign to highly aggressive, ultimately fatal courses. Reliable identification of risk of progression for individual patients is of pivotal importance. However, only biomarkers for highly aggressive tumors are established (CDKN2A/B and TERT), whereas no molecularly based stratification exists for the broad spectrum of patients with low- and intermediate-risk meningioma.

METHODS DNA methylation data and copy-number information were generated for 3,031 meningiomas (2,868 patients), and mutation data for 858 samples. DNA methylation subgroups, copy-number variations (CNVs), mutations, and WHO grading were analyzed. Prediction power for outcome was assessed in a retrospective cohort of 514 patients, validated on a retrospective cohort of 184, and on a prospective cohort of 287 multicenter cases.

RESULTS Both CNV- and methylation family–based subgrouping independently resulted in increased prediction accuracy of risk of recurrence compared with the WHO classification (c-indexes WHO 2016, CNV, and methylation family 0.699, 0.706, and 0.721, respectively). Merging all risk stratification approaches into an integrated molecular-morphologic score resulted in further substantial increase in accuracy (c-index 0.744). This integrated score consistently provided superior accuracy in all three cohorts, significantly outperforming WHO grading (c-index difference P < .005). Besides the overall stratification advantage, the integrated score separates more precisely for risk of progression at the diagnostically challenging interface of WHO grade 1 and grade 2 tumors (hazard ratio 4.34 [2.48-7.57] and 3.34 [1.28-8.72] retrospective and prospective validation cohorts, respectively).

CONCLUSION Merging these layers of histologic and molecular data into an integrated, three-tiered score significantly improves the precision in meningioma stratification. Implementation into diagnostic routine informs clinical decision making for patients with meningioma on the basis of robust outcome prediction.

J Clin Oncol 39:3839-3852. © 2021 by American Society of Clinical Oncology

ASSOCIATED CONTENT
Data Supplement
Author affiliations and support information (if applicable) appear at the end of this article.
Accepted on August 31, 2021 and published at ascpubs.org/journal/jco on October 7, 2021; DOI https://doi.org/10.1200/JCO.21.00784

INTRODUCTION Molecular markers have amended or replaced histologic classification and grading criteria for many brain tumor types. For meningioma, TERT promoter mutation or homozygous deletion of CDKN2A/B is included in the 2021 WHO classification as independent criteria of WHO grade 3 meningioma.1-3 However, the most pressing clinical need is to identify high-grade meningioma, but to distinguish patients with low or virtually none from those with intermediate risk of recurrence.4,5
CONTEXT

Key Objective
The WHO classification of meningiomas stratifies patient cohorts into three groups with low to high risk of progression. However, outcome for individual patients often deviates from the prediction based on conventional grading. Various approaches to increase risk prediction accuracy for individual patients with meningioma exist. Copy-number variations are enriched in aggressive meningiomas, and methylation-based classification was introduced as a novel tool for meningioma stratification. Yet, these approaches lack both comprehensive validation and integration into one unified classification concept, preventing their routine application.

Knowledge Generated
Our data delineate and comparatively validate the independent predictive power of WHO grading, specific copy-number variations, and methylation-based classification. Based on three independent cohorts, we devised and validated a superior, integrated grading algorithm (integrated score) leveraging the advantages of all three classification approaches.

Relevance
The significant increase in prediction accuracy of the integrated score, including a majorly more precise segregation of patients at the clinically challenging interface at WHO grade 1 and 2, provides a robust basis for clinical decision making.

METHODS
Details on sample collection, cohort composition, and mutational profiling are provided in the Data Supplement (online only). Lasso-selected CNVs (Data Supplement) were aggregated into a risk stratification (CNV-Lasso model) based on sum of CNVs (low: none, intermediate: 1-2, high: 3), given equal weight to all CNVs for practicability. The CNV-Literature model was similarly defined as a sum score based on the deletion of 1p, 6q, 10q, and 14q (low: none, intermediate: 1-2, high: ≥ 3).

