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Review

Looking at Optic Nerve Sheath Meningiomas Through Genetics—From Clinic to Bench and Back Again

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Abstract

Optic nerve sheath meningiomas (ONSMs) occupy a unique intersection between neuro-oncology and genetics. Although most cases arise in middle-aged women as solitary, slow-growing tumors, pediatric onset, bilateral disease, or rapid progression frequently signal an underlying germline alteration, most often in neurofibromatosis type II (NF2). This narrative review synthesizes the literature through May 2025, examining clinical behavior, imaging, pathology, hereditary syndromes, and the molecular drivers of ONSMs, with particular emphasis on NF2, SMARCB1, TRAF7, and recent copy-number and methylation studies. Classic sporadic ONSMs seldom exhibit loss of chromosome 22q. However, somatic *NF2* alterations and occasional changes in chromatin-remodeling genes still converge on Hippo pathway output (Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ)-driven transcriptional activity), phosphoinositide 3-kinase–protein kinase B (PI3K–AKT), and MAPK signaling. Emerging multi-omics data indicate that optic nerve tumors represent a molecularly distinct subset within the meningioma spectrum. This finding may explain the associated characteristically indolent growth and favorable response to conformal radiotherapy. Genotyping refines risk stratification: early *NF2* testing is warranted in children and in bilateral or atypical presentations, enabling timely surveillance and genetic counseling. While fractionated stereotactic radiotherapy remains the mainstay of therapy, pathway-targeted and gene-replacement strategies developed for *NF2*-associated tumors may soon expand therapeutic options. Given the site-specific diagnostic and functional constraints of peri-optic tumors, larger collaborative cohorts and genotype-guided trials are essential to translate these biological insights into precision care for patients with ONSMs.

Keywords: optic nerve neoplasms; meningioma; genetic counseling; optic nerve; neurofibromatosis 2; precision medicine

1. Introduction

Optic nerve sheath meningiomas (ONSMs) are rare, benign tumors that arise from the arachnoid cap cells surrounding the optic nerve. Although they represent only 1–2% of all meningiomas and 2% of orbital tumors, their clinical impact can be significant because of their proximity to the optic nerve and the potential for loss of visual function [1,2,3]. Most cases occur in middle-aged women (about 60–70%; mean age ~45 years) and generally exhibit a slow, indolent clinical course [2,4]. However, in pediatric patients or those with bilateral involvement, the likelihood of an underlying genetic syndrome—particularly neurofibromatosis type II (NF2)—is high [5,6].

Over the past decade, large-scale multi-omics studies have demonstrated that meningiomas comprise biologically heterogeneous entities that are not fully captured by histopathology alone. DNA methylation–based classification and integrative molecular schemes have improved clinically applicable stratification, including refined grading and outcome prediction, and they have begun to map subgroup-specific biological drivers and potential therapeutic vulnerabilities. This move toward DNA methylation–based and integrative molecular classification is particularly relevant for anatomically constrained, function-critical sites where traditional "benign" labeling may not reflect the patient-centered risk profile. While ONSM has not been systematically represented in these landmark cohorts, these classification frameworks motivate ONSM-focused molecular characterization and support interpreting ONSM within a modern, biology-informed meningioma continuum [7,8,9].

This introductory chapter summarizes the current state of knowledge on the epidemiological, clinical, and genetic aspects of ONSMs, thereby laying the groundwork for subsequent sections on molecular mechanisms, hereditary syndromes, and clinical implications. This review aims to bridge clinical and molecular insights into ONSMs and proposes a framework for integrating genetic findings into diagnosis, risk stratification, and therapeutic decision-making.

Rather than proposing a new standard of care, this review focuses on what makes ONSM a site-defined meningioma: vision-centered outcomes, peri-optic diagnostic constraints, and the disproportionate relevance of NF2-associated presentations in children and bilateral/atypical cases. We therefore integrate genetics, imaging pitfalls, and treatment evidence into a practical framework tailored to optic nerve–adjacent disease.

2. Epidemiology and Clinical Presentation

ONSMs account for roughly 1–2% of all meningiomas and about 2% of orbital tumors. They are the second most common primary optic nerve neoplasms, accounting for approximately one-third of all intrinsic optic nerve tumors [1]. The mean age at onset is approximately 40 years (i.e., the fourth decade of life), with a clear female predominance of roughly 60–70% [4,10]. Incidence in patients under 20 years is very low, at approximately 4% of pediatric cases [1,2]. ONSMs grow slowly yet progressively and may compress the optic nerve, causing gradual visual loss, optic disc edema followed by pallor and atrophy, and the appearance of optociliary shunt vessels (the Hoyt-Spencer triad), which occurs in only a minority of cases (≈20–30%) [2,11]. Other signs include mild proptosis, resistance to retropulsion of the globe, and visual-field defects—central, altitudinal, or peripheral—as well as transient visual obscurations, especially early in the disease [12,13].

Ocular motility disorders, or restrictive strabismus, can occur when the tumor extends within the orbit or involves the extraocular muscles [4]. In contrast, orbital pain is uncommon and generally associated with rapid growth or bony invasion [1,2,14]. In childhood, ONSM is rare (~2–4% of all cases) yet often more aggressive, with an estimated prevalence of 1:95,000–1:525,000 children [1]. Recent pediatric case series and reviews emphasize that diagnosis can be challenging and that presentation may already be associated with marked functional impairment, with a tendency to rapid visual decline over a short time course.

