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European Association of Neuro-Oncology guideline on molecular testing of meningiomas for targeted therapy selection

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Abstract

Meningiomas are the most common primary intracranial tumors of adults. For meningiomas that progress or recur despite surgical resection and radiotherapy, additional treatment options are limited due to a lack of proven efficacy. Meningiomas show recurring molecular aberrations, which may serve as predictive markers for systemic pharmacotherapies with targeted drugs or immunotherapy, radiotherapy, or radioligand therapy. Here, we review the evidence for a predictive role of a wide range of molecular alterations and markers including *NF2*, *AKT1*, *SMO*, *SMARCE1*, *PIK3CA*, *CDKN2A/B*, *CDK4/6*, *TERT*, *TRAF7*, *BAP1*, *KLF4*, *ARID1/2*, *SUFU*, PD-L1, SSTR2A, PR/ER, mTOR, VEGF(R), PDGFR, as well as homologous recombination deficiency, genomic copy number variations, DNA methylation classes, and combined gene expression profiles. In our assessment based on the established ESMO ESCAT (European Society for Medical Oncology Scale for Clinical Actionability of molecularTargets) evidence-level criteria, no molecular target reached ESCAT I (“ready for clinical use”) classification, and only mTOR pathway activation and *NF2* alterations reached ESCAT II (“investigational”) classification, respectively. Our evaluations may guide targeted therapy selection in clinical practice and clinical trial efforts and highlight areas for which additional research is warranted.

Keywords

meningioma | predictive marker | targeted therapy

Meningiomas are the most common intracranial tumors of adults and constitute approximately 40% of all primary central nervous system (CNS) tumors.¹ Most meningiomas are benign, with around 75%–80% of cases being classified as CNS World Health Organization (WHO) grade 1 according to the 5th edition of the WHO Classification of CNS Tumors (CNS5).² 20–25% of meningiomas show histopathological or molecular features

indicating higher risk of recurrence and are classified as CNS WHO grade 2 (15%–20% of cases) or 3 (1%–5% of patients).

According to international guidelines and established clinical practice, surgical resection is recommended for most meningiomas at diagnosis.³ Postoperative radiotherapy may be considered based on the extent of resection and histological grade. For progressive or recurrent meningioma, local

therapies (ie, further surgical resection or salvage radiotherapy) are commonly recommended. Other treatment options including various systemic therapies and targeted radionuclide therapy have been investigated, but none are established as management standards.³⁻⁶

Extensive molecular profiling efforts of meningiomas have led to the identification of multiple recurring aberrations and patterns on the genetic, epigenetic, transcriptomic, and protein levels.^{7,8} These alterations can be relevant to identifying early signs of progression in otherwise benign appearing meningiomas. Some of these molecular features may represent suitable targets for treatment with specific inhibitors, immunotherapies, or radioligands. Indeed, some clinical trials indicate potential clinical activity with some of these precision medicine approaches in meningiomas.^{5,6} Despite the fact that no approved targeted treatments are available for this tumor type, meningiomas may show potential targets for off-label targeted therapies in molecular screening efforts performed in the clinical routine.⁹ However, evidence-based evaluations of the clinical utility as treatment targets of the various molecular alterations typically found in meningiomas are widely missing so far.

In this guideline, we review the molecular alterations with potential therapeutic implications in meningiomas, similar to a prior European Association of Neuro-Oncology (EANO) guideline on glial, glioneuronal, and neuronal CNS tumors.¹⁰ This guideline will facilitate research efforts aiming at advancing precision medicine approaches for meningiomas. Furthermore, we hope to support decision-making in routine clinical practice, as modern molecular profiling methods often reveal potential treatment targets in meningiomas that may lead to therapeutic considerations by treating physicians or in tumor boards.⁹ To this end, we provide integrated and concise recommendations on testing for each individual alteration/marker based on evidence-level evaluations in the main text of this paper. Detailed discussions and literature reviews for most targets (excluding those with few available data) are provided in the [supplement](#) accompanying this publication.

Molecular Testing: How to Test

Multiple types of molecular markers are relevant for the diagnosis and treatment of meningiomas, and thus, a wide range of testing methods/assays can be used, mandating a careful selection of the most appropriate tool for the specific question and setting. Since the general recommendations about molecular testing of CNS neoplasms and the characteristics of each assay type are valid independent of the tumor type, readers can refer to the recently published EANO guidelines concerning the molecular diagnostic assessment of glial and glioneuronal tumors for a comprehensive review of this topic.¹⁰

Specifically for meningioma, the intra-tumoral heterogeneity needs to be accounted for when selecting areas for DNA/RNA extraction. For example, *TERT* promoter mutations or *CDKN2A/B* deletions can be restricted to more aggressive subclones, and methylation subgroup allocation can vary within a tumor.^{11,12} Identification of these areas

should be guided by morphology (cell density, prominent nuclei, high nucleus/cytoplasm ratio, and mitotic count), supported by immunohistochemistry (Ki-67, pHH3). This selection is suggested on the understanding that the more aggressive areas will determine the outcome. Morphological evaluation, and tissue size per se, may be limited in frozen material, hence FFPE tissue is typically more amenable to assess heterogeneity and select areas for DNA/RNA extraction. Of note, fibroblastic meningiomas often show limited detectable antibody binding, possibly due to their spindle-shaped cytology.¹³ Further detail on testing for individual markers is provided in the [supplement](#).

How to Report Findings

According to a recently published guideline of EANO on the use of molecular tools,¹⁴ the report of the results of molecular testing should include information on the exact type of test(s) performed, and on the origin (pathology number) and nature (formalin-fixed, paraffin-embedded [FFPE] vs snap frozen) of the sample used for analysis. Furthermore, information should be provided on how representative the sample is for the tumor of interest, highlighting indications for heterogeneity or low tumor cell content where applicable. The report of next-generation sequencing (NGS) data should include the list of the genes or otherwise determined target regions that were interrogated by the test or a reference where to find this information. Also, details of the identified alterations should be provided according to international standards as released by the Human Genome Variation Society (<https://varnomen.hgvs.org/>), including transcript identification (or genomic location with reference genome version), nucleotide and amino acid exchange, read depth at the respective position, and variant allele frequencies.¹⁵ Similarly, the genes/regions covered by (targeted or whole transcriptome) RNA sequencing should be reported, as well as the applied bioinformatics pipeline and the number of fusion reads. Also, the significance and functional plausibility (eg, retention of the kinase domain in a tyrosine kinase receptor) should be checked before reporting the presence of a gene fusion.^{14,16}

The report of the results of methylome profiling should (in addition to information on the amount of DNA input and the estimated tumor cell content/fraction of the extracted DNA) encompass information on the quality of bisulfite conversion, classifier version(s) used, highest scoring methylation category/categories with the respective calibrated score(s), and subclassification with score(s) if applicable. DNA methylome profiling by array-based analyses can also identify specific genomic alterations. However, in case the presence of gene fusions and/or particular mutations are suggested for which therapeutic approaches are considered, ultimate proof is warranted by orthogonal methodology (eg, sequencing).¹⁴

Integrated inspection of morphology, NGS, and/or methylation data is essential to assess the molecular data in the context of tumor cell content. Typically, this is not a similar challenge in meningioma tissue as, for example, in diffuse glioma. Yet, low fractions of canonical, presumably early mutations (*NF2*, *AKT1*, *TRAF7*, *SMO*) or low amplitudes of

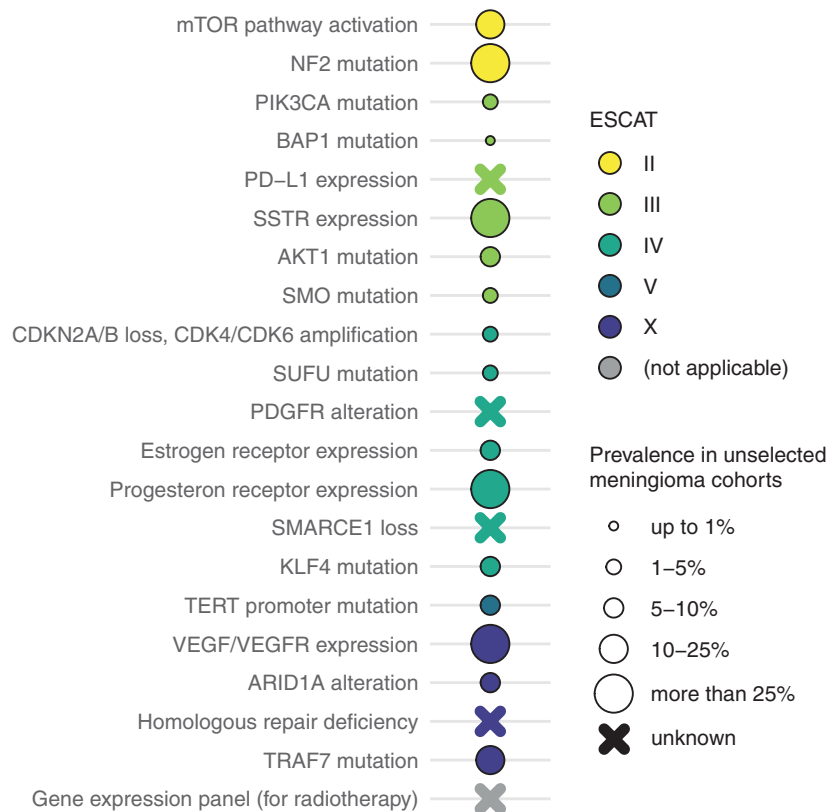


Figure 1. Overview of the frequency and ESCAT score of molecular targets found in meningiomas. Numbers as found in the literature. ARID1A, AT-rich binding domain protein 1A; BAP1, BRCA1-associated protein 1; CDK4/6, cyclin-dependent kinase 4/6; CDKN2A/B, cyclin-dependent kinase inhibitor 2A/B; ESCAT, European Society for Medical Oncology Clinical Actionability of molecular Targets; KLF4, Krüppel-like factor 4; mTOR, mammalian target of rapamycin; NF2, neurofibromin 2/schwannomin; PD-L1, programmed cell death ligand 1; PDGFR, platelet-derived growth factor receptor; PIK3CA, Phosphatidylinositol 3-kinase, catalytic subunit alpha; SMARCE1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin E1; SMO, smoothened; SSTR, somatostatin receptor; SUFU, suppressor of fused homolog; TERT, telomerase reverse transcriptase; TRAF7, TNF receptor-associated factor 7; VEGF(R), vascular endothelial growth factor (receptor).