For the integrated score, a multivariable Cox regression model with WHO grading, methylation family (MF), and the CNV-Lasso model was fitted (Data Supplement). No specific cutoff was used for MF allocation (Data Supplement). Hazard ratios of the model were translated into individual risk points based on the corresponding nomogram, with risk points for each risk factor restricted to a maximum of 4 (Data Supplement) and rounded to integers for practicability and interpretation. Patients were classified based on the sum into low (0-2), intermediate (3-5), and high (> 5) integrated risk. Cutpoints were selected based on clinically reasonable proportions and discriminative ability. Patients in validation cohorts were classified based on the scores and cutpoints as derived on the discovery cohort. Heterogeneity of prognostic effect of risk stratification between males and females was tested with the likelihood ratio test between a Cox model with and without interaction term.

RESULTS
Correlation of WHO Grade, CNVs, DNA Methylation, and Mutations
We analyzed 3,031 meningioma samples (Data Supplement), spanning all WHO grades and subtypes, for CNVs. Number of CNVs per sample increased with WHO grade (Data Supplement). All cases were allotted to one of the previously introduced six epigenetic MCs of meningioma. These six MCs encompass three MCs with benign outcome (ben-1, ben-2, and ben-3), two MCs with intermediate outcome (int-A and int-B), and one malignant MC with highly aggressive outcome (mal). Accordingly, these six MCs can be merged into three overarching groups, formerly referred to as combined clinical groups, for consistency with recent literature in the field herein now called methylation families: MF benign including MC ben-1, -2, and -3, MF intermediate encompassing int-A and -B, and MF malignant. In line with previous studies, the CNVs were highly distinct for the MCs: ben-1 shows consistently
deletions of 22q, ben-2 has virtually flat copy-number profiles, and ben-3 is characterized by whole-chromosomal gains. The number of whole-chromosome deletions increases in MC int-A/B (or the combined MF intermediate, respectively), and finally MC mal is characterized by numerous CNVs including focal homozygous deletions on 9p at the CDKN2A/B locus (Data Supplement). Virtually all CNVs either affect the whole arm or are absent (Data Supplement).

Distinct mutations also align with CNV patterns: Isolated NF2 mutations are frequently associated with WHO grade 1, isolated 22q deletion, and MC ben-1. AKT1, SMO, KLF4, and TRAF7 mutations are common in WHO grade 1 meningioma of MC ben-2 with flat copy-number profiles. Additional CNVs besides 22q deletion are accumulated in MC int-A and int-B, along with NF2 mutations and increasing WHO grade. Finally, meningiomas with highly perturbed genomes, including CDKN2A/B homozygous deletions, have mostly WHO grade 3 and MC mal classification, and are enriched for TERT promoter mutations (Fig 1B).

The most frequent alterations besides 22q deletion were deletions of 1p, 6q, 10q, and 14q. Their distribution indicates that the cascade of CNV accumulation is limited to NF2-altered meningiomas (Fig 1B). Accordingly, cases for which mutational data were available and which harbored AKT1, SMO, KLF4, and/or TRAF7 mutations rarely carried any CNVs (Fig 1B). Hence, these data on CNVs and mutations confirm the conclusions about characteristics of MCs and overarching MFs from the initial study.6 Oncogenetic trees support initiating 22q deletion in 68% of cases, followed by 1p deletion, and subsequently (in order of frequency) 6q, 18q, 14q, 7p, 10q, 4p, or 2p deletion, or combinations thereof (Figs 1C and 1D, Data Supplement).

Comparison of WHO Grading, CNVs, and MFs as a Model for Clinical Outcome Prediction

Next, we assessed the power of outcome prediction of these molecular parameters.

Within the 3,031 meningioma samples, retrospective clinical outcome data were available for one cohort of 514 individual cases, with a median follow-up time of 45 months and 169 events during follow-up (details on WHO grades, MCs, clinical parameters, and gene mutations are given in the Data Supplement). The two separate, fully independently gathered sets of other retrospectively (n = 287) cases were not included in these analyses to subsequently serve as validation cohorts (clinical parameters are given in the Data Supplement). WHO grade, sex, and extent of resection (Simpson grade 1-3 v 4 or 5) were significantly associated with progression. NF2 insertion or deletion, TERT promoter mutation, and homozygous deletion of CDKN2A/B were associated with unfavorable outcome (Data Supplement). Interestingly, TRAF7 and KLF4, or the compound non-NF2 group with TRAF7, AKT1, and/or KLF4 mutations were significantly associated with lower risk of progression (Data Supplement).