Taken together, pediatric series reporting rapid visual decline and a higher syndromic burden support a lower threshold for early NF2 evaluation and structured neuro-ophthalmic surveillance in children and adolescents rather than relying solely on paradigms derived from typical adult disease [6,15,16]. In one pediatric series, 35% of patients had neurofibromatosis type II, and more than half presented with an initial visual acuity of ≤20/200, followed by rapid deterioration within a few months [15]. Proptosis is common, occurring in 68% of cases, and may precede or follow visual loss [15]. Bilateral presentation is exceptional (<5%) but has been documented in children; the presence of NF2 increases the likelihood of multiple meningiomas, although a specific association with bilateral ONSM has not yet been firmly established [1,17].

3. Imaging and Differential Diagnosis

In the diagnosis of ONSM, the most sensitive imaging modality is contrast-enhanced Magnetic Resonance Imaging (MRI) with fat suppression, especially post-contrast fat-suppressed T1-weighted sequences. Orbito-cerebral MRI with gadolinium and fat-sat typically confirms the lesion: the hallmark sign is the “tram-track” (annular sheath enhancement) on axial images, whereas on coronal views the nerve appears as a non-enhancing dot surrounded by an enhancing ring (“doughnut sign”). The tram-track and doughnut signs are not present in every case and are not pathognomonic; however, they remain helpful in differentiating ONSM from optic nerve glioma, inflammatory optic neuritis, orbital pseudotumor, orbital lymphoma, and metastasis [18,19]. On MRI, ONSMs are iso- to hypointense on T1 and iso- to hyperintense on T2, with homogeneous gadolinium enhancement.

Growth is predominantly tubular (~60–65%), followed by globular (~25%) and fusiform (~10%) patterns [18]. Occasionally, perioptic cysts appear distal to the tumor—most often in intracanalicular lesions—probably reflecting impaired perineural CSF flow, although their pathogenesis is still speculative [20,21,22,23]. Finally, orbital computed tomography (CT) remains complementary: it outperforms MRI in detecting sheath calcifications and delineating optic canal bone changes, details that further characterize the tumor and its associated hyperostosis [18,20]. When considering differential diagnoses, the tumor that most often needs to be distinguished from an ONSM is an optic nerve glioma.

Gliomas are far more common in children and are strongly associated with neurofibromatosis type I. Radiologically, they present as an elongated, fusiform enlargement of the nerve, often reaching the optic chiasm, and are usually T2-hyperintense with variable post-contrast enhancement. A notorious diagnostic trap involves intracanalicular tumors: even a very small meningioma confined to the optic canal can produce marked visual loss and imitate the picture of demyelinating optic neuritis. For this reason, meticulous review of high-resolution, fat-suppressed, contrast-enhanced images through the optic canal is essential, as suboptimal plane selection or partial-volume artefacts can obscure the lesion [2,21,22,23].

In selected equivocal or complex cases, ^{68}Ga-DOTATATE Positron emission tomography (PET)/CT can raise non-invasive diagnostic specificity. Due to the high density of somatostatin receptor subtype 2 on menin-

gioma cells, ONSMs demonstrate pronounced tracer uptake, whereas optic nerve gliomas, lymphomas, and inflammatory masses remain low-avid. Several prospective series and case reports have reported sensitivities and specificities approaching 100%, and PET findings have directly influenced clinical management [24,25]. Although not yet standard of care, such multiparametric approaches can complement conventional MRI whenever the diagnosis remains uncertain.

4. Histopathology and Molecular Features

ONSMs are frequently driven by germline or somatic mutations of *NF2*, the tumor-suppressor gene on chromosome 22q that encodes the protein merlin [5]. Functional loss of merlin unleashes several oncogenic cascades—most notably Hippo pathway dysregulation culminating in increased nuclear YAP/TAZ (YAP1) transcriptional activity, alongside PI3K–AKT and RAS–MAPK signaling—thereby accelerating proliferation in both NF2-related and sporadic meningiomas [26]. While methylation-based classification has reshaped intracranial meningioma taxonomy, the ONSM-focused studies included in this review do not yet provide sufficiently consistent methylation subgroup reporting to support ONSM-specific subtype assignments; therefore, we retain a pathway-level discussion and highlight methylation profiling as a priority for future dedicated ONSM multi-omics cohorts.

,Orbital single-nucleotide polymorphism array (SNP-array) copy-number profiling is beginning to reveal further molecular distinctions. Ho et al. [27] analyzed 19 orbital meningiomas using high-resolution SNP arrays and reported monosomy 22/22q loss in 58% of cases overall (11/19). This alteration was frequent in spheno-orbital meningiomas (70%; 7/10) and primary intraorbital ectopic meningiomas (75%; 3/4), but was detected in only 1 of 5 primary optic nerve sheath meningiomas (20%). These findings support the concept that optic nerve sheath, primary intraorbital ectopic, and spheno-orbital meningiomas may represent molecularly distinct entities within the broader spectrum of orbital meningiomas. Collectively, these orbital meningioma copy-number profiling data and broader sequencing-based distinctions between *NF2*/22q-loss and non-*NF2* meningiomas reinforce the need to interpret ONSMs as a biologically heterogeneous group, although conclusions remain limited by the small number of primary ONSMs analyzed [2,27].

