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ERN GENTURIS CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS, TREATMENT, MANAGEMENT AND SURVEILLANCE OF PEOPLE WITH SCHWANNOMATOSIS

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ABSTRACT

A Guideline Group was convened from multiple specialties and with input from patients to develop the first comprehensive guideline for schwannomatosis. The Guideline Group undertook a thorough literature review in particular to identify previous guidelines and write recommendations particularly with regard to treatment and surveillance. A modified Delphi process was used to gain approval for recommendations which were further altered to provide maximal consensus.

Schwannomatosis is a tumour predisposition syndrome leading to the development of multiple benign nerve sheath schwannomas that are not intra-cutaneous and spare the eighth (vestibulocochlear) nerves. Two definitive genes (*SMARCB1* and *LZTR1*) have been identified on chromosome 22q centromeric to *NF2* that cause schwannoma development by a 3-event, 4-hit mechanism that leads to complete inactivation of each gene plus *NF2*. These genes together account for 70-85% of familial schwannomatosis and 30-40% of isolated cases with no family history. There is considerable overlap between mosaic NF2 and schwannomatosis in isolated cases. Screening with craniospinal MRI is recommended on a 2-3 yearly basis starting at symptomatic diagnosis or age 12-14 if molecularly confirmed in asymptomatic individuals with a relative affected with schwannomas. Whole body MRI may also be deployed and can alternate with craniospinal MRI if available. Ultrasound scans can be used especially in the limbs where typical pain is not associated with a palpable lump. Malignancy risk for the development of Malignant Peripheral Nerve Sheath Tumours should be suspected in anyone with rapidly growing tumours especially with functional loss and appears more common with *SMARCB1.* Pain is the most frequent symptom and is often intractable to standard neuropathic pain medication. Surgery to remove schwannomas is the most effective treatment, but must be balanced against potential loss of function if the adjacent nerve or structure are damaged. Radiation therapy is not generally recommended and it should be avoided in *SMARCB1* carriers. Assessment of the patient's psychosocial needs should be assessed at each visit as well as review of pain and pain medication. Genetic counselling should be guided ideally by both blood and tumour molecular testing and transmission risks will depend on whether a heterozygous pathogenic variant is identified.

GUIDELINE SUMMARY

This guideline has been drawn from the best available evidence and the consensus of experts in this area and it is regularly updated to reflect changes in evidence. The expectation is that clinicians will follow this guideline unless there is a compelling clinical reason to undertake different management, specific to an individual patient.

Exam or surveillance		**Interval**	**Age to start**	**Strength***
Schwannomatosis	Clinical examination and assessment for pain and neurological examination	Annual	12-14 years	Moderate
Schwannomas	Brain and spine MRI	According to specific gene / age recommendations	Diagnosis or 12-14 years	Strong
	Whole-Body MRI	Baseline or soon after. Consider alternating with Craniospinal-	Diagnosis or 12-14 years	Moderate
	Ultrasound	Consider for problem solving in limbs or intercostal-	As appropriate	Moderate

* This grading is based on published articles and expert consensus: strong - expert consensus AND consistent evidence, moderate - expert consensus WITH inconsistent evidence AND/OR new evidence likely to support the recommendation, weak - Expert majority decision WITHOUT consistent evidence

TABLE OF CONTENTS

1. INTRODUCTION

Schwannomatosis is characterised by the development of typically painful, benign nerve sheath tumours (schwannomas) on the spinal and peripheral nerves around the body (Dhamija et al. 1993, Evans et al. 2018). Cranial nerves are affected to a lesser extent and there is characteristic sparing of the 8th cranial nerve, which is the most commonly affected in sporadic / isolated non-hereditary cases (Dhamija et al. 1993, Evans et al. 2018). Intradermal schwannomas are characteristic lesions in neurofibromatosis 2 (NF2) and are absent in schwannomatosis. Vestibular schwannomas may occur in around 10% of *LZTR1* related schwannomatosis patients but seem to occur at any increased frequency in other types of schwannomatosis.

The 'term' schwannomatosis appears to date from the 1950s, but other terms such as neurilemmomatosis have also been coined. The early literature is confused as both schwannomatosis and neurilemmomatosis were terms used in Japan to include patients who clearly had NF2 with bilateral vestibular schwannomas (Matsuo et al. 1991, Iwabuchi et al. 1993). Nevertheless, in the mid-1990s a consensus began to develop that the entity schwannomatosis was distinct from NF2 (MacCollin et al. 1996, Pulst et al. 1997, Wolkenstein et al. 1997), although concern still existed over significant overlap with NF2 (Evans et al. 1997). The molecular mechanism of schwannomatosis shows different somatic point mutations in *NF2* between schwannomas in the same person (Jacoby et al. 1997); linkage analysis in a number of families to exclude the *NF2* locus on chromosome 22q (MacCollin et al. 2003) confirmed the existence of the separate entity. In 2007 a separate gene on chromosome 22 called *SMARCB1* was found to cause a subset of familial and sporadic/isolated cases of schwannomatosis (Hulsebos et al. 2007, Boyd et al. 2008, Hadfield et al. 2008, Sestini et al. 2008). The gene was also linked in at least some families to a tendency to develop meningiomas (Christiaans et al. 2011), although this tumour is still relatively uncommon even in *SMARCB1* related schwannomatosis (Hadfield et al. 2010, Evans et al. 2018). Seven years after identification of *SMARCB1* as a causal entity, a second 22q gene *LZTR1* was identified as a cause of schwannomatosis (Piotrowski et al. 2014). This again raised the overlap with NF2 as a number of cases developed unilateral vestibular schwannoma and met the Manchester diagnostic criteria for NF2 (Smith et al. 2015, Pathmanaban et al. 2017, Smith et al. 2017). Furthermore, many sporadically affected individuals that do not have either *LZTR1* or *SMARCB1* germline pathogenic variants but meet schwannomatosis criteria (MacCollin et al. 2005, Plotkin et al. 2013), have mosaic NF2 with identical pathogenic variants in two separate schwannomas (Smith et al. 2017, Evans et al. 2018, Kehrer-Sawatzki et al. 2018, Louvrier et al.

2018). The overlap from both the vestibular schwannomas occurring in *LZTR1* schwannomatosis and mosaic NF2 mimicking schwannomatosis has necessitated a re-evaluation of the existing diagnostic criteria (Evans et al. 2019) and an international effort has defined new criteria that will be published in 2022.

The overriding feature in individuals with schwannomatosis is pain, with little if any neurological deficit (Dhamija et al. 1993). Removal of schwannomas often results in complete resolution of pain symptoms (Dhamija et al. 1993). Life expectancy is not usually reduced, unlike in NF2 (Evans et al. 2018), but quality of life is strongly affected. Whilst there exists some concern over malignant potential in *SMARCB1* related schwannomatosis (Evans et al. 2012, Eelloo et al. 2019), this does not appear to be a feature of other types of schwannomatosis. Other common features of NF2 such as ependymomas and ocular features such as retinal hamartoma, epiretinal folds and juvenile cataracts have not been reported in schwannomatosis (Dhamija et al. 1993, Evans et al. 2018).