Univariable analysis corrected for multiple testing yielded significant prognostic effects for 14 different CNVs, including deletions proposed as risk markers before,10,11 such as 1p, 6q, 10q, and 14q (Data Supplement). Upon adjustment for WHO grade, age, sex, and localization, most of these markers remained significant (Table 1, Data Supplement). Of note, we also implemented the novel WHO criteria (TERT promoter mutation and CDKN2A/B homozygous deletion as criteria for anaplasia) throughout our analyses here (patient characteristics of cases for which the WHO 2021 grading criteria were available and prognostic impact of CNVs for WHO 2021 cases are provided in the Data Supplement). After further adjustment for methylation, only deletion of 1p remained an independent marker (Table 1, Data Supplement).

In line with early emergence in the oncogenetic trees, presence or absence of 1p can further stratify histologically WHO grade 1, grade 2, and the compound WHO grade 1 or 2 cases (Figs 2A and 2B). If 1p deletion is present, the outcome is similar to WHO grade 2 or MF int. This indicates that any meningioma with 1p deletion should be considered as at least WHO grade 2 (all cases in Fig 2B, WHO 1 or 2 only cases only in Fig 2C). Hence, 1p status is an attractive target for analysis because of its prognostic relevance, abundance in a large share of meningiomas, and assay availability.

To identify a three-tiered scheme based on CNVs only, we used a Lasso Cox model. This returned losses of 1p, 6q, and 14q as the most informative combination (c-index 0.715). On the other hand, testing a model based on CNVs that had been consistently proposed in the literature before,10,13,14 this model included deletion of 1p, 6q, 10q, and 14q. Accordingly, absence of any of these was categorized as low, up to two CNVs as intermediate, and three or more as high risk. Although largely identical to those CNVs arising from our data-driven approach, regarding them as a priori given reduces the need for overfitting correction because of variable selection in the discovery data set (c-index 0.715).

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As expected, these markers also clearly stratify by DNA methylation alone also yielded clinically distinct strata, confirming previous reports on the prediction power of methylation in meningioma15,16 (log-rank P < .0001, Fig 3E).
FIG 1. (continued on following page)
Next, we compared the prediction performance of the different models (Fig 3F, Data Supplement). The data-derived CNV-Lasso model has a c-index of 0.701, the CNV-Literature model 0.709, and the MFs 0.719 (Data Supplement). These three were all favorable compared with the WHO classification 2016 with a c-index at 0.683 and WHO classification 2021 with a c-index of 0.697 (Data Supplement). Brier prediction errors at 10 years are similar for all models (0.170-0.178) except for MFs with again a lower error (0.158, Data Supplement). The difference in prediction accuracy was significant for MFs versus WHO with \( P < .01 \) at 5 and \( P < .001 \) at 10 years. No significance was reached for the CNV models compared with the WHO grading (Data Supplement). This performance analysis focused on cases with \( TERT \) status available, as this is a requirement for WHO 2021, and same results were obtained when comparing to WHO 2016 grading available, also including cases with unknown \( TERT \) status (Data Supplement).

For validation, the superior performance of molecular approaches compared with WHO grading alone was confirmed in an independent retrospective cohort, with c-indices of 0.673 for WHO grading, 0.698 CNV-Lasso model, 0.701 CNV-Literature model, and 0.685 MFs. Intriguingly, while the molecular models were again superior to the WHO grades, the CNV models performed better than the MFs in this retrospective validation cohort (risk stratification for the different models in the Data Supplement).

**Combining the Outcome Prediction Models Toward an Integrated Classification**

Collectively, the molecularly guided approaches were consistently stronger in predicting risk of progression than the WHO grading. However, all models, including histologic grading, remained strong independent predictors (Data Supplement). Hence, a combined approach leveraging the strength of all these layers of information may yield an essential further advance in risk prediction.