Mutations in TRAF7, AKT1, SMO, KLF4, and SMARCE1 have been documented in subsets of intracranial meningiomas (e.g., anterior skull base, clear cell/spinal forms). These driver mutations have been described primarily in intracranial non-*NF2* meningiomas; ONSM-focused series have not emphasized them to date [28]. From a histopathological standpoint, ONSMs originate from meningothelial cells and grow circumferentially, forming a sheath around the optic nerve without infiltrating it. This defines their compressive yet well-demarcated nature [2,29,30]. Histologically similar to intracranial meningiomas, they display meningothelial, fibrous, transitional, psammomatous, secretory, or microcystic variants, often with characteristic “whorl” formations and psammoma bodies, without direct prognostic correlation [31]. The Ki-67 (MIB-1) proliferation index in benign meningiomas is generally <2%, and up to ~4% in WHO grade II. In a reported pediatric case of ONSM, Ki-67 was <4%, consistent with a WHO grade I or II tumor [32].

To contextualize these ONSM-limited datasets within the broader meningioma literature, large-scale molecular profiling shows that *NF2*–wildtype meningiomas commonly harbor recurrent alternative driver mutations—most often involving *TRAF7*, *AKT1*, *KLF4*, or SMO—and are frequently characterized by comparatively less extensive copy-number disruption, whereas *NF2*-inactivated tumors, often with 22q loss, tend to show broader chromosomal instability/copy-number alterations and cluster into biologically distinct groups with different clinical correlates and outcomes. Complementary DNA methylation–based schemes similarly delineate reproducible meningioma groups with distinct drivers and therapeutic vulnerabilities and demonstrate associations with clinical variables, including anatomical location [8,9,28,31].

5. Hereditary Syndromes and Genetic Counseling

NF2 is an autosomal dominant hereditary syndrome caused by mutations in the *NF2* gene on chromosome 22. It affects approximately 1 in 25,000 individuals and typically manifests during adolescence or early adulthood. NF2 predisposes to multiple nervous system tumors, including bilateral vestibular schwannomas, meningiomas, and schwannomas—potentially also involving the ONSM [2,33]. Meningiomas are common in NF2 patients (45–58%) and may include ONSM as secondary orbital tumors [34].

In a study by Bosch et al. (2006) [5], ONSMs were identified in 27% of NF2 patients (8 out of 30), with bilateral presentation in two cases, supporting an association between *NF2* mutations and optic nerve sheath meningioma development. Approximately half of all NF2 cases are caused by de novo mutations, and among these, up to ~60% represent postzygotic somatic mosaicism—where the mutation is present only in certain tissues (e.g., tumor) but not in leukocyte DNA. This can lead to false negatives in blood-based genetic testing [35]. In addition to ONSM, other ocular manifestations in NF2 patients commonly include juvenile-onset posterior subcapsular cataracts (reported in 60–80% of cases), retinal hamartomas, and epiretinal membrane changes, all of which can impair visual function [36].

In recent years, several studies have identified germline mutations associated with a predisposition to meningiomas, particularly among young patients and those

with multiple lesions. However, none of these genetic alterations have been linked to ONSM to date, suggesting that these tumors may represent a distinct clinical and genetic entity. One of the most recognized syndromes associated with mutations in the *SMARCE1* gene is the clear cell meningioma syndrome, a rare inherited condition typically observed in young individuals. Spinal or intracranial clear cell meningiomas characterize it. While this syndrome is clearly predisposing to meningioma development, no cases of ONSM have been described in patients with *SMARCE1* mutations [37].

A similar situation applies to *SMARCB1* mutations, a gene implicated in familial schwannomatosis, a condition characterized by the co-occurrence of multiple schwannomas and meningiomas, often located along the cerebral falx. Also, in this context, no cases of ONSM have been reported, and the risk of orbital involvement appears negligible [38]. Other predisposition genes included in differential-diagnosis panels—such as leucine zipper like post translational regulator 1 (*LZTR1*) (schwannomatosis) and SUFU negative regulator of hedgehog signaling (*SUFU*) (reported in an *NF2*-negative multiplex family with multiple meningiomas)—have been investigated in large targeted next-generation sequencing (NGS) cohorts spanning NF2, schwannomatosis, and meningiomatosis. In the study by Louvrier et al. [39], *LZTR1* pathogenic variants were frequently identified in schwannomatosis, whereas no *SUFU* variant was detected across the cohort, supporting *SUFU* as an infrequent cause within the meningioma predisposition spectrum assessed by this approach.

Taken together, the *SMARCE1* family report describing an autosomal-dominant predisposition to spinal and intracranial clear cell meningiomas and proposing neurologic examination plus brain-and-spine MRI surveillance for asymptomatic carriers [37], the *SMARCB1* kindred study showing a germline exon 2 missense variant associated with both meningiomas and schwannomas (with a strong predilection for falx-based cranial meningiomas) and tumor evolution characterized by retention of the *SMARCB1* mutant allele, acquisition of independent *NF2* mutations, and loss of heterozygosity (LOH) involving *SMARCB1/NF2* on chromosome 22 [38], and the large targeted NGS differential-diagnosis cohort that simultaneously interrogated *NF2*, *SMARCB1*, *LZTR1*, *SMARCE1*, and *SUFU*, highlighting both the diagnostic value of multigene testing and the importance of tumor analysis to detect low-level *NF2* mosaicism when blood testing is negative [39], collectively refine the genetic framework of meningioma-predisposition syndromes; importantly, optic nerve sheath meningiomas are not reported in these datasets.

Genetic counseling is recommended for patients with bilateral ONSM and in pediatric cases, as early-onset disease may occasionally be associated with NF2 [6,40]. Table 1 summarizes genetic syndromes related to ONSM.

Genetic testing for *NF2*—first on peripheral blood and, if negative, on tumor tissue to exclude mosaicism—is advised in pediatric patients or in those with bilateral ONSM, given that approximately 28% of children with ONSM harbor an *NF2* mutation [41].