CNVs, especially 22q deletion, may indicate low tumor cell content in the extracted area and possibly explain lower methylation scores.

Immunohistochemistry (IHC) data should include a description of potential heterogeneity, which controls were used and evaluated, and optimal information on the applied clone.¹⁷

Attributing Pathogenic Significance to Findings

Estimating and attributing the pathogenic significance to a detected variant or, more broadly, to a molecular alteration is a complex task requiring the integration of multiple layers of information. Useful data include the germline frequency of the variant, the specific position within the gene sequence, the existence of already-known variants at the same location, and the predicted impact on protein structure and function.^{15,18} For instance, a variant with a relatively high germline frequency is unlikely to be pathogenic, while an exon-located missense variant resulting

in a different amino acid or nonsense variant is more likely to be pathogenic.

Evaluation of these features should result in the classification of potential pathogenic significance. Concerning somatic variants in cancer, a 5-tier system has been proposed,¹⁵ similar to what has been established for a longer time for germline variants.¹⁹ This scoring system is based on the standardized evaluation of the previously mentioned features and results in the following 5 categories: benign, likely benign, variant of uncertain significance, likely oncogenic, and oncogenic.

Multiple databases have been created to collect data about the identified variants in different tumor types and to provide information regarding their frequency and potential pathogenicity, but coverage in terms of the analyzed neoplasms and genes varies since most frequent tumors are more represented. Moreover, changes in diagnostic classifications can limit the longitudinal value of collected data, although this pitfall is less relevant for meningiomas, since this has been a well-characterized diagnostic entity for a long time. In addition to general databases, gene-specific repositories are also available; for example, concerning meningiomas, a database of *NF2* variants is available (<https://databases.lovd.nl/shared/genes/NF2>).

Finally, the use of deep learning-based approaches is expected to improve the pathogenetic classification of newly detected variants in terms of clinical relevance, required resources, and consistency.²⁰

Attributing Clinical Significance to Findings

Meningiomas display a variety of recurring molecular aberrations. In order to grade the evidence for the relevance of these potential targets for targeted therapy, we are applying here the widely accepted European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT),²¹ which was also used in the prior EANO guideline on molecular testing.¹⁰ The ESCAT defines 6 levels of clinical evidence for molecular targets according to the implications for patient management (Table 1). While ESCAT was primarily developed for the assessment of genomic alterations, we apply it here in a broader sense and use it also for grading potential biomarkers defined by protein expression or assessed with other methods such as immunohistochemistry or molecular imaging (Figure 1).

Molecular Testing: When to Test

In meningioma, surgical resection and radiotherapy are established treatment options recommended at initial diagnosis and recurrence.³ Systemic pharmacotherapy and targeted radionuclide therapy are currently regarded as experimental and are to be considered only after exhaustion of surgical resections and radiotherapy options.⁵ Therefore, outside of clinical trials in the first-line setting, molecular testing intended for the selection of targeted therapy is not recommended at initial diagnosis but is potentially more relevant at recurrence and consideration of such a therapy line. However, information on the risk of recurrence based on molecular markers and subgroups (*TERT*, *CDKN2A/B*, DNA methylation) may already be advisable at initial diagnosis and, depending on the assay, already reveal predictive information discussed here. Guidance on the selection of molecular testing for prognostic markers in meningiomas and their integration into grading has recently been provided by the cIMPACT-NOW consortium.²² As recommended for glial tumors, molecular testing should be performed on the most recent tumor tissue sample whenever possible, as molecular alterations may change as tumors progress.¹⁰ Furthermore, the development of newer methodologies over time may also justify deferring analysis until clinically indicated, as novel techniques may be able to investigate multiple targets with a single test saving time and laboratory costs. Novel technology may also alleviate the current limitation of molecular testing due to cost, both of single analyses and of equipment in general. Concerning the testing strategy, high-throughput profiling for diagnostic markers may in parallel yield information on multiple of the potential targets discussed here. The gradual deterioration of nucleic acid in FFPE material over time can reduce the quality

of test results at a later stage, and therefore this has to be considered in the testing strategy.

Molecular Targets

Mammalian Target of Rapamycin (mTOR) Pathway Activation

The serine/threonine kinase mammalian target of rapamycin (mTOR) is a key regulator of a signaling axis involved in the control of cell growth, cell cycle progression, and protein synthesis. Activating mutations in *mTOR* or inactivating mutations in *TSC1* or *TSC2* can be detected by NGS panels, whole-exome sequencing (WES), or whole-genome sequencing (WGS). mTOR inhibitors are established and approved treatments for several tumor types. While mTOR pathway upregulation in meningiomas via these activating mutations is rare, upregulation of this pathway via inactivation of *NF2* is very common in these tumors and thus a potential target for therapeutic intervention.^{5,23–25} However, high-level evidence for the efficacy of this therapeutic approach is still lacking (as detailed in the supplemental information), rendering mTOR pathway activation an **ESCAT IIB** target.

Neurofibromin 2 (Merlin, Schwannomin; NF2)

NF2 non-synonymous inactivating mutations are the most common molecular alterations in meningioma, especially at the convexity, found in up to 60% of sporadic cases.²⁶ Loss of heterozygosity of chromosome arm 22q, on which *NF2* is located, is the most frequent chromosomal aberration in meningiomas and is part of a 2-step inactivation of *NF2*.²⁷ *NF2* encodes merlin, a cytoskeletal protein involved in contact inhibition, directly and indirectly regulating the activity of several protein kinases such as RTK, FAK and PI3K/Akt converging on mTOR, and activating the Hippo pathway. *NF2* copy number loss may be tested by comparative genome hybridization (CGH) arrays, reverse-type quantitative polymerase chain reaction (RT-qPCR), methylation sequencing, or other quantitative DNA analyses. Detection of *NF2* sequence variants requires DNA sequencing technology, in particular NGS.

Based on limited clinical trial results, *NF2* alterations are considered a predictive biomarker for patient treatment (**ESCAT IIB**),²¹ opening interesting perspectives, but lacking the basis for a strong recommendation. To date, most clinical trials employing *NF2* loss as a molecular target have been performed in recurrent or progressive, mostly heavily pretreated meningioma patients without a control arm. The mTOR inhibitor everolimus in combination with octreotide led to reduced growth rates as compared to the period prior to study enrollment in a small phase 2 clinical trial.²⁸ The ErbB2/EGFR inhibitor lapatinib likewise led to slowed tumor growth in another small phase 2 clinical trial.^{29,30} The FAK inhibitor GSK2256098 yielded stable disease in 8 of 24 higher-grade *NF2*-altered meningiomas in an uncontrolled phase 2 clinical trial.³¹ A prospective phase 2 platform trial has documented a radiographic response rate in 28% (5 of the 18 patients) in evaluable meningiomas

Table 1. European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT)²¹

	ESCAT evidence tier	Required level of evidence	Clinical value class	Clinical implication
Ready for routine use	I: Alteration-drug match is associated with improved outcomes in clinical trials.	IA: prospective, randomized clinical trials show the alteration-drug match in a specific tumor type results in a clinically meaningful improvement of a survival endpoint. IB: prospective, non-randomized clinical trials show that the alteration-drug match in a specific tumor type, results in clinically meaningful benefit as defined by ESMO MCBS 1.1. C: clinical trials across tumor types or basket clinical trials show clinical benefits associated with the alteration-drug match, with similar benefits observed across tumor types.	Drugs administered to patients with specific molecular alterations have led to improved clinical outcomes in the prospective clinical trial(s).	Access to the treatment should be considered a standard of care.
Investigational	II: alteration-drug match is associated with antitumor activity, but the magnitude of the benefit is unknown.	IIA: retrospective studies show patients with the specific alteration in a specific tumor type experience clinically meaningful benefits with the matched drug compared with alteration-negative patients. IIB: prospective clinical trial(s) show the alteration-drug match in a specific tumor type results in increased responsiveness when treated with a matched drug; however, no data currently available on survival endpoints	Drug administered to a molecularly defined patient population is likely to result in clinical benefit in a given tumor type, but additional data are needed.	Treatment is to be considered “preferable” in the context of evidence collection either as a prospective registry or as a prospective clinical trial.
Hypothetical target	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumor types(s) or with similar molecular alteration.	IIIA: clinical benefit demonstrated in patients with the specific alteration (as tiers I and II above) but in a different tumor type. Limited/absence of clinical evidence available for the patient-specific cancer type or broadly across cancer types. IIIB: an alteration that has a similar predicted functional impact as an already studied tier I abnormality in the same gene or pathway, but does not have associated supportive clinical data.	The drug was previously shown to benefit the molecularly defined subset in another tumor type (or with a different mutation in the same gene), efficacy, therefore, is anticipated but not proved.	Clinical trials are to be discussed with patients.
	IV: preclinical evidence of actionability.	IVA: evidence that the alteration or a functionally similar alteration influences drug sensitivity in preclinical in vitro or in vivo models. IVB: actionability predicted in silico.	Actionability is predicted based on preclinical studies, no conclusive clinical data are available.	Treatment should “only be considered” in the context of early clinical trials. Lack of clinical data should be stressed to patients.
Combination development	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit.	Prospective studies show that targeted therapy is associated with objective responses, but this does not lead to improved outcomes.	The drug is active but does not prolong PFS or OS, probably in part due to mechanisms of adaptation.	Clinical trials assessing drug combination strategies could be considered.
	X: lack of evidence for actionability	No evidence that the genomic alteration is therapeutically actionable	There is no evidence, clinical or preclinical, that a genomic alteration is a potential therapeutic target	The finding should not be taken into account for clinical decision

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associated with NF2-related schwannomatosis.³² These encouraging results warrant further evaluation in randomized clinical trials.