We combined all three models into an integrated, also three-tiered grading approach, using a multivariable Cox regression model. For each category, points from 0 to 4 are allotted (nomogram in the Data Supplement, algorithm in Fig 4A, correlation with other models Fig 4B, and decision tree in the Data Supplement). The sum of these morphologic and molecular alterations results in the grade (ie, low, intermediate, and high). This integrated model significantly stratified for outcome (Fig 4C) and has a significantly higher prediction accuracy in c-index (Fig 4D and Data Supplement) and lower prediction error than WHO grading alone in the discovery cohort at 5 (\( P = .002 \)) and at 10 years (\( P = .0001 \)) (Data Supplement). This holds true in a comparison of the integrated model to the 2021 WHO grading.

### TABLE 1. Prognostic Impact of Single Copy-Number Alterations in the Discovery Cohort

| CNV | N   | HR (95% CI) | \( P \)   | Adjusted \( P \) Value |
|-----|-----|------------|---------|----------------------|
| 1p loss adjusted for WHO grade, age, sex and location | 514 | 3.68 (2.45-5.51) | < .001 | < .001 |
| 6q loss | 514 | 2.36 (1.70-3.29) | < .001 | < .001 |
| 10q loss | 514 | 2.39 (1.65-3.46) | < .001 | < .001 |
| 7p loss | 514 | 2.04 (1.42-2.93) | < .001 | .002 |

| CNV | N   | HR (95% CI) | \( P \)   | Adjusted \( P \) Value |
|-----|-----|------------|---------|----------------------|
| 1p loss adjusted for WHO amended for \( TERT \) promoter and homozygous CDKN2A/B loss status adjusted for age, sex, and location | 399 | 3.43 (2.27-5.19) | < .001 | < .001 |
| 6q loss | 399 | 2.16 (1.55-3.02) | < .001 | < .001 |
| 10q loss | 399 | 2.05 (1.39-3.01) | < .001 | .005 |
| 1q gain | 399 | 1.97 (1.36-2.85) | < .001 | .006 |

| CNV | N   | HR (95% CI) | \( P \)   | Adjusted \( P \) Value |
|-----|-----|------------|---------|----------------------|
| 1p loss adjusted for WHO grade, MF, age, sex and location | 514 | 2.57 (1.64-4.05) | < .001 | < .001 |
| 6q loss | 514 | 1.67 (1.19-2.34) | .003 | .064 |
| 10q loss | 514 | 1.67 (1.14-2.45) | .009 | .175 |

Abbreviations: CNV, copy-number variation; HR, hazard ratio; MF, methylation family.
grading for both c-index ($P = .004$) and prediction error at 5 and 10 years ($P = .0021$ and $P = .0001$ respectively, Data Supplement). The integrated model is also significantly superior in c-index when compared with the CNV-Lasso model ($P = .008$) and to the CNV-Literature model ($P = .044$) (Data Supplement). Despite higher c-index for the integrated score, there was no significant difference to methylation ($P = .06$, Data Supplement) in this cohort.

In the retrospective validation cohort, the integrated model also resulted in significant outcome risk stratification ($P < .0001$, Data Supplement), and both the superior c-indices and Brier scores compared with WHO are replicated (Fig 4E, Data Supplement). In addition to being superior to WHO and CNV in the discovery cohort, the integrated score also significantly exceeds the predictive power of methylation families in the retrospective validation.