In the presence of a confirmed germline *NF2* mutation, genetic counseling should be offered to the patient and at-risk relatives, as autosomal dominant transmission can confer up to a 50% risk to offspring in germline cases [42]. Once a heritable *NF2* variant is identified, reproductive counseling is also appropriate, including discussion of prenatal diagnosis and assisted reproduction with preimplantation genetic testing (PGT) [42,43]. Patients should undergo regular clinical and imaging surveillance—typically including brain and orbital MRI—as recommended by clinical guidelines, although specific follow-up intervals are not uniformly defined across protocols.

6. Therapeutic Implications

6.1 Active Surveillance— "Watch and Wait"

Observation remains legitimate for adults with unilateral, radiologically stable ONSM and good visual function. However, much of the foundational longitudinal evidence supporting observation in ONSM and related settings derives from early-2000s series [44,45,46] and therefore predates many current monitoring standards. While these classic studies remain highly informative, their reported growth kinetics and visual trajectories warrant validation in larger contemporary cohorts using standardized high-resolution imaging and structured neuro-ophthalmic follow-up (including OCT-based metrics).

Long-term data clarify the stakes:

• Natural history. In a cohort of 43 patients (51 meningiomas), 63% of tumors showed no measurable growth (≤2 mm), whereas 37% increased by ~4 mm per year on average [44]. A Japanese series (67 patients, ≥5 years' follow-up) corroborated these findings: 37.3% exhibited radiographic growth, yet only 16.4% became symptomatic [45].

• Visual trajectory. Egan and Lessell's seminal study (16 untreated patients, mean 6.2 years) documented remarkably stable—occasionally improved—vision; decline, when it occurred, was gradual and attributable to nerve compression [46]. While the classic observational series remain foundational, much of the untreated natural-history evidence for ONSM derives from relatively small, older cohorts; therefore, these findings warrant validation in larger contemporary longitudinal datasets using standardized visual-function metrics and modern orbital imaging.

• Caveats. Not all observed cases follow a benign course. Parker et al. [2] reported progressive visual loss in 88% of conservatively managed cases, supporting close surveillance and timely treatment escalation when visual decline or tumor progression is documented. Long-term stereotactic radiotherapy series, including Ratnayake et al.

Table 1. Overview of genetic syndromes associated with meningioma predisposition and their relationship with optic nerve sheath meningiomas (ONSM).

Genetic syndrome	Association with ONSM	Other related manifestations
NF2 (classic or mosaic)	Yes, documented	Vestibular schwannomas, multiple meningiomas, cataracts, and retinopathy
SMARCE1	No evidence for ONSM	Clear cell meningiomas (spinal/intracranial only)
SMARCB1 (schwannomatosis)	No evidence for ONSM	Multiple schwannomas, falcine meningiomas
LZTR1, SUFU, others	Not documented	Predisposition to various schwannomas/meningiomas

NF2, neurofibromatosis type 2; *SMARCE1*, *SWI/SNF*-related BAF chromatin remodeling complex subunit E1; *SMARCB1*, *SWI/SNF*-related BAF chromatin remodeling complex subunit B1; *LZTR1*, leucine zipper-like post-translational regulator 1; *SUFU*, SUFU negative regulator of hedgehog signaling; ONSM, optic nerve sheath meningioma.

[47], further support radiotherapy as an effective vision-preserving strategy in progressive ONSM.

Practical takeaway: surveillance is defensible, but patients must understand that "stable today" does not guarantee "stable tomorrow". Close neuro-ophthalmic follow-up (visual acuity, fields, OCT, contrast sensitivity) is mandatory.

6.2 Radiotherapy (fSRT, IMRT, PBT)

Because ONSM threatens vision even when histologically benign, management is primarily evidence-based and vision-preserving rather than escalation-driven; consequently, conformal radiotherapy remains central once progression is documented. Modern image-guided radiotherapy is the frontline option once vision slips or growth accelerates:

• A meta-analysis of radiotherapy for ONSM, including 736 treated eyes, reported a pooled tumor control rate of 97.4% (95% CI, 96–98%) at a mean follow-up of approximately 46–47 months; visual acuity improved in 45% of cases, remained stable in 40%, and worsened in 15% [48]. Prospective fractionated stereotactic radiotherapy (fSRT) (Bonn, 12 patients). 50.4 Gy in 1.8 Gy fractions achieved 100% control, with visual gains in 53% and no grade ≥3 toxicity over three years [49].

• Comparative series (64 patients). Radiotherapy alone produced the best visual outcomes and the lowest permanent-complication rate (33% vs 66.7% with surgery or combined therapy) [50].

Dose-fractionation schemas vary, but the guiding principle is steep dose fall-off outside the sheath to spare retina, chiasm, and brain.

6.3 Surgery

Surgical resection plays a very limited role in the primary management of ONSM due to the high risk of irreversible optic nerve damage. Visual complications are frequent: because of the slow growth and peri-neural expansion typical of ONSM, radical surgical removal often requires transection of the optic nerve or its vascular supply, which leads to permanent visual loss. In a large historical review cited by Parker et al. [2], based on Dutton's analysis, surgery resulted in total loss of light perception in 78% of patients and severe visual worsening in an additional 16%, with only 6% experiencing any postoperative visual improvement [4]. Turbin et al. [50] reported similarly poor outcomes in a long-term comparative series: patients who underwent surgery alone had the highest rate of permanent complications (66.7%) and a significant decline in visual acuity during follow-up.