Phosphatidylinositol 3-Kinase, Catalytic Subunit Alpha (PIK3CA)

The PI3K/AKT/mTOR pathway impacts diverse cellular activities such as cell growth, proliferation, differentiation,

motility, and cellular survival and is altered in a large proportion of cancers.³³ *PIK3CA* variants are mostly encountered in WHO grade 1 and at a lower frequency in WHO grade 2 meningioma and are strongly enriched in the benign DNA methylation classes ben-1, ben-2, and ben-3.³⁴ Depending on the series, *PIK3CA* variants have been identified in approximately 1%–5% of meningiomas^{11,35,36} and typically occur in non-NF2 altered meningiomas. Among non-NF2 meningiomas, they are detected mutually exclusive to variants in *AKT1* and *SMO* (and mostly exclusive to

Krüppel-like factor 4 (KLF4)) but may frequently co-occur with *TRAF7* mutations.³⁶ *PIK3CA*-mutated tumors are typically encountered in the skull base.³⁶ *PIK3CA* mutations are usually detected with DNA sequencing panels. For other indications, *PIK3CA* inhibitors have already been approved (details in supplemental text). Preclinical data showed an additive inhibitory effect of the combination of the PI3K inhibitor alpelisib and MEK inhibitor trametinib on meningioma cell lines and primary cultures, reversing the AKT activation.³⁷ Currently, the safety of combining alpelisib with trametinib is being investigated in a phase 1 clinical trial involving patients with progressive refractory meningioma (registered under NCT03631953). *PIK3CA* alteration represents an **ESCAT IIIA** target.

BRCA1-Associated Protein 1

BRCA1-associated protein 1 (BAP1) is a member of the Polycomb group family, counteracting polycomb repressive complex 1-mediated histone ubiquitylation. It remodels chromatin and maintains a functional epigenetic landscape. *BAP1* mutations are enriched in malignant, including rhabdoid meningiomas, but represent under 1% of mutations across all meningiomas. *BAP1* germline mutations are associated with multiple types of malignancies, including mesothelioma, uveal melanoma, renal cell carcinoma, and infrequently (1%–4%), malignant meningiomas. Testing for *BAP1* alterations can be achieved by immunostaining, detecting loss of protein expression, or more comprehensively with next-generation sequencing methods.^{38–41} Treatment options have been evaluated in more common BAP1-associated malignancies and involve histone deacetylase (HDAC) inhibitors,⁴² enhancers of zeste homolog 2 (EZH2) inhibitors,⁴³ platinum agents,⁴⁴ poly-(ADP-ribose) polymerase (PARP) inhibitors,^{45,46} and immunotherapy^{47,48} (ESCAT IIA). However, in meningioma, controlled trials for *BAP1*-mutant meningiomas have not been conducted (ESCAT IIIA).

Programmed Death Ligand 1 (PD-L1)

Immune checkpoint inhibitors targeting PD-L1 and its receptor PD-1 have shown meaningful clinical benefit and are approved for the treatment of several extra-CNS tumor types. For some of these tumor types, treatment indication per approval is dependent on the demonstration of PD-L1 expression using a validated test.⁴⁹ There is limited evidence for the clinical efficacy of PD-1/PD-L1 inhibitors in meningioma and a lack of data on the predictive role of PD-L1 expression for immune checkpoint inhibitor activity. A small phase II trial investigating pembrolizumab in recurrent and progressive grades 2 and 3 meningiomas met its primary PFS endpoint but did not find a significant correlation between PD-L1 expression and outcome.⁵⁰ Another phase II study on nivolumab in meningiomas recurring after surgery and radiation therapy failed to meet its primary endpoint of PFS-6.⁵¹ In conclusion, PD-L1 testing as a basis for immune checkpoint inhibitor therapy is not recommended in the clinical routine and should only be considered in the context of clinical trials or well-annotated compassionate use

programs and prospective registries once standard treatment options are exhausted (**ESCAT IIIB**).

Somatostatin Receptor

Somatostatin receptor (SSTR)s are established targets for drug and radioligand therapies in endocrine cancers. In meningioma, SSTRs are widely expressed in meningiomas, particularly the SSTR2 subtype is found in approximately 80%–95% of cases.⁵²

SSTR2 represents an **ESCAT IIIA** target in meningiomas. There is proven efficacy of the radioligand [¹⁷⁷Lu]Lu-DOTATATE in SSTR2-positive (as determined by PET) neuroendocrine tumors based on randomized clinical trials.^{53,54} Furthermore, retrospective series and an interim analysis of a prospective single-arm study suggest potential efficacy for SSTR2-targeted radionuclide therapy in meningioma.^{55–58} To date there are no conclusive data on the efficacy of SSTR2-targeted radionuclide therapy from prospective controlled clinical trials in meningioma. The European Organization for Research and Treatment of Cancer is activating the first randomized clinical trial to investigate the efficacy of [¹⁷⁷Lu]Lu-DOTATATE in SSTR2-positive meningiomas (LUMEN-1, NCT06326190).

The somatostatin analogue lanreotide has been proven to be efficacious in enteropancreatic neuroendocrine tumors showing SSTR positivity (as determined by scintigraphy).⁵⁹ Another trial showed efficacy in controlling tumor growth in patients with metastatic neuroendocrine midgut tumors but did not use SSTR status as an inclusion criterion.⁶⁰ The efficacy of somatostatin analogs in meningiomas has been investigated in some studies but remains unknown due to methodological limitations.^{28,61,62}

At present, SSTR testing by immunohistochemistry or PET as a basis for targeted treatment is not recommended in the clinical routine for meningiomas and should only be considered in the context of clinical trials or well-annotated compassionate use programs and prospective registries once standard treatment options are exhausted (**ESCAT IIIA**).

AKT1

The *AKT1* gene is located on chromosome 14q32.33 and represents an oncogene that encodes protein kinase B alpha, beta, and gamma. Specific point mutations in *AKT1* (p.E17K) induce a conformational change in the protein, altering its localization from the cytoplasm to the plasma membrane, resulting in the constitutive activation of the AKT1 kinase and in the downstream activation of the mTOR and ERK1/2 signaling pathways. *AKT1* p.E17K mutations are found in 10% of meningiomas, typically in CNS WHO grade 1 anterior or middle skull base location, *NF2*-wildtype meningothelial or transitional meningiomas.^{63–65} *AKT1* mutations were not detected in radiation-induced meningiomas.^{66,67} There are several pharmacological AKT1 inhibitors, notably AZD5363 (capivasertib), which is approved for breast cancer patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer with one or more biomarker alterations (*PIK3CA*, *AKT1* or *PTEN*).⁶⁸ Capivasertib showed activity across several tumor types harboring *AKT1* p.E17K

mutations in a multihistology basket study.⁶⁹ Capivasertib has also shown activity in a single patient with *AKT1* p.E17K-mutant metastatic meningioma.⁷⁰ Overall, *AKT1* represents an **ESCAT IIIA** target in meningioma.

Smoothed

Smoothed (SMO) is a G protein-coupled receptor encoded by the *SMO* gene and contributes to the hedgehog signaling cascade. *SMO* mutations are a rare oncogenic event in meningiomas, occurring in about 5% of cases and associated with a skull base location, meningothelial histology, and CNS WHO grade 1 tumor.^{63,64} Recurrent *SMO* mutations (p.W535L and p.L412F) have been identified in meningiomas and are mutually exclusive with alterations in *NF2*, *AKT1*, *PIK3CA*, *TRAF7*, *KLF4* and *POLR2A*. *SMO* antagonists are approved for the treatment of basal cell carcinoma, a neoplasm characterized by alterations in the hedgehog pathway, usually consisting of *PTCH1* mutations and, more rarely, secondary to *SMO* alterations.^{71,72} Data regarding the treatment of *SMO*-mutant meningiomas are lacking. Vismodegib was administered in a *SMO*-mutant meningioma within the NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol T achieving a partial response.⁷³ According to current evidence, an **ESCAT IIIA** can be assigned, but novel data is expected in the coming months thanks to an ongoing phase II, multi-arm trial (NCT02523014), which is evaluating the efficacy of vismodegib for treatment of *SMO*-mutant meningiomas. Enrollment in a clinical trial with *SMO* antagonists should be considered in progressing/recurrent *SMO*-mutant meningiomas if conventional treatments including surgery and/or radiotherapy have been exhausted and clinical conditions allow further therapies.

Cyclin-Dependent Kinases and Inhibitors (CDKN2A/B, CDK4, CDK6)

The cyclin-dependent kinase inhibitor genes 2A (*CDKN2A*) and 2B (*CDKN2B*), as well as the cyclin-dependent kinase genes 4 (*CDK4*) and 6 (*CDK6*) encode regulators of the cell cycle and are frequently aberrant in various types of cancers. In meningiomas, homozygous *CDKN2A/B* deletions are found in ~5%–7% of cases and are associated with poor outcomes.^{74,75} Testing methods include CGH microarrays, copy number analyses from DNA methylation arrays, NGS, WES, WGS, or fluorescent in-situ hybridization.

The CDK4/6 inhibitors palbociclib, ribociclib, and abemaciclib showed preclinical efficacy; however, clinical efficacy remains unclear as only single-arm clinical trials have been completed or are planned in adult patients with meningioma (**ESCAT IVA**). Assessing homozygous *CDKN2A/B* deletion in meningiomas is currently only recommended for grading purposes or in the context of clinical trials.