### Table A

| CNV          | WHO | n   | Rec | CNVs | HR  | P       | IAp |
|--------------|-----|-----|-----|------|-----|---------|-----|
| loss1p       | 1   | 235 | 41  | 64   | 2.83 | .001    |     |
|              | 2   | 217 | 86  | 124  | 3.48 | <.001   |     |
|              | 1 or 2 | 452 | 127 | 188  | 3.81 | <.001   |     |
|              | 3   | 62  | 42  | 55   | 6.02 | .014    |     |
|              | All | 514 | 169 | 243  | 4.67 | <.001   | .417|
| loss6q       | 1   | 235 | 41  | 29   | 4.74 | <.001   |     |
|              | 2   | 217 | 86  | 68   | 2.04 | .001    |     |
|              | 1 or 2 | 452 | 127 | 97   | 3.19 | <.001   |     |
|              | 3   | 62  | 42  | 28   | 2.04 | .023    |     |
|              | All | 514 | 169 | 125  | 3.35 | <.001   | .174|
| loss14q      | 1   | 235 | 41  | 27   | 2.69 | .013    |     |
|              | 2   | 217 | 86  | 73   | 2.26 | <.001   |     |
|              | 1 or 2 | 452 | 127 | 100  | 2.99 | <.001   |     |
|              | 3   | 62  | 42  | 33   | 0.98 | .947    |     |
|              | All | 514 | 169 | 133  | 2.90 | <.001   | .040|
| loss10q      | 1   | 235 | 41  | 16   | 2.98 | .006    |     |
|              | 2   | 217 | 86  | 26   | 2.41 | <.001   |     |
|              | 1 or 2 | 452 | 127 | 42   | 2.75 | <.001   |     |
|              | 3   | 62  | 42  | 32   | 1.73 | .086    |     |
|              | All | 514 | 169 | 74   | 3.42 | <.001   | .676|

**FIG 2.** Risk on progression stratified for WHO grades in the presence of 1p, 6q, 14q, or 10q losses. (A) Forest plots on association of risk-of-progression with single CNVs stratified for the three WHO grades. (B) Comparative Kaplan-Meier analysis for time-to-progression stratified for WHO grade, combined methylation classes, and cases with and without deletion of chromosome 1p in all cases of the discovery cohort. (C) Separating WHO grade 1 cases with chromosome 1p loss among all WHO grade 1 cases and in turn delineating all WHO grade 2 cases without a chromosome 1p loss among the WHO grade 2 cases, identifies subgroups with majorly different outcome as expected from WHO grade alone. IAp denotes $P$ value of test on interaction between WHO grade and CNV. CNV, copy-number variation; HR, hazard ratio; IAp, interaction test $P$ value; MF-ben, methylation family benign; MF-int, methylation family intermediate; MF-mal, methylation family malignant; Rec, recurrences; TTP, time to progression.
FIG 3. (continued on following page)
validation cohort (difference in c-index \( P = .011 \), in Brier score \( P = .016 \)).

Finally, the integrated score also provides significant risk stratification in the prospective cohort (\( P = .0249 \), risk stratification is provided in the Data Supplement). In line with the other cohorts, the integrated score had the highest c-index (0.665 v 0.596-0.652 of the others). However, in this first prospectively collected data set on methylation in meningioma, the data set is not yet mature to reach significance (Data Supplement).

Neither sex (\( P = .7 \)) nor extent of resection (EOR; \( P = .5 \)) remained an independent prognostic factor when adjusting for the integrated score in Cox regression. Additionally, the prognostic effect of the integrated risk scores was not significantly different in male or female patients (\( P = .93 \)).

Among the compound WHO grade 1 and 2 meningiomas, cases with low risk in the integrated model had outcomes similar to the average WHO grade 1, despite having been diagnosed as WHO grade 2 (Fig 4F). In turn, histologically inconspicuous cases but with higher integrated model scores had outcomes identical to the average WHO grade 2. Of note, the integrated score separates low-risk from high-risk cases among WHO grade 1 or 2 cases more clearly than 1p status (Fig 2C v Fig 4F). Accordingly, the hazard ratio for low versus higher integrated scores among WHO grade 1 or 2 cases was 4.56 (2.97-7.00), 4.34 (2.48-7.57), and 3.34 (1.28-8.72) in the discovery, the retrospective, and the prospective validation cohorts, respectively (Data Supplement).