2. COMPOSITION OF THE GUIDELINE GROUP

The European Reference Network (ERN) Guideline Group for people with schwannomatosis was established by clinical geneticists and clinicians with expertise in neurology, neurosurgery, peripheral nerve surgery, dermatology, radiology, and anaesthetics as well as affected individuals and parent representatives. Although the guidelines are written primarily for geneticists, neurosurgeons and neurologists, they can also be used by other physicians, patients or other interested parties.

The Guideline Group was supported by a Core Working Group of ERN GENTURIS healthcare provider (HCP) members from different Member States and who are recognised experts and specialised in genetics and surgery and/or clinical practice and/or in the diagnosis and management of schwannomatosis.

Approach to secure views and preference of target population

ERN GENTURIS schwannomatosis Guideline Group was supported by a Patient Advisory Group of four affected individuals and parent representatives that have experience with schwannomatosis. Two patient representatives were present during the Guideline Group meetings.

Involving the patient and parent representatives in the development of these guidelines and in the Guideline Group helped to ensure that:

- the questions addressed are relevant to them and will make a positive impact on patient care.
- important aspects of the experience of illness are considered.

- critical clinical and patient important outcomes are identified and prioritised.
- the balance of benefits and harms of the intervention is appropriately considered, when recommendations are formulated in conjunction with patient values and preferences.

The Patient Advisory Group advised on the scope, target population and clinical questions the guideline aimed to address and rated the outcomes in terms of their importance. The group also reviewed the findings of the literature and recommendations.

3. CONFLICT OF INTERESTS

All members of the ERN GENTURIS schwannomatosis Guideline Group, including the Core Working Group, have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. Gareth Evans, Pierre Wolkenstein, and Rosalie Ferner report receipt of honoraria or consultation fees from AstraZeneca. Michel Kalamarides and Gareth Evans report receipt of honoraria or consultation fees from Recursion. Gareth Evans, Pierre Wolkenstein, and Eric Legius report receipt of honoraria or consultation fees from Springworks Therapeutics. Laura Papi reported receipt of grants/research support from Devyser. Nick Thomas reports participation in a company sponsored speaker's bureau from Stryker. David Pang reports reimbursement of travel expenses for medical conferences by Medtronic and Nevro Corp. All participants of the ERN GENTURIS schwannomatosis Delphi survey have provided disclosure statements on all relationships that they have that might be perceived to be a potential source of a conflict of interest. Helen Hanson report receipt of honoraria or consultation fees from Pfizer. Bernhard Frank reports receipt of honoraria from Gruenenthal UK and Gruenenthal Europe.

4. PURPOSE AND SCOPE OF THIS GUIDELINE

4.1. WHY WAS THIS GUIDELINE PRODUCED?

Before this guideline there were only limited guideline recommendations based on a guideline covering neurofibromatosis 2 (NF2) and related disorders; this only covered children and young adults. There remains substantial variability in clinical practice. Further genes causing schwannomatosis have been identified and the malignancy risk associated with SMARCB1 schwannomatosis has become clearer. There has also been growing evidence that many patients meeting schwannomatosis criteria actually have mosaic NF2. There is a consensus that such a guideline is overdue and will help patients and doctors in general to diagnose and treat the disease properly.

4.2. *WHO IS THE* GUIDELINE *FOR?*

The schwannomatosis Guideline Group has prepared this guideline document to assist health care professionals in evidence-based diagnosis, clinical management and surveillance of people with schwannomatosis. Although the guidelines are written primarily for geneticists, neurosurgeons, peripheral nerve surgeons and neurologists, they can also be used by other physicians, patients or other interested parties. Clinical guidelines are statements to support decision making, based on systematically evaluated evidence for a specified clinical circumstance. Whilst these clinical guidelines are based on the latest published evidence, care of each individual remains primarily the responsibility of their treating medical professionals. Decisions for care should always be based on the individual needs, person preferences and individual circumstances of each patient. Clinical guidelines should support clinical decision making, but never replace clinical professionals. Guidelines present recommendations based on expert opinion and published evidence and are not mandates. These guidelines do not signify nor intend to be a legal standard of care.

4.3. WHAT IS THE GUIDELINE ABOUT?

4.3.1 SCOPE

The scope of this guideline is to define the optimal diagnosis, clinical management and surveillance of people with schwannomatosis.

4.3.2 HEALTH QUESTIONS

It is critical to define the key clinical questions regarding diagnosis, clinical management and surveillance of people with schwannomatosis.

Key clinical questions include, but are not restricted, to:

- identify the diagnostic criteria and molecular diagnostics of schwannomatosis.
- identify what imaging and clinical follow up is beneficial after a diagnosis of schwannomatosis.
- specify which treatments are beneficial for the management of pain in schwannomatosis.
- identify what are the indications for surgery in schwannomatosis.
- state what is the role of VEGF inhibitors in schwannomatosis.

4.3.3 POPULATION

The target population for this guideline is all individuals with schwannomatosis. This population includes:

- People with inherited pathogenic variants in *SMARCB1* and a proven schwannoma.
- People with inherited pathogenic variants in *LZTR1* and a proven schwannoma.
- A healthy carrier of a *LZTR1* or *SMARCB1* pathogenic genetic variant with a parent with proven schwannomatosis.
- People with two schwannomas that are not intradermal, have both been analysed and found not to be due to either inherited NF2 or a shared *NF2* variant between the tumours.
- Presumed schwannomatosis when people have more than one proven schwannoma or one proven schwannoma and an additional nerve sheath tumour on MRI scan not affecting the vestibular nerves or within the skin itself where no inherited *NF2* variant is found in blood.

4.3.4 CARE SETTING

The guideline is intended to support the decision making of geneticists, neurosurgeons, peripheral nerve surgeons and neurologists in their decisions on diagnosis, clinical management and surveillance of people with schwannomatosis. The guideline can also be used by other physicians (general doctors, radiologists, dermatologists, pain management specialists, psychologists and other specialists involved in schwannomatosis care), patients or other interested parties.

Implementation of this guideline will require dissemination to the different stakeholders. Preferably, this European guideline should be adopted and diffused by the General Direction of Health of each European Country. Although a more fragmented, but rather more tangible approach will be to disseminate this guideline via professional and patient societies.