Suppressor of Fused Homolog

Suppressor of fused homolog (SUFU) is a negative regulator of the hedgehog signaling pathway.⁷⁶ In the presence

of hedgehog stimulation, activated GLI proteins are produced from the SUFU-GLI complex promoting the transcription of target genes. *SUFU* alterations are associated with development disorders and tumor predisposition.^{77,78} In the latter setting, *SUFU* exerts an onco-suppressor function, thus alterations resulting in a loss of function are observed. Initially, the association between germline pathogenetic *SUFU* variants and medulloblastoma was investigated and these alterations are a rare cause, compared to *PTCH1* mutations, of nevoid basal cell carcinoma syndrome (also known as Gorlin syndrome).^{79,80} Concerning meningiomas, *SUFU* mutations were initially reported in familial cases,^{81–83} but further cases demonstrated their occurrence also in sporadic cases with a frequency of up to 5%.^{84–86} *SUFU* mutations were associated with a concurrent *NF2* alteration, a convexity location, CNS WHO grade 3, and recurrent tumor. These findings are of interest considering that Smoothed (SMO) alterations, another protein of the hedgehog signaling cascade, are associated with an *NF2*-intact status, skull base location, and WHO grade 1.^{63,64} Most of the observed *SUFU* alterations are gene mutations, but focal exon deletions and gene rearrangements have also been reported. Based on these findings, *SUFU* alterations in routine diagnostics can be tested using a DNA NGS panel targeting the most frequently altered genes in meningiomas.⁸⁵ In terms of therapeutic relevance, *SUFU* protein is a downstream effector of SMO in the hedgehog pathway, thus SMO targeting is not effective.^{87,88} Further downstream inhibition of GLI proteins has been evaluated in preclinical models,^{89–99} but specific data about meningioma is lacking (**ESCAT IVA**). Molecular profiling should be proposed if clinically required or if a familial predisposition is suspected. In the latter setting, compliance with local regulations in terms of germline testing is warranted. If a *SUFU* alteration is detected, treatment should be proposed in the context of a clinical trial if available.

Platelet-Derived Growth Factor Receptors

Platelet-derived growth factor receptors (PDGFR)s are established targets in a variety of systemic cancers.¹⁰⁰ Early studies raised the possibility that platelet-derived growth factor (PDGF) may be involved in meningioma growth. The PDGF ligands AA and BB and PDGF receptor-beta are present in most meningiomas regardless of grade,^{101,102} which raised the possibility of an autocrine loop.¹⁰³ Administration of PDGF-BB to meningioma cells in culture stimulated growth while anti-PDGF-BB antibodies inhibited tumor cell growth.¹⁰³ These findings suggested that PDGFR inhibition may have therapeutic value in patients with meningiomas. However, trials with agents such as imatinib mesylate which inhibit PDGFR-alpha and -beta did not show any activity.¹⁰⁴ Other trials with multikinase inhibitors that targeted PDGFR, such as sunitinib, showed modest activity,¹⁰⁵ but this may be due primarily to its inhibition of VEGFR. More recent molecular analysis of meningiomas did not find evidence of PDGFR amplification or mutations.^{106,107} Therefore, testing for PDGFR alterations is discouraged in routine clinical practice and the use of PDGFR inhibitors should only be considered in the context of clinical trials (**ESCAT IVA**).

Progesterone Receptor and Estrogen Receptor

The steroid hormone receptors PR and ER are established targets for antihormonal treatment in breast cancer.^{108,109} Overall, 76% of meningiomas express PR and 6% express ER. While some evidence for therapeutic actionability is available from preclinical studies, conclusive data indicating clinically relevant efficacy are lacking. A phase III trial failed to show an effect of the PR inhibitor mifepristone on failure-free or overall survival of unresectable meningioma.¹¹⁰ Therefore, testing for PR or ER expression as a basis for antihormonal treatment is discouraged for the clinical routine and should only be considered in the context of clinical trials (**ESCAT IVA**). In contrast, progestin is known to increase the risk for meningioma and is associated with enrichment of PIK3CA mutations.^{111,112}

SWI/SNF Related, Matrix-Associated, Actin Dependent Regulator of Chromatin E1 (SMARCE1)

SMARCE1 is a subunit of the chromatin-remodeling SWI/SNF (or BAF) complex. SMARCE1 loss drives the development of clear cell meningiomas and is a biomarker for this diagnosis.^{113,114} Genes encoding mSWI/SNF complexes are mutated in over 20% of human cancers.¹¹⁵ They have in common the disruption of members of the functional complex, comprising SMARCA4/2, ARID1A/B, SMARCB1, and SMARCE1 subunits.^{116,117} Treatment of SMARCE1-deficient meningioma cells with small molecule inhibitors degrading bromodomain containing 9 (BRD9), a non-canonical barrier-to-autointegration factor (BAF) component, leads to their selective growth inhibition, although clinical evidence is missing.¹¹⁸ SMARCE1 is an **ESCAT IVA** target.

Krüppel-like factor 4

KLF4 is a transcription factor involved in a variety of cellular signaling pathways.^{119–124} *KLF4* mutations have a high rate of co-occurrence with *TRAF7* mutations. Detection of mutations in *KLF4/TRAF7* is the molecular hallmark of secretory meningiomas.¹²⁵ In unselected meningioma groups, *KLF4*-mutated tumors are detected in about 6%–9%.^{63,85} Among non-*NF2* meningiomas, *KLF4* mutations can be found in up to 38%.¹²⁶ The *KLF* mutation is a typical hotspot mutation, affecting codon 409 which results in a lysine to glutamine exchange (p.K409Q).^{122,125} *KLF4* status may be assessed together with other relevant genes, especially *TRAF7* and *NF2*, through NGS panel sequencing.⁸⁵ There is only one preclinical study available, showing the potential activity of the mTOR inhibitor temsirolimus in *KLF4* (p.K409Q)-mutated meningioma.¹²² *KLF4* represents an **ESCAT IVA** target.

Telomerase Reverse Transcriptase

Telomerase reverse transcriptase (*TERT*) hotspot mutations have been detected in 5%–6% of all meningiomas and are generally associated with an aggressive clinical course.^{127,128} *TERT* promoter mutations are an independent criterion for CNS WHO grade 3 meningioma regardless of histology

type. Preclinical and clinical studies using *TERT* as a therapeutic target in meningiomas are missing so far (**ESCAT V**). Testing for *TERT* promoter mutations in meningiomas is recommended for grading and prognostic purposes.

Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptors

Vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptors (VEGFR) are well-established targets in cancer.¹²⁹ VEGF and its receptors are frequently expressed in meningiomas and are likely to be important for tumor growth and production of peritumoral edema.^{130,131} Several retrospective studies have shown the possible benefit of bevacizumab in slowing tumor growth in recurrent meningiomas.^{132–137} An uncontrolled multicenter phase 2 trial of bevacizumab in 42 patients with recurrent meningiomas showed that it was well-tolerated. Bevacizumab did not produce any radiographic responses but progression-free survival at 6 months (PFS-6) was 87% for grade 1 meningiomas, 77% for grade 2 meningiomas, and 46% for grade 3 meningiomas,¹³⁸ which appears superior to historical benchmarks of 29% for grade I meningiomas and 26% for WHO grade 2/3 meningiomas.⁴ Bevacizumab has also been combined with everolimus in a small uncontrolled prospective study in 18 patients with progressive, refractory meningioma. The best response of stable disease (SD) was observed in 15 patients (88 %) and 6 patients had SD for more than 12 months. Median PFS was 22 months (95 % CI: 4.5–26.8).¹³⁹

Some VEGFR inhibitors have also shown possible benefit in uncontrolled studies in patients with recurrent meningioma. In a phase 2 trial of the VEGFR, platelet-derived growth factor receptor (PDGFR) and c-kit inhibitor, sunitinib in 36 heavily pretreated CNS WHO grades 2 and 3 meningioma patients, PFS-6 was 42%,¹⁰⁵ compared to the historic PFS-6 benchmark of 26% for grade 2 and 3 meningiomas.⁴ Expression of VEGFR2 on tumor cells was associated with PFS, showing a median PFS of 1.4 months in VEGFR2-negative patients versus 6.4 months in VEGFR2-positive patients ($P = .005$). There have also been case reports suggesting benefits from other multitarget VEGFR inhibitors such as cabozantinib.¹⁴⁰

While testing for VEGF or VEGFR is not recommended as a molecular predictive biomarker (**ESCAT X**), the use of bevacizumab and VEGFR inhibitors such as sunitinib can be considered for patients with refractory recurrent meningiomas, although more definitive clinical trials evaluating these agents are needed.

AT-Rich Binding Domain Protein 1A

AT-rich binding domain protein 1A (ARID1A) has multiple biological roles and is involved in diverse processes including DNA damage repair, maintenance of genomic integrity, cell cycle regulation, epithelial–mesenchymal transition, and steroid receptor response, and functions as a tumor suppressor. The *ARID1A* gene is mutated in nearly half of ovarian clear cell carcinomas and around one-third of endometrial and ovarian carcinomas of the

endometrioid type.¹⁴¹ *ARID1A* gene alterations have been described in 5.4% of meningiomas, with a higher prevalence in recurrent tumors and an association with adverse prognosis.^{86,142} Experimental strategies for inducing synthetic lethality in ARID1A-deficient cancers including inhibitors of PARP, EZH2, BET, ataxia telangiectasia and Rad3-related protein (ATR), and HDAC are under investigation.¹⁴¹ Furthermore, the high prevalence of *ARID1A* mutations in mismatch repair deficient cancers suggests that it has the potential to be a biomarker predicting sensitivity to immune checkpoint inhibition.¹⁴¹ However, no preclinical or clinical data on targeted therapy of *ARID1A* mutant meningiomas exist and HRD testing is discouraged outside of specifically designed clinical trials (**ESCAT X**).

Homologous Recombination Deficiency

Homologous recombination deficiency (HRD) is a well-established predictive factor for the magnitude of response to PARP inhibitor therapy in ovarian cancer.^{143,144} An association of HRD-like signatures with radiation-associated meningiomas and with the malignant methylation class has been reported.¹⁴⁵ There are no preclinical or clinical data on the activity of PARP inhibitors in meningioma, and HRD testing is discouraged outside of specifically designed clinical trials (**ESCAT X**).