Surgical intervention may be considered only in exceptional cases—such as rapidly progressive vision loss or severe intracranial extension. Roser et al. [51] found that, among these selected patients, vision was preserved or improved in 50% of cases, although long-term recurrence led to visual decline in approximately 20%. Nevertheless, surgery remains an exceptional and non-generalizable approach in the management of ONSM. Table 2 (Ref. [2,4,48]) lists the therapeutic options in managing ONSM.

6.4 Pharmacological and Genetic Therapies

Currently, no pharmacological therapies have been approved specifically for ONSM. Radiotherapy remains the standard treatment. However, increasing interest has been directed toward targeted drug strategies originally developed for NF2-associated meningiomas, whose molecular mechanisms serve as a model for ONSM.

Several studies have documented that loss of *NF2* gene function, encoding the tumor suppressor protein merlin, leads to uncontrolled activation of oncogenic pathways such as mTOR, PI3K/AKT, MEK/MAPK, vascular endothelial growth factor (VEGF), and focal adhesion kinase/Src kinase (FAK/Src)—many of which are under investigation as therapeutic targets [33,43]. In pediatric NF2-related schwannomatosis, pharmacotherapy is increasingly explored, with the strongest clinical experience for anti-VEGF therapy (bevacizumab), and additional phase II efforts reported for agents such as lapatinib and VEGFR-targeted vaccine approaches; gene therapy remains largely preclinical [41].

In parallel, gene therapy approaches are emerging as promising experimental strategies:

• Preclinical studies have shown that reintroducing wild-type *NF2* into tumor cells reduces proliferation, suppresses angiogenesis, and induces apoptosis in both *in vitro* and *in vivo* mouse models [52].

Table 2. Summary of current and emerging therapeutic approaches for optic nerve sheath meningiomas (ONSM), including tumor control, visual outcomes, and key clinical considerations.

Approach	Tumor control	Visual outcomes	Key comments
Observation	Low	Frequent visual deterioration	Only feasible in selected cases with close monitoring [2]
Radiotherapy (IMRT/fSRT/PBT)	97–100%	83–100% stability or improvement	First-line treatment in symptomatic cases [48]
Surgery	Low	6% improvement/94% worsening	High risk of blindness; reserved for disfiguring proptosis [4]
Targeted therapies	Under evaluation	Data not yet available	Ongoing trials in NF2; possible future application to ONSM

fSRT, fractionated stereotactic radiotherapy; IMRT, intensity-modulated radiotherapy; PBT, proton beam therapy.

Table 3. Experimental targeted and gene-based therapeutic strategies under investigation for *NF2* -related tumors and their potential applicability to optic nerve sheath meningiomas (ONSM).

Approach	Current status	Applicability to ONSM
mTOR, MEK, focal adhesion kinase (FAK), vascular endothelial growth factor (VEGF) inhibitors	Phase II clinical trials are ongoing	Potentially applicable
Gene therapy (*NF2* gene replacement)	Preclinical (adeno-associated virus (AAV)-mediated)	Promising, needs translation to ONSM models
Suicide gene therapy (interleukin-1β-converting enzyme, caspase-1 or ICE, Gasdermin, ASC)	Preclinical in *NF2* schwannoma models	Requires validation in ONSM

• "Suicide gene" therapies have also been explored, such as the delivery of caspase-1 or pro-apoptotic genes like Gasdermin-D and apoptosis-associated speck-like protein containing a CARD (ASC) using adeno-associated virus (AAV) vectors, leading to significant tumor regression in *NF2*-associated schwannoma mouse models [53].

Despite encouraging results, no clinical trials are currently underway for ONSM or NF2-related meningiomas, and these approaches remain at the preclinical stage [52,53]. Although not directly tested in ONSM, these gene therapy strategies provide a biologically relevant platform—especially for sporadic or *NF2*-associated cases—where restoring merlin function could potentially halt tumor progression or enhance the efficacy of targeted therapies. Table 3 lists various gene-based therapeutic strategies. Fig. 1 shows the clinical, genetic, and therapeutic framework for ONSM.

6.5 Towards an Integrated Management Framework: From Clinic to Bench and Back Again

The central aim of this review is to translate syndromic and molecular insights into a pragmatic, vision-centered management pathway for this site-defined meningioma. In pediatric and adolescent ONSM, diagnosis can be particularly challenging, and tissue sampling is often avoided because biopsy may be technically difficult and can jeopardize vision; therefore, multidisciplinary discussion and tailored imaging strategies—such as CT to document calcification and, in selected cases, somatostatin receptor imaging with DOTATATE PET when conventional imaging is inconclusive—can be key to establishing the diagnosis and guiding management [6]. Importantly, pediatric optic nerve sheath meningiomas have been described as potentially more aggressive, with a meaningful proportion occurring in the context of NF2 (approximately one-quarter to one-third across published pediatric series and reviews), and ONSM may represent an early manifestation of the syndrome; accordingly, once ONSM is diagnosed in a child, an early *NF2*-focused genetic evaluation and genetics-informed surveillance should be considered, rather than extrapolating solely from paradigms derived from typical adult disease [15,16,40,41].

When clinical suspicion remains high despite negative blood testing, the substantial burden of mosaicism in NF2-related schwannomatosis becomes clinically consequential. In a large, highly ascertained English cohort, only ~23% of patients had inherited NF2 from an affected parent, while de novo disease remained common; among de novo cases, almost half were mosaic. Taken together with evidence that mosaic *NF2* can evade detection on peripheral blood testing because the pathogenic variant may be absent from hematopoietic lineages, these data support integrating tumor-based molecular analysis when tumor material is available, as this can strengthen molecular confirmation in otherwise blood-negative patients [35,42,43].