4.3.5 EPIDEMIOLOGY & AETIOLOGY

Epidemiology: As schwannomatosis was only really recognised as a separate entity to NF2 in the 1990's there is limited evidence of its true epidemiology. A small Finnish study from Helsinki University Hospital with a catchment area (population, 1,713,000) assessed incidence of NF2 and schwannomatosis from January 1, 1985, to December 31, 1995 (Antinheimo et al. 2000). The Finnish Population Register Centre was used to identify relatives of all the patients, and their data were linked further to the Finnish Cancer Registry to find NF2-related tumours. Detailed pedigrees were constructed for the patients with NF2 and schwannomatosis patients with relatives with histologically verified schwannomas and patients younger than 25 years of age at the time of diagnosis. Approximately 3% (12 of 455) of the schwannoma patients had multiple schwannomas in association with NF2, and 2% (11 of 455) had schwannomatosis without NF2. Two of the patients with schwannomatosis (2 of 11) had familial schwannomatosis. They estimated that the birth occurrence of NF2 was 1 in 87,410. And concluded that this was likely similar albeit slightly lower for schwannomatosis. This led several agencies including the Children's Tumor Foundation and the National Institutes of Health (NIH) to erroneously quote figures of incidence of up to 1 in 40,000. This was based on the premise that if schwannomatosis had a similar incidence to NF2 then the most widely quoted figure for NF2 was based on a UK study from North West England giving an NF2 incidence at birth of 1 in 33-40,000 (Evans et al. 1992). This finally led Manchester to assess the schwannomatosis incidence in 2018 (Evans et al. 2018). Schwannomatosis and NF2 cases were ascertained from the Manchester region of England (population=4.8 million) and from across the UK. Point prevalence and birth incidence were calculated from regional birth statistics. Genetic analysis was also performed on *NF2, LZTR1 and SMARCB1* on blood and tumour DNA samples when available. Regional point prevalence for schwannomatosis and NF2 were 1 in 126,315 and 50,500, respectively, with calculated birth incidences of 1 in 68,956 and 1 in 27,956. Mosaic NF2 causes a substantial overlap with schwannomatosis resulting in the misdiagnosis of at least 9% of schwannomatosis cases. LZTR1-associated schwannomatosis also caused a small number of cases that are misdiagnosed with NF2 (1%-2%), due to the occurrence of a unilateral vestibular schwannoma with other schwannomas. Although it is possible that cases of schwannomatosis

are still unascertained the Manchester region is likely amongst the most ascertained of any region worldwide given a more than 30-year interest. As such the likely birth incidence of schwannomatosis is around 1 in 60-70,000, but prevalence is likely lower at below 1 in 100,000 as most cases are sporadic/isolated and will not present until their 30's or older. There is a concern regarding the frequency of *LZTR1* pathogenic variants in the general population. We therefore assessed the rate of probable *LZTR1* loss of function variants in gnomAD (https://gnomad.broadinstitute.org/gene/ENSG00000099949?dataset=gnomad-Accessed Oct 24th 2020). There were 406 of a mean of 126,124 individuals with nonsense, frameshift or canonical splice region variants equivalent to 1 in 310. This compares to a likely frequency of only 1 in 255,390 for *LZTR1* schwannomatosis (27% of 1 in 68,956). This means potentially only 1 in 823 people in the general population with an *LZTR1* pathogenic variant would get a clinical diagnosis of schwannomatosis, although a proportion of others may develop a single schwannoma.

Aetiology: Schwannomatosis is an autosomal dominant tumour predisposition syndrome with strong overlap with neurofibromatosis-2 (NF2). Both conditions predispose individuals to development of schwannomas, although NF2 also strongly predisposes to meningiomas and to a lesser extent ependymoma. Whilst around half of NF2 cases are inherited the majority of schwannomatosis cases are sporadic/isolated. Despite their phenotypic similarities, schwannomatosis has previously been shown to be a distinct entity from NF2 (Jacoby et al. 1997, MacCollin et al. 2003), mainly discriminated by the absence of vestibular schwannomas. In 2007 *SMARCB1* was identified as a cause of schwannomatosis families and a minority of sporadic/isolated schwannomatosis patients were shown to have pathogenic variants in the gene which lies centromeric to the NF2 gene on chromosome 22q (Hulsebos et al. 2007, Boyd et al. 2008, Hadfield et al. 2008, Sestini et al. 2008). After identification of *SMARCB1* unilateral vestibular schwannoma (VS) was reported to appear to occur in a non-SMARCB1 related schwannomatosis family as well as other isolated cases (Smith et al. 2012). A Children's Tumor Foundation workshop acknowledged that the widely quoted schwannomatosis diagnostic criteria (MacCollin et al. 2005) should not have VS as a complete exclusion criterion for schwannomatosis (Plotkin et al. 2013). No definitive diagnosis of VS has been reported in *SMARCB1* related schwannomatosis (Smith et al. 2014). However, with identification of the *LZTR1* gene in 2014 (Piotrowski et al. 2014) it became clear that VS did occur in the context of LZTR1 related schwannomatosis (Smith et al. 2015, Smith et al. 2017). Indeed, it has been shown that isolated cases of VS aged under 25 years can harbour pathogenic variants in *LZTR1* (Pathmanaban et al. 2017).

The schwannomas occurring in both SMARCB1 and LZTR1 related schwannomatosis are all caused by acquired aberrations in the *NF2* gene that causes loss of both copies as second and tertiary events. The underlying tendency starts with an inherited variant in *SMARCB1* or *LZTR1* then loss of the normal copy of 22q followed by an acquired pathogenic variant in *NF2* on the same copy of chromosome 22q as the germline variant in *SMARCB1* or *LZTR1*.

Figure 1: Chromosome 22 showing locations of *SMARCB1*, *LZTR1* and *NF2* and typical deletion of the second copy removing all 3 genes (Evans et al. 2021). The 3MB deletion represents the velo-cardio-facial syndrome recurrent 22q11 deletion.