**DISCUSSION**

To identify robust markers for risk stratification of patients with meningiomas, and devise a grading schema thereof, we here interrogated a comprehensive set of meningiomas on multiple levels, from copy number through epigenomics to mutations. First, we further substantiated that meningioma can be separated into two major subsets: one with initiating 22q/NF2 alteration and the potential to acquire additional CNVs and to progress, and one with AKTI/KLF4/TRA7/SMO/Pik3CA mutations and no recurrent CNVs. This is in line with previous studies on the molecular landscape and genomic instability of NF2-mutant meningiomas.15-24

Among the CNVs arising in NF2-mutant cases, the most informative single marker is deletion of 1p. The addition of 1p assessment in WHO grade 1 and 2 cases substantially increases the prediction accuracy (Figs 2A and 2B): Histologically inconspicuous cases, thus compatible with WHO grade 1, but prone to progression or recurrence, can be singled-out by identification of 1p deletion. In turn, meningioma with higher mitotic count, thus allotted to WHO grade 2, but lack of 1p alteration, can be categorized as WHO grade 1 (Fig 2C).

However, 1p status alone does not adequately dissect for the full range of meningioma. In three cohorts, we here validated that methylation stratifies the entire landscape of meningioma with higher accuracy than the WHO grading approach. These data emphasize the role of methylation in meningioma that has been proposed by several studies before15,16,25 and provides the first methylation-based classification that has now been validated over multiple cohorts, including prospectively accrued cases, after its introduction in 2017.6

Alternative to methylation, CNVs can serve as a strong prediction model, assessing only three (Lasso model) or four (Literature model) chromosomal arms. The strength of pre-existing data in this field is reflected by the fact that our data sets on > 3,000 meningiomas heuristically yielded virtually the same selection of markers (1p, 6q, and 14q) that could also be derived from our survey of literature on smaller cohorts. Previous technologic obstacles to implement CNV assessment are now overcome by increased use of high-throughput platforms.

However, all three approaches (histology, methylation, and CNVs) have their specific value and advantages. For instance, an anaplastic meningioma with RB1 deletion or a rhabdoid meningioma WHO grade 3 with deletion on chromosome 3 encompassing BAP1 do not qualify for a high-risk tier by CNV, but are identified as MF mal by methylation (Data Supplement).

In turn, some meningiomas cannot unequivocally be assigned to one of the MFs,26 yielding comparatively low, but still informative scores in the meningioma methylation classifier (Data Supplement). For parenchymal brain tumor samples with low scores, CNVs are already leveraged to render a clear diagnosis (eg, 7/10 alteration in glioblastoma). This was not available for meningioma as yet.

To harmonize the integration of these three layers, histology, CNVs, and methylation, we developed the integrated score. Although both MFs and CNVs have independently...
### WHO grading

| Grade | Value |
|-------|-------|
| Grade 1 | 0     |
| Grade 2 | 1     |
| Grade 3 | 2     |

### MF

| Category | Value |
|----------|-------|
| Ben      | 0     |
| Int      | 2     |
| Mal      | 4     |

### Losses chromosome 1p, 6q, 14q

| Present | Value |
|---------|-------|
| None    | 0     |
| 1-2     | 2     |
| 3       | 3     |

### Integrated model score

| Integrated Score | Value |
|------------------|-------|
| Low              | 0     |
| Int              | 1     |
| High             | 2     |

#### Integrated Score for Meningioma Classification

**FIG 4.** (continued on following page)
FIG 4. (Continued). The integrated model combines WHO grading, CNVs, and MFs. For each of the three components of the integrated model (WHO grading, methylation, and CNVs), a value between 0 and 4 is added to the total score. (A) The combined score ranges from 0 to 9 and stratifies low (0-2), intermediate (3-5), and high (6-9) risk for progression meningiomas. (B) Cross-over model illustrating the distribution of cases in the discovery cohort over the different components of the integrated model. (C) Kaplan-Meier analysis of progression-free survival for cases stratified for based on the integrated model. (D) Brier prediction score analysis shows lower error rate, thus higher prediction accuracy, for the integrated model in the discovery and (E) retrospective validation cohorts. (F) Separating WHO grade 1 intermediate-risk and WHO grade 2 low-risk cases identifies true high-risk cases among WHO grade 1, and true low-risk cases among WHO grade 2 cases. ben, benign; CNV, copy-number variation; int, intermediate; mal, malignant; MF, methylation family.