TNF Receptor-Associated Factor 7

The TNF receptor-associated factor 7 (*TRAF7*) gene is a tumor suppressor gene located on chromosome 16p13.3. The frequency of missense mutations in *TRAF7* across meningiomas is 20%–25% and these mutations typically affect CNS WHO grade 1 tumors, with preferential location in the base of the skull and an association with brain invasion.⁶³ Otherwise these mutations are rare but may be found in intraneural perineuriomas and mesotheliomas. In meningioma, *TRAF7* mutations are commonly detected by gene panel sequencing and mutually exclusive with *NF2* mutations, but may co-occur with mutations in *KLF4* or *AKT1*.¹⁴⁶ Somatic *TRAF7* mutations have also been identified in normal-appearing leptomeninges.¹⁴⁷ They are not found in radiation-associated meningiomas⁶⁴ nor in the pediatric population.¹⁴⁸ Germ-line mutations of *TRAF7* cause congenital heart defects.¹⁴⁹ *TRAF7*-mutant meningioma primary cultures lack cilia, and *TRAF7* knockdown causes cardiac, craniofacial, and ciliary defects in *Xenopus* and zebrafish, suggesting a mechanistic convergence for *TRAF7*-driven meningiomas and developmental heart defects.¹⁵⁰ The consequences of *TRAF7* mutations are thought to include disruption of the catalytic activity of the E3 ubiquitin ligase interaction with the MAPK pathway and RAS GTPases, resulting in altered actin dynamics and promoting anchorage-independent growth.¹⁵¹ At present, *TRAF7* mutations must be considered a non-druggable alteration (**ESCAT X**).

Other molecular markers/signatures

Moving beyond molecular markers that affect a single gene or locus, specific markers or a combination thereof

can have prognostic or predictive value in meningioma patients. Since the 1960s, the occurrence of copy-number variations (CNV) has been studied in meningioma.¹⁵² Heterozygous loss of chromosome 22q that harbors the *NF2* gene, is present in more than half of meningiomas and is an important part of the 2-step inactivation of *NF2* activity.^{34,153} In meningioma, specific CNVs are associated with increased risk for progression and therefore several models to utilize CNVs for risk prediction have been proposed.^{154,155} So far, the most consistent marker is the loss of chromosome 1p.^{34,153,156,157} Models that include multiple CNVs and other (molecular) information attribute points to losses in chromosomes 1p/6q/14q, WHO grade and epigenetic status (integrated risk score)³⁴ or 1p, 3p, 4p/q, 6p/q, 10p/q, 14q, 18p/q, 19p/q, *CDKN2A/B* and mitotic count (integrated grade).¹⁵³

More recently, meningioma molecular fingerprinting was expanded to the level of whole genome analyses.^{11,34,106,158–161} First, epigenetic profiling identified 3 meningioma methylation families termed benign, intermediate, and malignant.¹¹ These methylation classes can be subdivided into methylation classes ben-1, ben-2, ben-3, int-A, int-B, and mal. Other epigenetic subclassification systems have been proposed, with varying overlap.^{106,159,161} The recent cIMPACT-NOW update 8 provides recommendations on their integration into diagnostics.²² Each methylation family and class is associated with specific clinical outcomes and molecular alterations. To further investigate the biological and clinical relevance of overarching meningioma molecular families, epigenetic profiling was expanded with (single cell) RNA sequencing and CNV-analysis either stepwise^{159,160} or in an integrated prognostic model.¹⁰⁶ Extracting the common divider between molecular groups defined by either epigenetics, transcriptomics, CNV-profiles and *NF2*-status identified 3 prognostic molecular subtypes: low risk *NF2*-altered and *NF2*-wildtype groups and a high(er) risk *NF2*-altered group.¹⁶¹

Taken together, CNVs and advanced molecular-based risk prediction models can have value in risk attribution to meningioma patients. They are, however, (currently) not targetable and their clinical value needs to be further investigated for possible inclusion in future guidelines.

Predictive Markers of Radiotherapy

DNA methylation profiling, RNA sequencing, copy number variants, DNA sequencing, targeted gene expression profiling, and histological features provide robust prognostic information for postoperative meningioma outcomes, either alone or in integrated models.^{11,34,106,153,158–160,162–168} These myriad approaches for meningioma molecular classification demonstrate biological concordance across unsupervised systems, but concordance across unsupervised and supervised systems that incorporate or were trained on clinical endpoints is poor. Both unsupervised and supervised approaches for meningioma molecular classification remain prognostic for clinical outcomes in patients who were treated with postoperative radiotherapy,^{160,169} including in patients who were treated with postoperative radiotherapy on prospective clinical trials.^{157,166} Prediction of postoperative radiotherapy responses remains an active

area of investigation. Some unsupervised approaches appear unable or have not been tested to predict radiotherapy responses,¹⁶⁰ but targeted gene expression profiling has recently been proposed as a robust system for distinguishing meningiomas that benefit from postoperative radiotherapy from meningiomas where radiotherapy appears to offer no benefit.¹⁶⁶ Having been tested for analytical and clinical validity in more than 2000 meningiomas from 13 medical centers across 3 continents, including in patients who were treated with postoperative radiotherapy on prospective clinical trials,¹⁶⁶ this 34-gene expression biomarker is a promising candidate for implementation in routine clinical decision making but requires prospective multicenter validation in randomized clinical trials (ESCAT assessment not applicable, as it was developed for drug treatments). Likewise, a very recent study has proposed a combined DNA methylation- and RNA expression-based risk assessment that identifies radiation-resistant meningiomas.¹⁷⁰ Collectively, these studies both suggest that molecular high-throughput data may reveal patterns that are able to stratify for cases with differential responses to radiotherapy. However, since both studies yielded and validated different marker sets, there is so far no integrated interpretation and recommendation on these approaches feasible.

Conclusions and Future Outlook

Meningiomas harbor a number of recurring molecular alterations that may be amenable to targeted therapy. So far, sufficient data from prospective clinical trials are missing to justify clear recommendations for molecularly targeted therapy in routine practice. However, ongoing efforts aim at translating personalized treatment with specific inhibitors, immunotherapies, radioligand therapies, and radiotherapy based on molecular analysis of meningioma samples into clinical use. The evidence-based evaluation of molecular targets presented here may support decision-making in molecular tumor boards aiming to identify potential treatments for patients with meningiomas guide and are intended to facilitate clinical studies.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<https://academic.oup.com/neuro-oncology>).

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Author contributions

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Conflict of interest statement

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References

- Ostrom QT, Price M, Neff C, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. *Neuro Oncol.* 2023;25(12 suppl 2):iv1-iv99.
- Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: A summary. *Neuro Oncol.* 2021;23(8):1231-1251.
- Goldbrunner R, Stavrinos P, Jenkinson MD, et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro Oncol.* 2021;23(11):1821-1834.
- Kaley T, Barani I, Chamberlain M, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: A RANO review. *Neuro Oncol.* 2014;16(6):829-840.
- Mair MJ, Berghoff AS, Brastianos PK, Preusser M. Emerging systemic treatment options in meningioma. *J Neurooncol.* 2022;161(2):245-258.
- Wang JZ, Landry AP, Raleigh DR, et al. Meningioma: International Consortium on Meningiomas (ICOM) consensus review on scientific advances & treatment paradigms for clinicians, researchers, and patients. *Neuro Oncol.* 2024;26(10):1742-1780.
- Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: Novel therapeutic opportunities. *Nat Rev Neurol.* 2018;14(2):106-115.
- Wang JZ, Nassiri F, Aldape K, von Deimling A, Sahm F. The epigenetic landscape of meningiomas. *Adv Exp Med Biol.* 2023;1416:175-188.
- Luger AL, König S, Samp PF, et al. Molecular matched targeted therapies for primary brain tumors-a single center retrospective analysis. *J Neurooncol.* 2022;159(2):243-259.
- Capper D, Reifenberger G, French PJ, et al. EANO guideline on rational molecular testing of gliomas, glioneuronal, and neuronal tumors in adults for targeted therapy selection. *Neuro Oncol.* 2023;25(5):813-826.
- Sahm F, Schrimpf D, Stichel D, et al. DNA methylation-based classification and grading system for meningioma: A multicentre, retrospective analysis. *Lancet Oncol.* 2017;18(5):682-694.
- Vasudevan HN, Choudhury A, Hilz S, et al. Intratumor and informatic heterogeneity influence meningioma molecular classification. *Acta Neuropathol.* 2022;144(3):579-583.
- Boulagnon-Rombi C, Fleury C, Fichel C, et al. Immunohistochemical approach to the differential diagnosis of meningiomas and their mimics. *J Neuropathol Exp Neurol.* 2017;76(4):289-298.
- Sahm F, Brandner S, Bertero L, et al. Molecular diagnostic tools for the World Health Organization (WHO) 2021 classification of gliomas, glioneuronal and neuronal tumors; an EANO guideline. *Neuro Oncol.* 2023;25(10):1731-1749.
- Horak P, Griffith M, Danos AM, et al. Standards for the classification of pathogenicity of somatic variants in cancer (oncogenicity): Joint recommendations of Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC). *Genet Med.* 2022;24(5):986-998.
- Heyer EE, Deveson IW, Wooi D, et al. Diagnosis of fusion genes using targeted RNA sequencing. *Nat Commun.* 2019;10(1):1388.
- Sahm F, Aldape KA, Brastianos PK, et al. cIMPACT-NOW Update 8: clarifications on WHO grading and molecular risk parameters for meningiomas. *Neuro-Oncol.* 2024;noae170. (online first).
- Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: A joint consensus recommendation of the association for molecular pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn.* 2017;19(1):4-23.