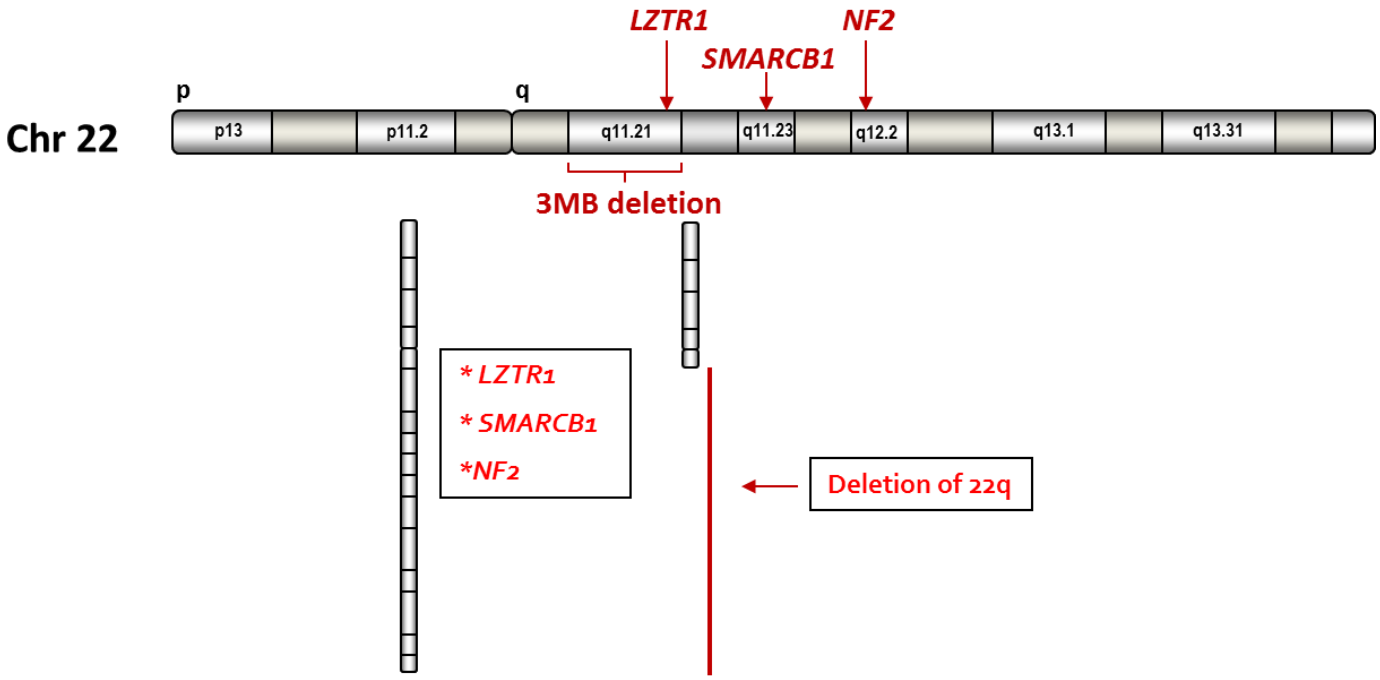
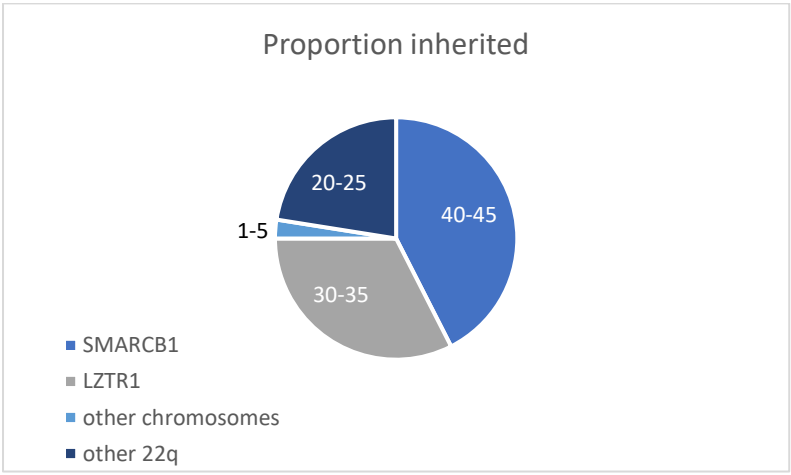
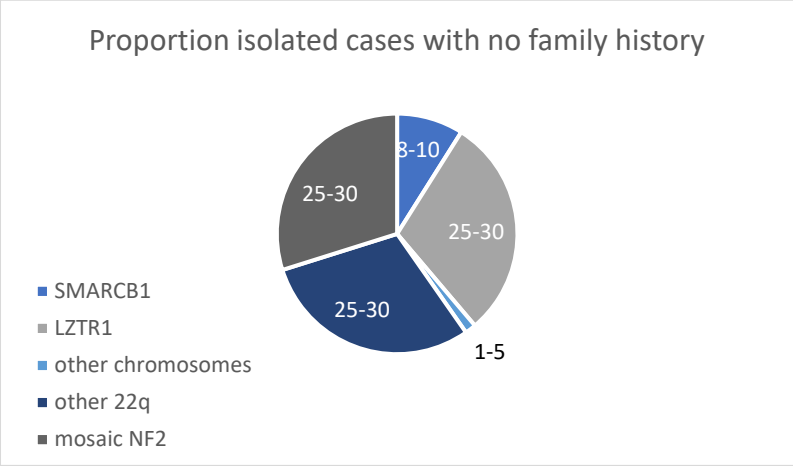


Figure 2: Pie chart showing frequencies of *SMARCB1*. *LZTR1* and mosaic *NF2* as causes of inherited and isolated cases with no family history schwannomatosis





This follows an apparent three event, four hits pattern (Sestini et al. 2008). The initial event is an inherited or very occasionally mosaic pathogenic variant in *SMARCB1* or *LZTR1* which is followed by loss of the normal copy of chromosome 22q and then by a somatic mutation in the *NF2* gene as the third event (Sestini et al. 2008). The deletional loss of chromosome 22q causes loss of copies of both *NF2* and the relevant schwannomatosis genes. It is not known why the vestibular and other cranial nerves are relatively spared in schwannomatosis nor why intradermal schwannomas are absent in schwannomatosis (Evans et al. 2018). ***SMARCB1* and *LZTR1* account for around 70-86% of inherited schwannomatosis and only 30-40% of isolated cases without family history (Evans et al. 2018),** as such further schwannomatosis genes are likely to exist including an additional gene on chromosome 22q and likely a non 22q gene. Nonetheless at least some of the missing heritability will be due to non-typical pathogenic variants in the existing genes (Smith et al. 2020) as well as mosaicism of *NF2* causing around 40-50% of non *LZTR1/SMARCB1* sporadic/isolated cases (Evans et al. 2018). Where possible analysis of two tumours should be performed in sporadic/isolated cases to confirm or refute mosaic NF2. Overall, around 27-30% of schwannomatosis cases are caused by *LZTR1* and this is much more frequent than *SMARCB1* in isolated cases with no family history (10%) with penetrance of *LZTR1* even in families meeting clinical criteria substantially reduced.

5. RECOMMENDATIONS

Recommendations in this guideline are divided into eight sections: Clinical overview, Diagnosis, Imaging, Genotype Specific Imaging Surveillance, Annual Clinical Assessment, Non-Surgical Pain Management, Surgical Intervention, Non-surgical Intervention.

5.1. CLINICAL OVERVIEW RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Life expectancy in schwannomatosis **is not** usually affected, unlike NF2. Pain **is** a prominent feature, especially for people with a *LZTR1* germline pathogenic variant.	strong
Rec. 2	A changing tumour, in someone with *SMARCB1* germline pathogenic variant, especially one causing functional impairment, **should** prompt exclusion of malignant transformation.	strong
Rec. 3	*LZTR1* germline pathogenic variant is associated with higher risk of unilateral vestibular schwannomas; therefore these tumours **should not** be considered an exclusion criterion for the diagnosis of schwannomatosis.	strong

5.2. DIAGNOSIS RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Germline pathogenic variant in *SMARCB1* or *LZTR1* **should** be considered diagnostic of schwannomatosis in the presence of someone with a proven schwannoma.	strong
Rec. 2	Where possible, analysis of two tumours **should** be performed in sporadic cases to confirm or refute mosaic NF2. Schwannomatosis is characterised by multiple tumours harbouring independent somatic pathogenic variants in the *NF2* gene which are not present in their constitutional DNA.	strong
Rec. 3	Baseline investigations to confirm schwannomatosis **should** include brain and internal auditory meati MRI with at least 3mm and preferably ≤1mm cuts through the internal auditory meatus to rule out bilateral vestibular schwannomas (NF2).	moderate