FIG 5. Overview on clinical, histologic, epigenetic, and genetic characteristics in the three risk groups of the integrated model. Histologic subtypes present in < 5% of the cases are grouped under other. The outer ring in the histology subtype plots represents the corresponding WHO grade. *Indicates a homozygous loss of CDKN2A/B. ben, benign; CNV, copy-number variation; F, female; int, intermediate; M, male; mal, malignant; MF, methylation family.
proven strong predictors in the cohorts analyzed here, the integrated score was consistently superior, delineating three distinct risk groups (Fig 5). Intriguingly, the CNV models are more accurate in early follow-up, most pronounced in the retrospective validation cohort, whereas the benefit of methylation arises later. This
is in line with the concept that epigenetic characteristics can predate other genetic or morphologic changes. An unfavorable MF may indicate ultimately aggressive growth, but does not stratify between those that are already in an aggressive stage or are just prone to transformation. The short-term course is more accurately reflected by CNVs and histology.

Regarding underlying technology, the implementation of methylation into the WHO classification will foster its wider availability. In low-throughput settings, nanopore sequencing provides results identical to arrays for assigning MF and identification of prognostic copy-number alterations (Data Supplement).

Subjecting every meningioma to a comprehensive work-up may still not be feasible. We thus identified histologic subtypes in which further assessment is required (Data Supplement) and devised an efficient, stepwise workflow for diagnostic routine (Fig 6).

Further studies may even incorporate the molecular layers into risk-prediction before surgery. A risk prediction score obtained from circulating DNA, potentially extended with radiologic features, may identify the growth and transformation potential of incidental meningioma, guiding therapy decisions.27

The integrated molecular-morphologic score has immediate effect on risk stratification for a substantial number of patients (Data Supplement) and holds potential to transform the work-up of diagnostic meningioma samples similar to the extent that molecular profiling has changed assessment and consecutive treatment decisions for parenchymal brain tumors.

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EQUAL CONTRIBUTION
S.L.N. Maas, D. Stichel, T. Hielscher, and P. Sievers contributed equally to this work.
A. von Deimling and F. Sahm co-supervised this work.

SUPPORT
Supported by the Else Krönner Fresenius Foundation (EKFS, Grant Nos. 2015_A_60 and 2017_EKES.24), the German Cancer Aid (Grant No. 70112956), and the Hertie Foundation (Hertie Network of Excellence in Clinical Neuroscience).

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.00784.

DATA SHARING STATEMENT
Upon reasonable request, the DNA methylation, mutational, and clinical outcome data can be shared.

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ACKNOWLEDGMENT
The authors thank Laura Dörner, Lea Hofmann, Lisa Kreinbihl, and Moritz Schalles for excellent technical assistance, and the DKFZ Genome and Proteome Core Facility for support in DNA methylation analysis.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Integrated Molecular-Morphologic Meningioma Classification: A Multicenter Retrospective Analysis, Retrospectively and Prospectively Validated

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/wc or ascopubs.org/jco/authors/author-center.

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Consulting or Advisory Role: Bayer Suisse
Research Funding: Lilly, Bayer, Roche, PharmaMar, Pfizer
Patents, Royalties, Other Intellectual Property: patent on using DNA methylation profiling for tumor classification

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Research Funding: Lilly, Bayer, Roche, PharmaMar, Pfizer

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Research Funding: Merck Serono, Novocure, Merck Sharp & Dohme, Apogenix, Queregen Pharmaceuticals

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Research Funding: Roche, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Bristol Myers Squibb, Daiichi Sankyo, AbbVie
Travel, Accommodations, Expenses: Roche, GlaxoSmithKline, Bristol Myers Squibb, MSD, Mundipharma

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Patents, Royalties, Other Intellectual Property: Patent for IDH1R132H antibody H09 administered by the German Cancer Center (DKFZ), Patent for BRAFV600E antibody VE1 administered by the German Cancer Center (DKFZ), DNA methylation-based method for classifying tumor species EP16710700
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No other potential conflicts of interest were reported.