Genetic findings then "return to the clinic" primarily by refining counseling around inheritance and transmission risk. NF2 follows an autosomal dominant pattern: once a germline pathogenic variant is established, each child has a 50% probability of inheriting the variant. By contrast, individuals with mosaic NF2 may have a reduced likelihood of transmission because the alteration may not be present

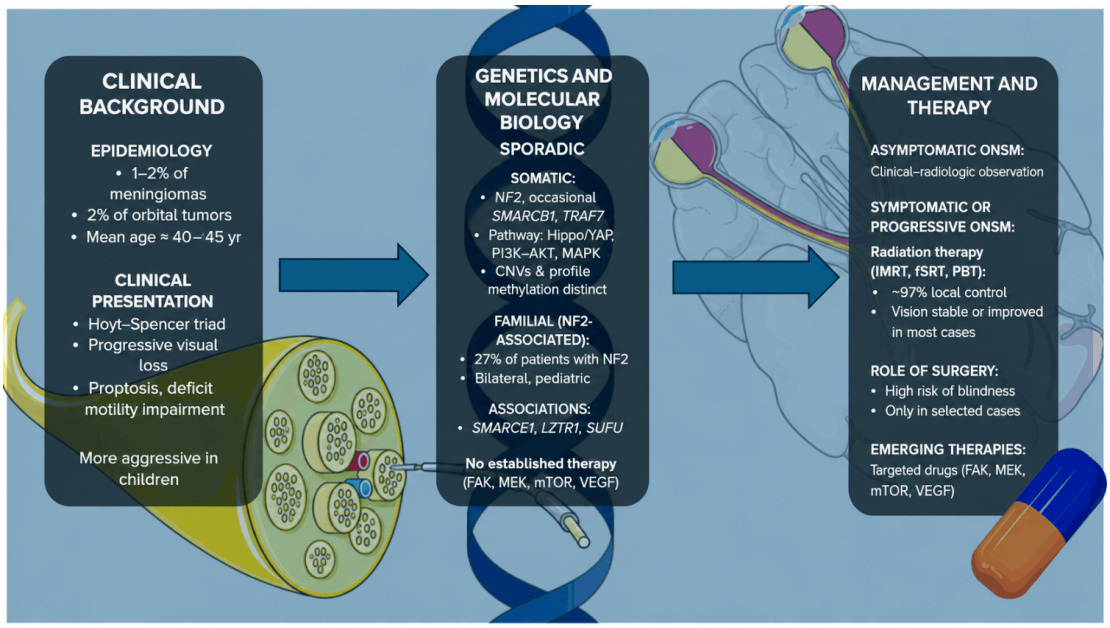

Fig. 1. Clinical, genetic, and therapeutic framework for optic nerve sheath meningiomas (ONSMs). The schematic summarizes the key clinical features and epidemiologic context of ONSMs, including the typical adult unilateral presentation and the more aggressive pediatric or bilateral patterns; the major molecular determinants, highlighting*NF2* alterations, related signaling pathways, copy-number differences, and still limited methylation-profiling data; and current management, including clinical–radiological observation in selected stable cases, radiotherapy as the main vision-preserving strategy for symptomatic or progressive disease, and the limited role of surgery. Emerging targeted approaches under investigation, including FAK-, MEK-, mTOR-, and VEGF-directed strategies, are also indicated. Image(s) provided by Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

in all germ cells; however, when transmission occurs, affected offspring typically manifest a more severe phenotype consistent with germline carriage rather than parental mosaicism [43]. The high proportion of de novo and mosaic cases observed in contemporary population datasets further underscores why counseling should explicitly address mosaicism and its implications for both blood-based testing and recurrence-risk discussions [35,42].

Therapeutic decisions are still anchored to documented visual function over time and to radiological behavior, but the same clinical pathway can be framed within a genetics-aware risk discussion. In selected adults with unilateral ONSM, good baseline vision, and no imminent radiological concern, an initial observation-first approach is reasonable because a subset can remain stable for years; however, across published series, visual deterioration is common under observation. Accordingly, surveillance should be offered only after explicit counseling about this risk and with planned neuro-ophthalmic follow-up (serial acuity/field assessment) plus periodic imaging, with treatment escalation when objective visual decline emerges [2,44,45,46].

Once objective visual decline or other disease progression is documented, radiotherapy delivered with contemporary conformal techniques—most commonly fSRT or intensity-modulated radiotherapy (IMRT), with proton beam therapy (PBT) used in selected settings—has become the preferred vision-sparing approach for primary ONSM, achieving very high local control (approximately 97% in pooled analyses and near-complete control in stereotactic series) with generally favorable functional outcomes [48,49,50]. In contrast, surgical management is usually avoided when useful vision remains because resection frequently jeopardizes optic nerve perfusion and has historically been associated with marked postoperative visual deterioration; accordingly, surgery is typically reserved for selected scenarios such as the need for tissue diagnosis, blindness with consideration of (debulking or en bloc) resection, disfiguring proptosis, and posterior/intracranial extension or rapid visual decline where decompression is judged necessary [2,4,50,51].