Rec. 4	In people in whom schwannomatosis is clinically suspected and without germline pathogenic variants in *SMARCB1* or *LZTR1*, and without the diagnostic characteristics of NF2, RNA testing **should** be considered (for instance, for deep intronic *SMARCB1* variant associated with schwannomatosis). Due to the increased malignancy risk in schwannomatosis associated with *SMARCB1* this additional step is important as when found it allows confirmation of the diagnosis and the ability to offer pre-symptomatic testing to relatives.	moderate
Rec. 5	In people with schwannomatosis at reproductive age or at transition, a discussion of the likely risks of transmission to offspring and the options for testing in pregnancy and pre-implantation diagnosis **should** be undertaken.	strong
Rec. 6	Affected people and at-risk offspring **should** be told the risk of transmission is 50% in those with germline inherited variants. In those isolated cases with no family history with negative testing of *LZTR1* and *SMARCB1* the transmission rate is <10%. Reduced penetrance in *LZTR1* **should** be discussed.	strong

5.3. IMAGING RECOMMENDATIONS

Recommendations		Strength
Rec. 1	For tumour surveillance or screening MRI **should** be used. PET scanning **should not** be used for diagnosis or surveillance of schwannomas.	moderate
Rec. 2	A baseline assessment including full craniospinal MRI and/or whole-body MRI **should** be carried out as soon after diagnosis as the MRIs can be conducted without general anaesthetic (typically late childhood; 12-14 years) and should be repeated in early adulthood or if symptoms evolve.	moderate
Rec. 3	The frequency of repeat MRI **should** be determined by clinical judgement guided by the presence of changing symptoms.	moderate

Rec. 4	It is expected that routine repeat MRI are conducted at intervals of 2-3 years. More frequent MRI **should not** be conducted unless the person's symptoms change.	moderate
Rec. 5	In patients with localised pain and/or associated neurologic focal deficit, without an obvious schwannoma localised MRI **should** be performed using thin slices (<3mm) in order to detect very small but functionally significant schwannomas.	moderate
Rec. 6	For targeted investigation of pain, ultrasound (in the hands of someone experienced at imaging schwannomas) **may be** a useful problem-solving modality.	weak

5.4. Genotype Specific Imaging Surveillance Recommendations

Please consider all recommendation in section 5.3 Imaging recommendations.

Recommendations		Strength
Rec. 1	*SMARCB1*: the following baseline investigation **should** be performed at diagnosis: MRI brain and spine, and whole-body MRI.	moderate
Rec. 2	*LZTR1:* the following baseline investigation **should** be performed at diagnosis: 1). High-resolution brain MRI with fine cuts (<3 mm) through the internal auditory canal and spine MRI 2). Whole body MRI. * *Note people with *LZTR1* pathogenic variants detected incidentally with no personal or family history of schwannomas and no pain or other schwannoma symptoms should not undergo MRI imaging to detect schwannomas as their risks are likely well below 1%.	moderate
Rec. 3	If tumours are present at baseline MRI imaging, imaging **should** be repeated every 2-3 years, unless there is a change in symptoms or if tumours are present on brain imaging in which case an MRI at 12 months is indicated. Small (less than 1 cm) asymptomatic non-CNS tumours detected on whole body MRI particularly in the limbs **may not** require repeat imaging if no symptoms or signs develop.	moderate

Rec. 4	If there is a change in symptoms, localised MRI **should** be performed according to clinical manifestations, and **should** be repeated at an increased frequency as determined by the clinical presentation.	moderate

5.5. Annual Clinical Assessment Recommendations

Recommendations		Strength
Rec. 1	At each review visit there **should** be: • Full assessment of pain history • Full neurological examination • Assessment of Quality of Life using a recognised tool e.g. EQ-5D • Assessment of psychological needs of the patient	strong

5.6. Non-Surgical Pain Management Recommendations

Recommendations		Strength
Rec. 1	Multidisciplinary pain management focusing on symptom management and targeting pain related disability using a bio-psychosocial approach **should** be used.	moderate
Rec. 2	Radiotherapy is likely to increase the risk of malignant transformation in people with schwannomatosis. Radiotherapy **should** only be considered in growing schwannomas that cannot be treated surgically or by other therapies.	strong
Rec. 3	Painful schwannomas have a significant neuropathic component, drugs such as tricyclic antidepressants and gabapentinoids **should** be used first line, and SSRI or other ASD (Topiramate, Carbamazepine, Oxcarbazepine) second line.	moderate
Rec. 4	Chronic use of opioids **is not** recommended due to their poor effect on neuropathic pain and associated tolerance, dependency and hyperalgesia.	strong
Rec. 5	Transient Receptor Potential Vanilloid 1 (TRPV1) antagonists [capsaicin and some cannabinoid receptor ligands] **may be** effective in intractable pain because of Schwann cell expression of nerve growth factor.	weak

5.7. Surgical Intervention Recommendations

Recommendations		Strength
Rec. 1	For those with painful schwannomas, if surgery is possible without neurological deficit, then early surgical intervention **should** be offered.	strong
Rec. 2	If surgery is performed on symptomatic schwannomas, it **should** be by surgeons with experience resecting nerve sheath tumours.	strong
Rec. 3	Some lesions are not surgically removable, and operations are linked to increased morbidity. So, assessment of the likelihood of success and the risks of neurological deficit **should** include assessment by a surgeon with significant experience resecting nerve sheath tumours	strong
Rec. 4	The use of intraoperative neurophysiological monitoring **should** be considered and is essential for surgery on critical nerves.	moderate
Rec. 5	If surgery fails to relieve local pain or symptoms, repeated surgeries to the same symptomatic area **should** be avoided as they offer diminishing benefit to pain control and may contribute to worsening of the schwannomatosis pain syndrome.	moderate
Rec. 6	Use of spinal cord stimulation is an emerging therapeutic option and **should** be considered by multidisciplinary teams on an individual basis.	weak

5.8. Non-Surgical Intervention Recommendations

Recommendation		Strength
Rec. 1	Bevacizumab **probably should** be actively considered along with all other treatment options in the multidisciplinary team review, specifically in patients with multiple rapidly enlarging tumours, which are symptomatic in terms of pain and/or neurological deficit, and for those which are inoperable.	weak

6. METHODS FOR GUIDELINE DEVELOPMENT

6.1. *FORMULATING AND GRADING STATEMENTS AND CONSENSUS BUILDING*

Literature search

The literature search in PubMed, using the following term: schwannomatosis [Title/Abstract] resulted in 354 published articles. Additional articles were requested from experts in the field and references of all the articles were considered. After collecting additional references and excluding papers not relevant to the diagnosis, treatment, management or surveillance of schwannomatosis a total of 237 papers were considered in the development of the guideline.

Method for formulating recommendations

In day-to-day practice, clinicians will not have the time to explore the evidence as thoroughly as a Guideline Group, nor devote as much thought to the trade-offs, or the possible underlying values and preferences in the population. Therefore, the Core Working Group has made recommendations even when confidence in effect estimate is low and/or desirable and undesirable consequences are closely balanced. Such recommendations have been classified as 'weak' and been qualified. The recommendations have been graded on the quality of evidence; balance between benefits and harms; include the values and preferences of patients; and consider the feasibility, equity & acceptability of implementation and use.

Literature was reviewed along with expert opinion to draft recommendations based on literature and experts' experiences and knowledge.