19. Richards S, Aziz N, Bale S, et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424.
20. Li Q, Ren Z, Cao K, et al. An artificial intelligence-empowered platform for clinical interpretation of somatic mutations in cancer. *Sci Adv*. 2022;8(18):eabj1624.
21. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29(9):1895–1902.
22. Sahm F, Aldape KD, Brastianos PK, et al. cIMPACT-NOW Update 8: Clarifications on molecular risk parameters and recommendations for WHO grading of meningiomas. *Neuro Oncol*. Published online August 30, 2024;noae170.
23. Pachow D, Wick W, Gutmann DH, Mawrin C. The mTOR signaling pathway as a treatment target for intracranial neoplasms. *Neuro Oncol*. 2015;17(2):189–199.
24. Pinker B, Barciszewska AM. mTOR signaling and potential therapeutic targeting in meningioma. *Int J Mol Sci*. 2022;23(4):1978.
25. Graillon T, Tabouret E, Salgues B, et al. Innovative treatments for meningiomas. *Rev Neurol (Paris)*. 2023;179(5):449–463.
26. Papi L, De Vitis LR, Vitelli F, et al. Somatic mutations in the neurofibromatosis type 2 gene in sporadic meningiomas. *Hum Genet*. 1995;95(3):347–351.
27. Rutledge MH, Sarrazin J, Rangaratnam S, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. *Nat Genet*. 1994;6(2):180–184.
28. Graillon T, Sanson M, Campello C, et al. Everolimus and octreotide for patients with recurrent meningioma: Results from the phase II CEVOREM trial. *Clin Cancer Res*. 2020;26(3):552–557.
29. Osorio DS, Hu J, Mitchell C, et al. Effect of lapatinib on meningioma growth in adults with neurofibromatosis type 2. *J Neurooncol*. 2018;139(3):749–755.
30. Karajannis MA, Legault G, Hagiwara M, et al. Phase II trial of lapatinib in adult and pediatric patients with neurofibromatosis type 2 and progressive vestibular schwannomas. *Neuro Oncol*. 2012;14(9):1163–1170.
31. Brastianos PK, Twohy EL, Gerstner ER, et al. Alliance A071401: phase II trial of focal adhesion kinase inhibition in meningiomas with somatic NF2 mutations. *J Clin Oncol*. 2023;41(3):618–628.
32. Plotkin SR, Yohay KH, Nghiemphu PL, et al; INTUITT-NF2 Consortium. Brigatinib in NF2-related schwannomatosis with progressive tumors. *N Engl J Med*. 2024;390(24):2284–2294.
33. Fruman DA, Chiu H, Hopkins BD, et al. The PI3K pathway in human disease. *Cell*. 2017;170(4):605–635.
34. Maas SLN, Stichel D, Hielscher T, et al; German Consortium on Aggressive Meningiomas (KAM). Integrated molecular-morphologic meningioma classification: a multicenter retrospective analysis, retrospectively and prospectively validated. *J Clin Oncol*. 2021;39(34):3839–3852.
35. Berghoff AS, Hielscher T, Ricken G, et al. Prognostic impact of genetic alterations and methylation classes in meningioma. *Brain Pathol*. 2022;32(2):e12970.
36. Abedalthagafi M, Bi WL, Aizer AA, et al. Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. *Neuro Oncol*. 2016;18(5):649–655.
37. Mondelli G, Mougé G, Darriet F, et al. Co-targeting MAP kinase and PI3K-Akt-mTOR pathways in meningioma: Preclinical study of Alpelisib and Trametinib. *Cancers (Basel)*. 2022;14(18):4448.
38. van de Nes JAP, Nelles J, Kreis S, et al. Comparing the prognostic value of BAP1 mutation pattern, chromosome 3 status, and BAP1 immunohistochemistry in uveal melanoma. *Am J Surg Pathol*. 2016;40(6):796–805.
39. Koopmans AE, Verdijk RM, Brouwer RWW, et al. Clinical significance of immunohistochemistry for detection of BAP1 mutations in uveal melanoma. *Mod Pathol*. 2014;27(10):1321–1330.
40. Righi L, Duregon E, Vatrano S, et al. BRCA1-associated protein 1 (BAP1) immunohistochemical expression as a diagnostic tool in malignant pleural mesothelioma classification: A large retrospective study. *J Thorac Oncol*. 2016;11(11):2006–2017.
41. Shankar GM, Santagata S. BAP1 mutations in high-grade meningioma: Implications for patient care. *Neuro Oncol*. 2017;19(11):1447–1456.
42. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): A phase 3, double-blind, randomised, placebo-controlled trial. *Lancet Oncol*. 2015;16(4):447–456.
43. Zauderer MG, Szlosarek PW, Le Moulec S, et al. EZH2 inhibitor tazemetostat in patients with relapsed or refractory, BAP1-inactivated malignant pleural mesothelioma: A multicentre, open-label, phase 2 study. *Lancet Oncol*. 2022;23(6):758–767.
44. Hassan R, Morrow B, Thomas A, et al. Inherited predisposition to malignant mesothelioma and overall survival following platinum chemotherapy. *Proc Natl Acad Sci U S A*. 2019;116(18):9008–9013.
45. George TJ, DeRemer DL, Parekh HD, et al. Phase II trial of the PARP inhibitor, niraparib, in BAP1 and other DNA damage response (DDR) pathway deficient neoplasms including cholangiocarcinoma. *J Clin Oncol*. 2020;38(4_suppl):TPS591–TPS591.
46. Hassan R, Mian I, Wagner C, et al. Phase II study of olaparib in malignant mesothelioma (MM) to correlate efficacy with germline and somatic mutations in DNA repair genes. *J Clin Oncol*. 2020;38(15_suppl):9054–9054.
47. Dual checkpoint blockade takes aim at relapsed mesothelioma. *Cancer Discov*. 2017;7(8):OF7.
48. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): Preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol*. 2017;18(5):623–630.
49. Vranic S, Gatalica Z. PD-L1 testing by immunohistochemistry in immunoncology. *Biomol Biomed*. 2023;23(1):15–25.
50. Brastianos PK, Kim AE, Giobbie-Hurder A, et al. Phase 2 study of pembrolizumab in patients with recurrent and residual high-grade meningiomas. *Nat Commun*. 2022;13(1):1325.
51. Bi WL, Nayak L, Meredith DM, et al. Activity of PD-1 blockade with nivolumab among patients with recurrent atypical/anaplastic meningioma: Phase II trial results. *Neuro Oncol*. 2022;24(1):101–113.
52. Agopian M, Carnot M, Denis C, Martin E, Gauchotte G. Hormone receptor expression in meningiomas: A systematic review. *Cancers*. 2023;15(3):980.
53. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of (177)Lu-Dotatate for Midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125–135.
54. Strosberg JR, Caplin ME, Kunz PL, et al; NETTER-1 investigators. (177)Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): Final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(12):1752–1763.
55. Miran C, Duun-Henriksen AK, Maier A, et al. Somatostatin receptor-targeted radiopeptide therapy in treatment-refractory meningioma: Individual patient data meta-analysis. *J Nucl Med*. 2021;62(4):507–513.
56. Minczeles NS, Bos EM, de Leeuw RC, et al. Efficacy and safety of peptide receptor radionuclide therapy with [(177)Lu]Lu-DOTA-TATE in 15