Finally, a bench-to-bedside perspective points to translational opportunities that are already supported by what is known about *NF2*/merlin biology, even if direct ONSM-specific therapeutic evidence is still missing. Across NF2-associated tumors, merlin loss has been linked to dysregulation of several druggable signaling axes—most consistently PI3K/AKT–mTOR and RAS–RAF/MEK/ERK, with additional involvement of adhesion-related FAK/SRC signaling and VEGF-mediated angiogenic pathways that have been explored therapeutically (e.g., pathway inhibition and anti-VEGF strategies). In

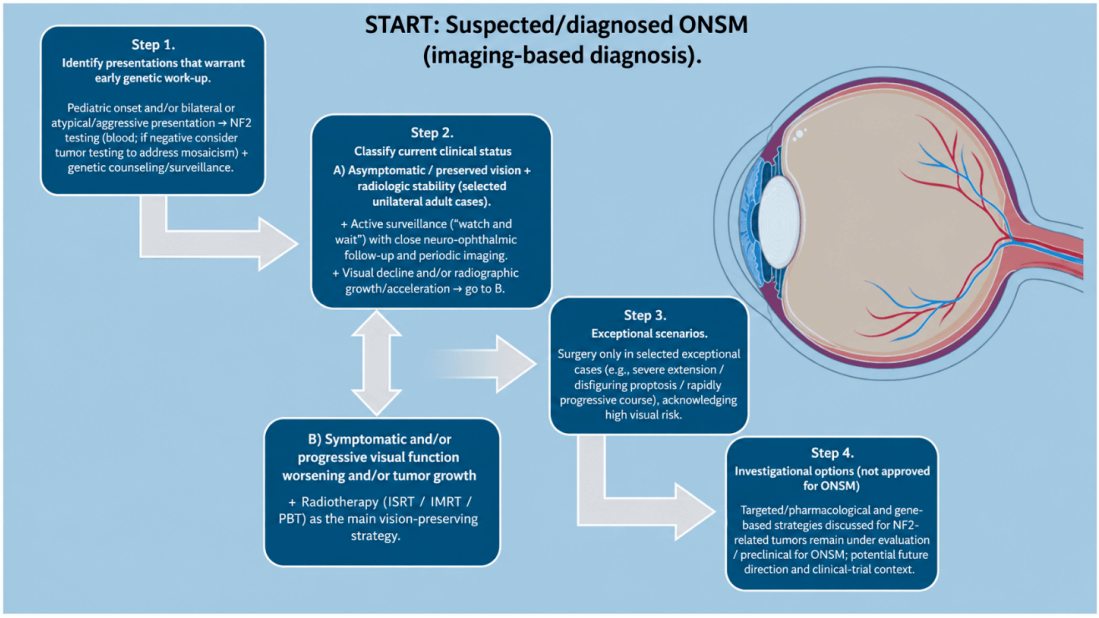

Fig. 2. Management decision algorithm for optic nerve sheath meningioma (ONSM) by presentation type. The flowchart summarizes a pragmatic, imaging-based pathway for ONSM management as described in this review. After radiological suspicion/diagnosis, early genetic work-up is prioritized in pediatric cases and/or bilateral or atypical/aggressive presentations, with *NF2* testing (blood; if negative, consider tumor testing to address mosaicism) and genetic counseling/surveillance. Patients are then stratified by clinical course: asymptomatic/stable cases with preserved vision and radiological stability may undergo active surveillance with close neuro-ophthalmic follow-up and periodic imaging, whereas symptomatic and/or progressive disease (visual worsening and/or tumor growth) is directed to radiotherapy (fSRT/IMRT/PBT) as the main vision-preserving strategy. Surgery is reserved for selected exceptional scenarios, given the high visual risk. Targeted pharmacological and gene-based approaches remain investigational and are included as future directions rather than established ONSM treatments. Abbreviations: fSRT, fractionated stereotactic radiotherapy; IMRT, intensity-modulated radiotherapy; PBT, proton beam therapy; NF2, neurofibromatosis type II. Image(s) provided by Servier Medical Art (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

parallel, gene-based approaches aimed at restoring wild-type NF2/merlin function have shown encouraging preclinical activity in NF2-related tumor models, and gene-therapy concepts have also been tested in meningioma systems (including wild-type *NF2* insertion, oncolytic viral strategies, and RNA-based silencing approaches), although clinical translation remains limited and no direct ONSM data are currently available [33,41,43,52,53].

To facilitate clinical translation, Fig. 2 summarizes a simplified decision algorithm for ONSM management according to presentation (asymptomatic/stable vs symptomatic/progressive), based on the strategies discussed in this section.

7. Conclusions

ONSM are uncommon, yet their intimate relationship with the optic nerve means that even small lesions can threaten vision and, with it, quality of life [2,4]. Historically, we either watched and waited or, when symptoms dictated, applied fractionated radiotherapy. Today, the main added value is a more structured integration of syndromic genetics and emerging molecular data into risk stratification and future trial directions, while current evidence still supports observation in selected cases and conformal radiotherapy for progression. Routine *NF2* testing can identify heritable cases early and guide both clinical and reproductive counseling—an especially valuable advance for pediatric patients or those with bilateral disease [41,54]. The continued absence of links to other syndromic genes (*SMARCE1*, *SMARCB1*, *LZTR1*, *SUFU*) reinforces the view that ONSM form a genetically and clinically distinct branch of the meningioma family [54]. Molecular data points in the same direction. Canonical mutations that dominate skull-base and spinal meningiomas (*TRAF7*, *AKT1*, *SMO*, *KLF4)* have not been captured in ONSM [28]. Copy-number work by Ho et al. [27] is equally striking: only 20% of ONSM lose chromosome 22q, compared with 80% of other orbital meningiomas, suggesting a genomic signature that underlies their orbital tropism and typically indolent course.