Recommendations were written in one of four stylistic formats: Should, Should Probably, Should Probably Not, Should Not

- Should & Should Not, were taken to mean - most well-informed people (those who have considered the evidence) would take this action
- Should Probably & Should Probably Not, were taken to mean - the majority of informed people would take this action, but a substantial minority would not

Grading of the recommendations

As the volume of peer-reviewed evidence for rare diseases is typically limited due to the small population sizes, and it is unlikely that the evidence will ever reach a fraction of that for a more common disease, it creates a difficulty when considering the grading of the strength of evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

As is typical for many rare diseases, the volume of peer-reviewed evidence available to consider for these guidelines was small and came from a limited number of articles, which typically reported on small samples or series. If the evidence is categorised and then graded using standard approaches, that are designed to differentiate evidence, in circumstances when there are large numbers of papers and there are likely to be more trials, then its small volume means it would be graded as low. This is not an accurate reflection of the combination of the experts' experience and clinical consensus with the available evidence. This is further compounded as there is a low likelihood of additional volumes of evidence that could change the recommendation.

For this reason, and to **balance the weight of both published evidence and quantify the wealth of expert experience and knowledge**, ERN GENTURIS uses the following scale to grade the recommendation:

Strength	Grading of Recommendation
Strong	Expert consensus AND consistent evidence
Moderate	Expert consensus WITH inconsistent evidence AND/OR new evidence likely to support the recommendation
Weak	Expert majority decision WITHOUT consistent evidence

Expert consensus (an opinion or position reached by a group as whole) or expert majority decision (an opinion or position reached by the majority of the group) is established after reviewing the results of the modified Delphi approach (step 9) within the Core Working Group.

The findings of the literature review will be organised against the PICO questions and outcomes.

In addition, strength of recommendation has been determined through a consensus-based approach (modified Delphi) and through active engagement of affected individuals and parent representatives, specifically balancing the desirable and undesirable consequences of surveillance and alternative care strategies, quality of evidence, and values and preferences held by the patient representatives.

The quantification of strength for a recommendation is a composite of harm and benefit. As a general note for these recommendations, the harms a recommendation seeks to address are often clear, however the

magnitude of the benefit of a specific recommendation are often not as clear. Therefore, the published evidence for a recommendation can be often classified 'weak', even when experts are convinced that the recommendation is correct.

Consensus building using a modified Delphi approach

After drafting recommendations amongst the Guideline Group these were subjected to a modified Delphi assessment. Delphi is a structured communication technique or method in which opinions of a large number of experts are asked on a topic in which there is no consensus, and this was used as a consensus building exercise. The goal is to reach consensus after several rounds of questionnaires.

Experts included in this exercise included the members of the Core Working Group, the Schwannomatosis Guideline Group, the Patient Advisory Group, as well as other (external) experts identified by the Guideline Group.

The survey existed of four rounds, in which the threshold for consensus was defined by a simple majority of the survey participants agree with the recommendation (>60% rated "agree" or "totally agree"). Recommendations were graded using a 4-point Likert scale (totally disagree, disagree, agree, totally agree) and a justification for the given rating was obligatory. Even if consensus was met recommendations were still modified if a higher consensus was thought achievable from written responses.

All recommendations developed by the ERN GENTURIS Schwannomatosis Guideline Group were selected to proceed in the Delphi procedure. The facilitator of the Delphi survey provided anonymised summaries of the experts' decisions after each round as well as the reasons they provided for their judgements. All recommendations passed the threshold for consensus after the first round. The Guideline Group discussed the comments given to all recommendations and decided to adjust five recommendations. These were subjected to the experts' opinion in the second round of the survey. For each recommendation the original recommendation with the overall rating from the first round was presented, as well as the new recommendation, where changes to the original were indicated. All recommendations reached a higher percentage of agreement after the second round. However, the Guideline Group had discussed the need of adding two new recommendations and adaptation of one which were submitted in a third round of the Delphi. The new recommendations scored over 90% agreement, while the adapted recommendation scored less. This recommendation was again modified by the Guideline Group, together with two other recommendations, and submitted to a fourth round. An increase was seen in the agreement percentage for

two recommendations, a decrease for one. For the latter, the Guideline Group decided to use the original recommendation (with the highest consensus).

We would like to thank the experts that were specifically consulted to participate in the Delphi survey:

Name	Speciality/ Role	Affiliation
Helen Hanson	Cancer Genetics (consultant)	St Georges University Hospital's NHS Foundation Trust, United Kingdom
Miriam J. Smith	Cancer Genomics (Senior Lecturer)	The University of Manchester, United Kingdom
Amy Taylor	Genetic Counsellor (Lead Consultant)	Cambridge University Hospitals NHS Foundation Trust, United Kingdom
Eva Trevisson	Clinical Geneticist	University of Padova, Italy
Monique Anten	Neurologist	Maastricht UMC+, the Netherlands
Said Chosro Farschtschi	Neurologist	University Medical Center Hamburg Eppendorf, Germany
C. Oliver Hanemann	Neurologist	Peninsula Medical School, Brain Tumour Centre, Plymouth, United Kingdom
Victor Mautner	Neurologist	University Medical Center Hamburg Eppendorf, Germany
Ciaran Bolger	Neurosurgeon	Royal College of Surgeons in Ireland, Beaumont Hospital, Ireland
Frank van Calenbergh	Neurosurgeon	University hospital Leuven - Gasthuisberg, Leuven, Belgium
Bernhard Frank	Consultant in pain medicine	The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom

6.2. *Internal and External review*

ERN GENTURIS has actively involved external experts from different speciality areas that are relevant to the scope of the guideline to review the findings and recommendations developed in this guideline by participation in the Guideline Group or as a Delphi participant.

In addition, the schwannomatosis Guideline Group engaged with the European Journal of Human Genetics as an independent review of the guideline.

ERN GENTURIS first published the Guideline for the diagnosis, management, treatment and surveillance of schwannomatosis in 2022.

6.3. *TIMELINE AND PROCEDURE FOR UPDATING THE GUIDELINE*

Any new evidence that has been published will be updated to the Network clinical leads, on an annual basis and consideration for updating the guideline thereafter. New versions will be published on the Network's website and circulated through the ERN GENTURIS Members.

6.4. *FUNDING AND FINANCIAL SUPPORT*

This guideline document was developed with the financial support of the European Commission. No external sources of funding and support have been involved. ERN GENTURIS is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission. EU funding is limited to administrative assistance and travel and meeting expenses. For more information about the ERNs and the EU health strategy, please visit http://ec.europa.eu/health/ern. Potential conflict of interest for the individual authors and Delphi participants are listed in chapter 3.

7. SUMMARY OF EVIDENCE AND RECOMMENDATIONS

7.1. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS FOR CLINICAL OVERVIEW

There are no large studies dealing with familial schwannomatosis. This means that life expectancy has not been evaluated routinely. Evans and colleagues in their study about schwannomatosis epidemiology (Evans et al. 2018) compare life expectancy of people with schwannomatosis and NF2. Life expectancy was significantly better in schwannomatosis (mean age at death 76.9) compared with NF2 (mean age at death 66.2; p=0.004). A hallmark of schwannomatosis is severe chronic localised or diffuse pain that negatively impacts the patient's quality of life (Mansouri et al. 2020). Pain without a visible or palpable mass was the most common presenting feature in schwannomatosis cases, along with a peripheral nerve tumour.