- patients with progressive treatment-refractory meningioma. *Eur J Nucl Med Mol Imaging*. 2023;50(4):1195–1204.
57. Kurz SC, Zan E, Cordova C, et al. Evaluation of the SSTR2-targeted radiopharmaceutical ¹⁷⁷Lu-DOTATATE and SSTR2-specific ⁶⁸Ga-DOTATATE PET as imaging biomarker in patients with intracranial meningioma. *Clin Cancer Res*. 2024;30(4):680–686.
 58. Seystahl K, Stoecklein V, Schüller U, et al. Somatostatin receptor-targeted radionuclide therapy for progressive meningioma: Benefit linked to ⁶⁸Ga-DOTATATE/-TOC uptake. *Neuro Oncol*. 2016;18(11):1538–1547.
 59. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224–233.
 60. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: A report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656–4663.
 61. Norden AD, Ligon KL, Hammond SN, et al. Phase II study of monthly pasireotide LAR (SOM230C) for recurrent or progressive meningioma. *Neurology*. 2015;84(3):280–286.
 62. Jensen LR, Maier AD, Lomstein A, et al. Somatostatin analogues in treatment-refractory meningioma: A systematic review with meta-analysis of individual patient data. *Neurosurg Rev*. 2022;45(5):3067–3081.
 63. Clark VE, Erson-Omay EZ, Serin A, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. *Science*. 2013;339(6123):1077–1080.
 64. Brastianos PK, Horowitz PM, Santagata S, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. *Nat Genet*. 2013;45(3):285–289.
 65. Sahm F, Bissel J, Koelsche C, et al. AKT1E17K mutations cluster with meningothelial and transitional meningiomas and can be detected by SFRP1 immunohistochemistry. *Acta Neuropathol*. 2013;126(5):757–762.
 66. Bleeker FE, Felicioni L, Buttitta F, et al. AKT1(E17K) in human solid tumours. *Oncogene*. 2008;27(42):5648–5650.
 67. Carpten JD, Faber AL, Horn C, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. *Nature*. 2007;448(7152):439–444.
 68. Turner NC, Oliveira M, Howell SJ, et al; CAPItello-291 Study Group. Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2023;388(22):2058–2070.
 69. Hyman DM, Smyth LM, Donoghue MTA, et al. AKT inhibition in solid tumors with AKT1 mutations. *J Clin Oncol*. 2017;35(20):2251–2259.
 70. Weller M, Roth P, Sahm F, et al. Durable control of metastatic AKT1-mutant WHO Grade 1 meningothelial meningioma by the AKT inhibitor, AZD5363. *J Natl Cancer Inst*. 2017;109(3):1–4.
 71. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366(23):2171–2179.
 72. Sekulic A, Migden MR, Lewis K, et al; ERIVANCE BCC investigators. Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC. *J Am Acad Dermatol*. 2015;72(6):1021–1026.
 73. Tsao AS, Song Z, Ho AL, et al. Phase II study of vismodegib in patients with SMO or PTCH1 mutated tumors: results from NCI-MATCH ECOG-ACRIN Trial (EAY131) Subprotocol T. *J Clin Oncol*. 2022;40(16_suppl):3010–3010.
 74. Sievers P, Hielscher T, Schrimpf D, et al. CDKN2A/B homozygous deletion is associated with early recurrence in meningiomas. *Acta Neuropathol*. 2020;140(3):409–413.
 75. Wang JZ, Patil V, Liu J, et al; International Consortium on Meningiomas (ICOM). Increased mRNA expression of CDKN2A is a transcriptomic marker of clinically aggressive meningiomas. *Acta Neuropathol*. 2023;146(1):145–162.
 76. Jing J, Wu Z, Wang J, et al. Hedgehog signaling in tissue homeostasis, cancers, and targeted therapies. *Signal Transduct Target Ther*. 2023;8(1):315.
 77. Dubourg C, Carré W, Hamdi-Rozé H, et al. Mutational spectrum in holoprosencephaly shows that FGF is a new major signaling pathway. *Hum Mutat*. 2016;37(12):1329–1339.
 78. De Mori R, Romani M, D'Arrigo S, et al. Hypomorphic recessive variants in SUFU impair the sonic hedgehog pathway and cause Joubert syndrome with Cranio-facial and skeletal defects. *Am J Hum Genet*. 2017;101(4):552–563.
 79. Pastorino L, Giorzo P, Nasti S, et al. Identification of a SUFU germline mutation in a family with Gorlin syndrome. *Am J Med Genet A*. 2009;149A(7):1539–1543.
 80. Chen Y, Zhang H, Zhao Y, Ma J. Congenital medulloblastoma in two brothers with SUFU-mutated Gorlin-Goltz syndrome: case reports and literature review. *Front Oncol*. 2022;12:988798.
 81. Kijima C, Miyashita T, Suzuki M, Oka H, Fujii K. Two cases of nevoid basal cell carcinoma syndrome associated with meningioma caused by a PTCH1 or SUFU germline mutation. *Fam Cancer*. 2012;11(4):565–570.
 82. Aavikko M, Li SP, Saarinen S, et al. Loss of SUFU function in familial multiple meningioma. *Am J Hum Genet*. 2012;91(3):520–526.
 83. Askaner G, Lei U, Bertelsen B, Venzo A, Wadt K. Novel SUFU frame-shift variant leading to meningioma in three generations in a family with Gorlin syndrome. *Case Rep Genet*. 2019;2019:9650184.
 84. Clark VE, Harmancı AS, Bai H, et al. Recurrent somatic mutations in POLR2A define a distinct subset of meningiomas. *Nat Genet*. 2016;48(10):1253–1259.
 85. Mawrin C, Koch R, Waldt N, et al. A new amplicon-based gene panel for next generation sequencing characterization of meningiomas. *Brain Pathol*. 2022;32(2):e13046.
 86. Williams EA, Santagata S, Wakimoto H, et al. Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. *Acta Neuropathol Commun*. 2020;8(1):171.
 87. Kool M, Jones DTW, Jäger N, et al; ICGC PedBrain Tumor Project. Genome sequencing of SHH medulloblastoma predicts genotype-related response to smoothened inhibition. *Cancer Cell*. 2014;25(3):393–405.
 88. Robinson GW, Orr BA, Wu G, et al. Vismodegib exerts targeted efficacy against recurrent sonic hedgehog-subgroup Medulloblastoma: Results From phase II pediatric brain tumor consortium studies PBTC-025B and PBTC-032. *J Clin Oncol*. 2015;33(24):2646–2654.
 89. Lospinoso Severini L, Ghirga F, Bufalieri F, et al. The SHH/GLI signaling pathway: A therapeutic target for medulloblastoma. *Expert Opin Ther Targets*. 2020;24(11):1159–1181.
 90. Lauth M, Bergström A, Shimokawa T, Toftgård R. Inhibition of GLI-mediated transcription and tumor cell growth by small-molecule antagonists. *Proc Natl Acad Sci U S A*. 2007;104(20):8455–8460.
 91. Wickström M, Dyberg C, Shimokawa T, et al. Targeting the hedgehog signal transduction pathway at the level of GLI inhibits neuroblastoma cell growth in vitro and in vivo. *Int J Cancer*. 2013;132(7):1516–1524.
 92. Kim J, Aftab BT, Tang JY, et al. Itraconazole and arsenic trioxide inhibit Hedgehog pathway activation and tumor growth associated with acquired resistance to smoothened antagonists. *Cancer Cell*. 2013;23(1):23–34.
 93. Beauchamp EM, Ringer L, Bulut G, et al. Arsenic trioxide inhibits human cancer cell growth and tumor development in mice by blocking Hedgehog/GLI pathway. *J Clin Invest*. 2011;121(1):148–160.
 94. Li XY, Zhou LF, Gao LJ, et al. Cynanbungeigenin C and D, a pair of novel epimers from *Cynanchum bungei*, suppress hedgehog

- pathway-dependent medulloblastoma by blocking signaling at the level of Gli. *Cancer Lett.* 2018;420:195–207.
95. Infante P, Mori M, Alfonsi R, et al. Gli1/DNA interaction is a druggable target for Hedgehog-dependent tumors. *EMBO J.* 2015;34(2):200–217.
 96. Berardozi S, Bernardi F, Infante P, et al. Synergistic inhibition of the Hedgehog pathway by newly designed Smo and Gli antagonists bearing the isoflavone scaffold. *Eur J Med Chem.* 2018;156:554–562.
 97. Hyman JM, Firestone AJ, Heine VM, et al. Small-molecule inhibitors reveal multiple strategies for Hedgehog pathway blockade. *Proc Natl Acad Sci U S A.* 2009;106(33):14132–14137.
 98. Manetti F, Stecca B, Santini R, et al. Pharmacophore-based virtual screening for identification of negative modulators of GLI1 as potential anticancer agents. *ACS Med Chem Lett.* 2020;11(5):832–838.
 99. Maresca L, Crivaro E, Migliorini F, et al. Targeting GLI1 and GLI2 with small molecule inhibitors to suppress GLI-dependent transcription and tumor growth. *Pharmacol Res.* 2023;195:106858.
 100. Zou X, Tang XY, Qu ZY, et al. Targeting the PDGF/PDGFR signaling pathway for cancer therapy: A review. *Int J Biol Macromol.* 2022;202:539–557.
 101. Hermanson M, Funa K, Hartman M, et al. Platelet-derived growth factor and its receptors in human glioma tissue: Expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops. *Cancer Res.* 1992;52(11):3213–3219.
 102. Kirsch M, Wilson JC, Black P. Platelet-derived growth factor in human brain tumors. *J Neurooncol.* 1997;35(3):289–301.
 103. Todo T, Adams EF, Fahlbusch R, Dingermann T, Werner H. Autocrine growth stimulation of human meningioma cells by platelet-derived growth factor. *J Neurosurg.* 1996;84(5):852–8; discussion 858.
 104. Wen PY, Yung WKA, Lamborn KR, et al. Phase II study of imatinib mesylate for recurrent meningiomas (North American Brain Tumor Consortium study 01-08). *Neuro Oncol.* 2009;11(6):853–860.
 105. Kaley TJ, Wen P, Schiff D, et al. Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma. *Neuro Oncol.* 2015;17(1):116–121.
 106. Nassiri F, Liu J, Patil V, et al. A clinically applicable integrative molecular classification of meningiomas. *Nature.* 2021;597(7874):119–125.
 107. Bi WL, Greenwald NF, Abedalthagafi M, et al. Genomic landscape of high-grade meningiomas. *npj Genomic Med.* 2017;2(1):15.
 108. Loibl S, André F, Bachelot T, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2024;35(2):159–182.
 109. Gennari A, André F, Barrios CH, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol.* 2021;32(12):1475–1495.
 110. Ji Y, Rankin C, Grunberg S, et al. Double-blind phase III randomized trial of the Antiprogesterin agent mifepristone in the treatment of unresectable meningioma: SWOG S9005. *J Clin Oncol.* 2015;33(34):4093–4098.
 111. Peyre M, Gaillard S, de Marcellus C, et al. Progesterin-associated shift of meningioma mutational landscape. *Ann Oncol.* 2018;29(3):681–686.
 112. Nguyen P, Roland N, Neumann A, et al. Prolonged use of norgestrel acetate and risk of intracranial meningioma: A population-based cohort study. *Lancet Reg Health Eur.* 2024;42:100928.
 113. Tauziède-Espariat A, Parfait B, Besnard A, et al. Loss of SMARCE1 expression is a specific diagnostic marker of clear cell meningioma: A comprehensive immunophenotypic and molecular analysis. *Brain Pathol.* 2018;28(4):466–474.
 114. Sievers P, Sill M, Blume C, et al; German Consortium “Aggressive Meningiomas”. Clear cell meningiomas are defined by a highly distinct DNA methylation profile and mutations in SMARCE1. *Acta Neuropathol.* 2021;141(2):281–290.
 115. Kadoch C, Hargreaves DC, Hodges C, et al. Proteomic and bioinformatic analysis of mammalian SWI/SNF complexes identifies extensive roles in human malignancy. *Nat Genet.* 2013;45(6):592–601.
 116. Mashtalir N, D’Avino AR, Michel BC, et al. Modular organization and assembly of the SWI/SNF family chromatin remodeling complexes. *Cell.* 2018;175(5):1272–1288.e20.
 117. Mashtalir N, Suzuki H, Farrell DP, et al. A structural model of the endogenous human BAF complex informs disease mechanisms. *Cell.* 2020;183(3):802–817.e24.
 118. St Pierre R, Collings CK, Samé Guerra DD, et al. SMARCE1 deficiency generates a targetable mSWI/SNF dependency in clear cell meningioma. *Nat Genet.* 2022;54(6):861–873.
 119. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell.* 2006;126(4):663–676.
 120. Wang Y, Yang C, Gu Q, et al. KLF4 promotes angiogenesis by activating VEGF signaling in human retinal microvascular endothelial cells. *PLoS One.* 2015;10(6):e0130341.
 121. Rowland BD, Bernards R, Peeper DS. The KLF4 tumour suppressor is a transcriptional repressor of p53 that acts as a context-dependent oncogene. *Nat Cell Biol.* 2005;7(11):1074–1082.
 122. von Spreckelsen N, Waldt N, Poetschke R, et al. KLF4(K409Q)-mutated meningiomas show enhanced hypoxia signaling and respond to mTORC1 inhibitor treatment. *Acta Neuropathol Commun.* 2020;8(1):41.
 123. von Spreckelsen N, Waldt N, Timmer M, et al. Clinical characteristics and magnetic resonance imaging-based prediction of the KLF4(K409Q) mutation in meningioma. *World Neurosurg.* 2021;154:e665–e670.
 124. Tsytyskova AV, Wiley G, Li C, et al. Mutated KLF4(K409Q) in meningioma binds STRs and activates FGF3 gene expression. *iScience.* 2022;25(8):104839.
 125. Reuss DE, Piro RM, Jones DTW, et al. Secretory meningiomas are defined by combined KLF4 K409Q and TRAF7 mutations. *Acta Neuropathol.* 2013;125(3):351–358.
 126. Youngblood MW, Miyagishima DF, Jin L, et al. Associations of meningioma molecular subgroup and tumor recurrence. *Neuro Oncol.* 2021;23(5):783–794.
 127. Sahm F, Schrimpf D, Olar A, et al. TERT promoter mutations and risk of recurrence in meningioma. *J Natl Cancer Inst.* 2016;108(5):djv377–djv374.
 128. Spiegl-Kreinecker S, Lötsch D, Neumayer K, et al. TERT promoter mutations are associated with poor prognosis and cell immortalization in meningioma. *Neuro Oncol.* 2018;20(12):1584–1593.
 129. Pérez-Gutiérrez L, Ferrara N. Biology and therapeutic targeting of vascular endothelial growth factor A. *Nat Rev Mol Cell Biol.* 2023;24(11):816–834.
 130. Preusser M, Hassler M, Birner P, et al. Microvascularization and expression of VEGF and its receptors in recurring meningiomas: Pathobiological data in favor of anti-angiogenic therapy approaches. *Clin Neuropathol.* 2012;31(5):352–360.
 131. Fiani B, Jarrah R, Bhandarkar AR, et al. Peritumoral edema in meningiomas: pathophysiology, predictors, and principles for treatment. *Clin Transl Oncol.* 2023;25(4):866–872.
 132. Dasanu CA, Alvarez-Argote J, Limonadi FM, Codreanu I. Bevacizumab in refractory higher-grade and atypical meningioma: The current state of affairs. *Expert Opin Biol Ther.* 2019;19(2):99–104.
 133. Alanin MC, Klausen C, Caye-Thomasen P, et al. Effect of bevacizumab on intracranial meningiomas in patients with neurofibromatosis type 2 - a retrospective case series. *Int J Neurosci.* 2016;126(11):1002–1006.