Therapeutically, radiotherapy achieves excellent local control in ONSM. A meta-analysis including 736 treated eyes reported a pooled tumor control rate of 97.4% (95% CI, 96–98%) at a mean follow-up of approximately 46–

47 months; visual acuity improved in 45% of cases, remained stable in 40%, and worsened in 15% [48]. Surgery, once standard, is reserved for exceptional scenarios because the risk of permanent blindness remains high [2,4,50]. The biological frontier is only beginning to open. Gene- and pathway-targeted strategies that suppress NF2-related schwannomas and meningiomas—wild-type *NF2* replacement, AAV-mediated "suicide" genes, inhibitors of mTOR, PI3K/AKT, and FAK/Src—have yet to be tested directly in ONSM, but the rationale is compelling [27,52,53,54,55,56]. Notably, the phase II trial Alliance A071401 (NCT02523014) reported a 6-month PFS of 83% (95% CI 52–98%) for WHO grade I *NF2*-mutant meningiomas treated with the FAK inhibitor GSK2256098 and confirmed a favorable safety profile [57]. No gene therapy is currently approved for ONSM. Still, AAV-based delivery of neuroprotective factors such as BDNF and SIRT1 preserves retinal ganglion cells after optic nerve injury and in glaucoma models [58,59,60]. These findings offer a biologically grounded framework for future integrative treatments that could tackle both tumor control and neural preservation.

In summary, ONSMs are not simply meningiomas in an unusual location; they are a clinically and molecularly distinct entity that demands tailored diagnostics and bespoke therapy. Progress will hinge on multi-omics classification and genotype-driven trials that can finally replace empirical decision-making with true precision medicine.

8. Future Directions

We acknowledge that ONSM-specific studies are few and heterogeneous; therefore, we intentionally adopt a narrative scoping approach to synthesize what is currently supported and to delineate actionable gaps for multicenter, molecularly characterized cohorts. Although optic nerve sheath meningiomas are typically WHO grade I and remain primarily managed with observation or conformal radiotherapy, evidence from the broader intracranial meningioma literature suggests that systemic immunomodulatory approaches may eventually become relevant for selected aggressive or refractory situations. Large translational cohorts indicate that meningiomas often display a macrophage-dominant, immunosuppressive microenvironment; higher infiltration by pro-tumoral tumor-associated macrophages correlates with more aggressive clinical behavior and inferior outcomes, and methylation-based immune deconvolution has been proposed as a practical strategy to support patient stratification in future immunotherapy trials [61]. In this context, early single-arm phase II experiences with PD-1 blockade in recurrent WHO grade 2–3 meningiomas have shown variable activity: nivolumab was generally well tolerated but did not meet its prespecified efficacy target despite a PFS-6 of 42.4% and rare durable responses, with most tumors exhibiting low tumor mutational burden and low baseline T-cell infiltration [62]. A separate phase II study of pembrolizumab likewise suggested disease stabilization in a subset of recurrent high-grade cases (PFS-6 48%; median PFS 7.6 months) [63]. Taken together, these data do not support routine checkpoint inhibitor use in unselected meningioma patients; rather, they argue for biomarker- and microenvironment-informed development (e.g., identifying subgroups more likely to benefit and addressing macrophage-driven immune suppression) and for rational combinations, including integration with radiotherapy to enhance intratumoral immune activation [61,62,63].

Motivated by the proposed synergy between radiotherapy and immune checkpoint blockade, early-phase clinical work is testing whether stereotactic re-irradiation can be feasibly combined with PD-1 inhibition (nivolumab) with or without CTLA-4 blockade (ipilimumab) in patients with recurrent, radiation-relapsed WHO grade II–III meningiomas; in the reported phase I experience (ETCTN 10186), no dose-limiting toxicities were observed across the evaluated regimens and the nivolumab–ipilimumab schedule selected as the maximum tolerated combination was considered tolerable, with preliminary activity signals reported while central imaging review remained ongoing [63,64]. In parallel, preclinical studies are exploring radiosensitization strategies in meningioma models: selective pharmacologic HDAC6 inhibition (Cay10603) given before irradiation countered radiation-associated HDAC6 upregulation and synergistically increased cytotoxicity in both 2D cultures and 3D spheroid systems, alongside amplified DNA damage signals and reduced nuclear accumulation of β-catenin/MCM2 with downstream suppression of c-myc [65]. Separately, patient-derived primary meningioma cultures exposed to 5-aminolevulinic acid (5-ALA) showed dose- and time-dependent growth inhibition with intracellular protoporphyrin IX accumulation, and combining 5-ALA (at patient-specific IC50) with a clinically relevant 2-Gy X-ray dose produced stronger growth inhibition than either treatment alone across cases, although the magnitude of effect varied by patient [66]. Whether these combination concepts—checkpoint blockade plus (re-)irradiation, or molecular radiosensitizers—can be translated safely and effectively to the peri-optic setting of ONSM is unknown; given the heterogeneity of meningioma immune biology and the current need for better immunocompetent models and molecularly informed patient stratification, dedicated translational models and multicenter, molecularly characterized cohorts will be necessary before benefit–risk can be defined for optic nerve–adjacent disease [63].

Author Contributions

MC and MZ designed the research study. CG, MC, FD, PB, MB, SGN and MZ performed the research. MC, MZ, FD, PB, SGN, and MB analyzed the data. MC, MZ, CG, MB, and SGN wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have

participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest. The Mediterranean Foundation "G.B. Morgagni" is the affiliated institution of Caterina Gagliano, and this relationship did not influence the judgments in data interpretation or manuscript writing.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/FBS46877.

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