It has been demonstrated that schwannomas in the context of familial schwannomatosis although histologically identical to non-familial schwannomas, harbour a very distinct phenogenomic profile (Mansouri et al. 2020). Schwannomas from patients harbouring germline mutations in *LZTR1* show higher prevalence of somatic mutations and deletions in *NF2*, higher Copy Number Variation (CNV), and prevalence of pain and the SH3PXD2A-HTRA1 fusion. It has been suggested that activation of the DNA damage response and chromosomal instability seen here in samples with *LZTR1* pathogenic variants may be in part due to the recognised role of RAS activation. Painful schwannomas also show distinct upregulation of mTOR, and activation of angiogenesis-regulating pathways including PIGF, VEGF, and RAF.

Malignancy is thought to occur rarely in schwannomatosis. Recently several cases have been described mainly in patients harbouring germline mutations in *SMARCB1* gene. A clear increased risk of a malignant peripheral nerve sheath tumour has been stablished (Evans et al. 2012) although it is possible that a more extended malignancy phenotype associated with a *SMARCB1* pathogenic variant does exist (Eelloo et al. 2019). Due to this increased risk, a changing tumour, in someone with *SMARCB1* germline pathogenic variant, especially one causing functional impairment, should prompt exclusion of malignant transformation.

Clinically, schwannomatosis is distinguished from NF2 by the absence of bilateral vestibular schwannomas and ependymomas (Evans et al. 2018, Evans et al. 2019). Previously, a vestibular schwannoma was considered an exclusion criterion for schwannomatosis (Baser et al. 2006). However, the identification of

LZTR1 as a cause of schwannomatosis reduces the specificity of these more inclusive criteria and even the presence of bilateral VS is now no longer sufficient to be certain that an individual has NF2 (Smith et al. 2015, Smith et al. 2017). Furthermore, *LZTR1* Germline pathogenic variants have been recently associated with higher risk of Unilateral Vestibular Schwannomas (Pathmanaban et al. 2017). Therefore, unilateral vestibular schwannomas should not be considered an exclusion criterion for the diagnosis of schwannomatosis in the absence of proven germline or mosaic NF2 (Evans et al. 2018, Evans et al. 2019).

Segmental schwannomatosis is characterized by multiple schwannomas affecting one-limb or less than 5 contiguous segments of spine. The incidence of segmental forms among schwannomatosis patients remains to be determined precisely but has been reported as high as 30% in some series (27 out of 87 patients (Merker et al. 2012). The genetics of segmental schwannomatosis remain incompletely understood with the description of germline *LZTR1* mutations in 33% (Alaidarous et al. 2019) to 40% (Farschtschi et al. 2016) of patients. Those findings suggest that segmental schwannomatosis might be different from a presumed somatic mosaicism. Surgical resection of tumours seems to be effective on pain control in segmental schwannomatosis patients (Alaidarous et al. 2019), but is characterized by a high rate of recurrence (5/9, 55%,(Alaidarous et al. 2019)) or by the systematic appearance of new tumours (4/4, 100%, (Chick et al. 2017)). After surgery, neurological deficit seems to be more frequent than in sporadic cases, presumably due to the presence of several contiguous tumours in the same nerve, mimicking a rosary, but, in general, transient and clinical symptoms disappear in the month following surgery (Chick et al. 2017).

Recommendations		Strength
Rec. 1	Life expectancy in schwannomatosis **is not** usually affected, unlike NF2. Pain **is** a prominent feature, especially for people with a *LZTR1* germline pathogenic variant.	strong
Rec. 2	A changing tumour, in someone with *SMARCB1* germline pathogenic variant, especially one causing functional impairment, **should** prompt exclusion of malignant transformation.	strong
Rec. 3	*LZTR1* germline pathogenic variant is associated with higher risk of unilateral vestibular schwannomas; therefore these tumours **should not** be considered an exclusion criterion for the diagnosis of schwannomatosis.	strong
References: (Baser et al. 2006, Evans et al. 2012, Smith et al. 2015, Pathmanaban et al. 2017, Smith et al. 2017, Evans et al. 2018, Eelloo et al. 2019, Evans et al. 2019, Mansouri et al. 2020)		

7.2. Summary of evidence and guideline Recommendations for Diagnosis

Germline Pathogenic variants in *SMARCB1* or *LZTR1* should be considered diagnostic of schwannomatosis in the presence of someone with a proven schwannoma (Evans et al. 2018). Schwannomatosis (MIM #162091) is a genetic tumour-predisposing syndrome that affects approximately 1 in 125,000 individuals (Evans et al. 2018) and is characterised by the development of multiple non-intradermal schwannomas (SWNs), mainly in the peripheral nerves (90%) and spinal nerves (75%), and, less commonly, cranial nerves.

Considerable overlap has been noted between schwannomatosis and NF2 in terms of the occurrence of the associated types of tumour, but both diseases are regarded as separate clinical entities. Germline pathogenic variants in *SMARCB1* are found in 48% of familial and 10% of sporadic schwannomatosis, while germline *LZTR1* mutations are found in 38% of familial and 30% of sporadic schwannomatosis (Evans et al. 2018). Further schwannomatosis predisposition genes may well exist, but they still remain to be discovered or fully validated beyond a single family such as *DGCR8* (Rivera et al. 2020).

The data on penetrance are limited, though it is less than 100% for both SMARCB1 and LZTR1-related schwannomatosis. Reduced penetrance is more frequently reported in individuals with LZTR1-related schwannomatosis. Both genes, *SMARCB1* and *LZTR1*, have been related with other predisposing syndromes. Because of that, schwannomatosis can only be diagnosed when the carrier is also diagnosed with a confirmed schwannoma. Where possible, analysis of two tumours should be performed in sporadic/isolated cases to confirm or refute mosaic *NF2*. Schwannomatosis is characterised by multiple tumours harbouring independent pathogenic variants in the *NF2* gene which are not present in their constitutional DNA.

The clinical overlap between schwannomatosis and NF2 renders differential diagnosis somewhat difficult, particularly in sporadic/isolated and mosaic cases with multiple schwannomas but without bilateral vestibular schwannomas and detect- able germline NF2 gene mutations (Evans et al. 2018, Evans et al. 2019).

Comprehensive mutation analysis of all three genes, *LZTR1, SMARCB1,* and *NF2*, in people with schwannomatosis should be performed to identify the complete mutational spectra and the number of mutational hits that affect these genes. This approach should identify tumour heterogeneity and help to

distinguish between mosaic NF2 and schwannomatosis, since some NF2 patients with somatic mosaicism for an *NF2* gene mutation fulfil the diagnostic criteria for schwannomatosis (Kehrer-Sawatzki et al. 2017).

Cranial scan MRI with at least 3mm cuts through the internal auditory meatus should be performed to rule out bilateral vestibular schwannomas (NF2).

All patients require a full assessment to exclude additional tumours. This assessment should include full brain, auditory meati and spine magnetic resonance imaging with an NF2 protocol that includes 3-mm imaging-section thickness through the internal auditory meatus and after the use of contrast imaging with gadolinium. A full dermatologic examination for NF2 plaques and an ophthalmologic examination for retinal hamartoma and lens opacity are also advised.