134. Nunes FP, Merker VL, Jennings D, et al. Bevacizumab treatment for meningiomas in NF2: a retrospective analysis of 15 patients. *PLoS One*. 2013;8(3):e59941.
135. Nayak L, Iwamoto FM, Rudnick JD, et al. Atypical and anaplastic meningiomas treated with bevacizumab. *J Neurooncol*. 2012;109(1):187–193.
136. Alexander AY, Onyedimma C, Bhandarkar AR, et al. The role of bevacizumab for treatment-refractory intracranial meningiomas: A single institution's experience and a systematic review of the literature. *Acta Neurochir*. 2022;164(11):3011–3023.
137. Franke AJ, Skelton WPIV, Woody LE, et al. Role of bevacizumab for treatment-refractory meningiomas: A systematic analysis and literature review. *Surg Neurol Int*. 2018;9:133.
138. Erratum: This is a corrigendum to: Kumthekar et al. A multi-institutional phase II trial of bevacizumab for recurrent and refractory meningioma, *Neuro-Oncology Advances*, Volume 4, Issue 1, January–December 2022, vda123, <https://doi.org/10.1093/oaajnl/vda123>. *Neurooncol Adv*. 2023;5(1):vda103.
139. Shih KC, Chowdhury S, Rosenblatt P, et al. A phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive intracranial meningioma. *J Neurooncol*. 2016;129(2):281–288.
140. Kotecha R, Tonse R, Appel H, et al. Regression of intracranial Meningiomas following treatment with Cabozantinib. *Curr Oncol*. 2021;28(2):1537–1543.
141. Li JJ, Lee CS. The role of the AT-rich interaction domain 1A gene (ARID1A) in human carcinogenesis. *Genes*. 2024;15(1):5.
142. Chaluts D, Dullea JT, Ali M, et al. ARID1A mutation associated with recurrence and shorter progression-free survival in atypical meningiomas. *J Cancer Res Clin Oncol*. 2023;149(8):5165–5172.
143. Miller RE, Leary A, Scott CL, et al. ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. *Ann Oncol*. 2020;31(12):1606–1622.
144. González-Martín A, Harter P, Leary A, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(10):833–848.
145. Paramasivam N, Hübschmann D, Toprak UH, et al. Mutational patterns and regulatory networks in epigenetic subgroups of meningioma. *Acta Neuropathol*. 2019;138(2):295–308.
146. Dogan H, Blume C, Patel A, et al. Single-cell DNA sequencing reveals order of mutational acquisition in TRAF7/AKT1 and TRAF7/KLF4 mutant meningiomas. *Acta Neuropathol*. 2022;144(4):799–802.
147. Boetto J, Plu I, Ducos Y, et al; Brainbank Neuro-CEB Neuropathology Network. Normal meninges harbor oncogenic somatic mutations in meningioma-driver genes. *Acta Neuropathol*. 2023;146(6):833–835.
148. Kirches E, Sahm F, Korshunov A, et al. Molecular profiling of pediatric meningiomas shows tumor characteristics distinct from adult meningiomas. *Acta Neuropathol*. 2021;142(5):873–886.
149. Castilla-Vallmanya L, Selmer KK, Dimartino C, et al; Undiagnosed Diseases Network, Care4Rare Canada Consortium. Phenotypic spectrum and transcriptomic profile associated with germline variants in TRAF7. *Genet Med*. 2020;22(7):1215–1226.
150. Mishra-Gorur K, Barak T, Kaulen LD, et al. Pleiotropic role of TRAF7 in skull-base meningiomas and congenital heart disease. *Proc Natl Acad Sci U S A*. 2023;120(16):e2214997120.
151. Najm P, Zhao P, Steklov M, et al. Loss-of-function mutations in TRAF7 and KLF4 cooperatively activate RAS-Like GTPase signaling and promote meningioma development. *Cancer Res*. 2021;81(16):4218–4229.
152. Zang KD, Singer H. Chromosomal constitution of meningiomas. *Nature*. 1967;216(5110):84–85.
153. Driver J, Hoffman SE, Tavakol S, et al. A molecularly integrated grade for meningioma. *Neuro Oncol*. 2021;24(5):796–808.
154. Magill ST, Vasudevan HN, Seo K, et al. Multiplatform genomic profiling and magnetic resonance imaging identify mechanisms underlying intratumor heterogeneity in meningioma. *Nat Commun*. 2020;11(1):4803.
155. Domingues PH, Sousa P, Otero A, et al. Proposal for a new risk stratification classification for meningioma based on patient age, WHO tumor grade, size, localization, and karyotype. *Neuro Oncol*. 2014;16(5):735–747.
156. Ketter R, Urbschat S, Henn W, et al. Application of oncogenetic trees mixtures as a biostatistical model of the clonal cytogenetic evolution of meningiomas. *Int J Cancer*. 2007;121(7):1473–1480.
157. Maas SLN, Sievers P, Weber DC, et al. Independent prognostic impact of DNA methylation class and chromosome 1p loss in WHO grade 2 and 3 meningioma undergoing adjuvant high-dose radiotherapy: Comprehensive molecular analysis of EORTC 22042-26042. *Acta Neuropathol*. 2023;146(6):837–840.
158. Nassiri F, Mamatjan Y, Suppiah S, et al; International Consortium on Meningiomas. DNA methylation profiling to predict recurrence risk in meningioma: Development and validation of a nomogram to optimize clinical management. *Neuro Oncol*. 2019;21(7):901–910.
159. Choudhury A, Magill ST, Eaton CD, et al. Meningioma DNA methylation groups identify biological drivers and therapeutic vulnerabilities. *Nat Genet*. 2022;54(5):649–659.
160. Choudhury A, Chen WC, Lucas CHG, et al. Hypermitotic meningiomas harbor DNA methylation subgroups with distinct biological and clinical features. *Neuro Oncol*. 2023;25(3):520–530.
161. Bayley JC, Hadley CC, Harmanci AO, et al. Multiple approaches converge on three biological subtypes of meningioma and extract new insights from published studies. *Sci Adv*. 2022;8(5):eabm6247.
162. Olar A, Wani KM, Wilson CD, et al. Global epigenetic profiling identifies methylation subgroups associated with recurrence-free survival in meningioma. *Acta Neuropathol*. 2017;133(3):431–444.
163. Olar A, Goodman LD, Wani KM, et al. A gene expression signature predicts recurrence-free survival in meningioma. *Oncotarget*. 2018;9(22):16087–16098.
164. Chen WC, Vasudevan HN, Choudhury A, et al. A prognostic gene-expression signature and risk score for meningioma recurrence after resection. *Neurosurgery*. 2021;88(1):202–210.
165. Chen WC, Magill ST, Wu A, et al. Histopathological features predictive of local control of atypical meningioma after surgery and adjuvant radiotherapy. *J Neurosurg*. 2018;130(2):443–450.
166. Chen WC, Choudhury A, Youngblood MW, et al. Targeted gene expression profiling predicts meningioma outcomes and radiotherapy responses. *Nat Med*. 2023;29(12):3067–3076.
167. Youngblood MW, Duran D, Montejo JD, et al. Correlations between genomic subgroup and clinical features in a cohort of more than 3000 meningiomas. *J Neurosurg*. 2019;133(5):1345–1354.
168. Patel AJ, Wan YW, Al-Ouran R, et al. Molecular profiling predicts meningioma recurrence and reveals loss of DREAM complex repression in aggressive tumors. *Proc Natl Acad Sci U S A*. 2019;116(43):21715–21726.
169. Vaubel RA, Kumar R, Weiskittel TM, et al. Genomic markers of recurrence risk in atypical meningioma following gross total resection. *Neurooncol Adv*. 2023;5(1):vda004.
170. Wang JZ, Patil V, Landry AP, et al. Molecular classification to refine surgical and radiotherapeutic decision-making in meningioma. *Nat Med*. 2024;30(11):3173–3183.