In people in whom schwannomatosis is clinically suspected and without germline pathogenic variants in *SMARCB1* or *LZTR1*, and without the diagnostic characteristics of NF2, RNA testing should be considered (for the deep intronic *SMARCB1* variant associated with schwannomatosis (Smith et al. 2020).

Due to the increased malignancy risk in schwannomatosis associated with *SMARCB1* this additional step is important as when found it allows confirmation of the diagnosis and the ability to offer prenatal and preimplantation testing to relatives.

Malignancy is thought to occur rarely in schwannomatosis. However, recently a case was described showing three separate synchronous primary malignancies in a patient with SMARCB1-associated schwannomatosis (Eelloo et al. 2019), other cases of Malignant Peripheral Nerve Sheath Tumour (MPNST) have also been published (Evans et al. 2012).

The family history of some individuals diagnosed with schwannomatosis may appear to be negative because of failure to recognise the disorder in family members, reduced penetrance, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo.* However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption should also be considered.

Each child of an individual with schwannomatosis and a germline heterozygous variant in *LZTR1* or *SMARCB1* has a 50% chance of inheriting the *LZTR1 or SMARCB1* pathogenic variant. However, penetrance is reduced and there is phenotypic variability within families. The risk to other family members depends on the status of the proband's parents: if a parent has the *LZTR1* or *SMARCB1* pathogenic variant, his or her family members may be at risk.

Pre-conceptional genetic counselling is highly recommended to discuss inheritance, intrafamilial variability, and reproductive options. Available reproductive options include preconception, prenatal, and postnatal testing, as well as alternative family building options, such as the use of donor gametes or adoption. If the pathogenic variant is known, a family may consider *in vitro* fertilisation (IVF) with preimplantation genetic testing for monogenic disorders (PGT-M), or prenatal diagnostic testing. Prenatal diagnosis for the familial variant can be performed via chorionic villus sampling (CVS), amniocentesis or Cell-free foetal DNA (cfDNA). As with any prenatal testing or screening, genetic counselling is recommended to discuss the benefits, limitations, and risks of each option.

Recommendations		Strength
Rec. 1	Germline pathogenic variant in *SMARCB1* or *LZTR1* **should** be considered diagnostic of schwannomatosis in the presence of someone with a proven schwannoma.	strong
Rec. 2	Where possible, analysis of two tumours **should** be performed in sporadic cases to confirm or refute mosaic NF2. Schwannomatosis is characterised by multiple tumours harbouring independent somatic pathogenic variants in the NF2 gene which are not present in their constitutional DNA.	strong
Rec. 3	Baseline investigations to confirm schwannomatosis **should** include brain and internal auditory meati MRI with at least 3mm and preferably ≤1mm cuts through the internal auditory meatus to rule out bilateral vestibular schwannomas (NF2).	moderate
Rec. 4	In people in whom schwannomatosis is clinically suspected and without germline pathogenic variants in *SMARCB1* or *LZTR1*, and without the diagnostic characteristics of NF2, RNA testing **should** be considered (for instance, for deep intronic *SMARCB1* variant associated with schwannomatosis). Due to the increased malignancy risk in schwannomatosis associated with *SMARCB1* this additional step is important as when found it allows confirmation of the diagnosis and the ability to offer pre-symptomatic testing to relatives.	moderate

Rec. 5	In people with schwannomatosis at reproductive age or at transition, a discussion of the likely risks of transmission to offspring and the options for testing in pregnancy and pre-implantation diagnosis **should** be undertaken.	strong
Rec. 6	Affected people and at-risk offspring should be told the risk of transmission is 50% in those with germline inherited variants. In those isolated cases with no family history with negative testing of LZTR1 and SMARCB1 the transmission rate is <10%. Reduced penetrance in LZTR1 should be discussed.	strong
References: (Kehrer-Sawatzki et al. 2017, Evans et al. 2018, Eelloo et al. 2019, Evans et al. 2019, Rivera et al. 2020, Smith et al. 2020)		

7.3. Summary of evidence and guideline Recommendations for Imaging

Imaging plays an important role in both the diagnosis and follow up management of people with schwannomatosis. At baseline, radiological assessment is important in facilitating the diagnostic exclusion of NF2 (Merker et al. 2012, Smith et al. 2017, Plotkin et al. 2018), through close scrutiny of the internal auditory meatus (IAMs) to assess for and exclude, the presence of bilateral vestibular schwannomas (Smith et al. 2017, Ahlawat et al. 2020). The use of CT is not indicated in this regard and certainly not justified on the basis of radiation exposure, unless there is a contraindication to MRI. An MRI protocol that includes fine slice T1-weighted imaging (3mm or less slice thickness, with no interslice gap), with both pre- and post-contrast assessment through the IAMs is vital. A volume acquired, heavily T2-weighted assessment e.g. B FFE, CISS or FIESTA acquisition may also be beneficial in this regard. Such acquisitions will also afford the opportunity to assess the other cranial nerves and identify non-vestibular cranial nerve schwannomas, whilst excluding bilateral VS in the process. Whilst assessment of the cranial nerves is important, this should not be at the expense of adequate assessment of the remainder of the brain, which should follow the SIOPE guidelines at baseline. In addition, assessment of the central nervous system will not be complete, without appropriate spinal assessment for intra-axial, extra-axial intradural and extradural spinal lesions.

Whole body MRI (WB-MRI) should not be used *in lieu* of formal cranial MRI at baseline assessment, and it should be recognised that it will not afford the same level of detailed assessment of the spine that targeted cranio-spinal assessment can provide. However, it does provide an important adjunct in regard to both baseline and follow-up assessment of internal tumour load (Plotkin et al. 2012, Merker et al. 2014, Ahlawat

et al. 2016, Ahlawat et al. 2020). As such, it can provide additional data to aid in lesion characterisation, through the addition of more advanced physiological imaging sequences, such as diffusion-weighted imaging, which have shown some promise in radiologically phenotyping peripheral nerve sheath tumours in regard to their malignant potential (Fayad et al. 2013, Ahlawat et al. 2016). Again, in this regard, PET scanning and the additional radiation burden thus incurred, is not considered warranted in these patients.

In relation to follow-up, the routine radiological surveillance of people with schwannomatosis does not mandate the timing intervals of such imaging (in a stable patient) any sooner than 2 -3 years (dependant on local practice). In such stable patients, one can consider alternating whole-body MRI with spinal MRI as part of a routine surveillance regimen, particularly given the complimentary data (such as scoliosis assessment etc.) that WB-MRI can provide in this cohort of patients (Jaremko et al. 2012).

This is in contrast to the clinical scenario of a patient with changing symptoms. In such instances earlier imaging will be mandated to investigate alterations in neurological symptoms or the evolution of localised pain. In addition, targeted MRI will be necessary (including <3mm fine cut sequences, with no interslice gap, including pre- and post-contrast acquisitions) through the clinically targeted regions of concern. Again, in such cases, PET is not thought to be of benefit. However, in skilled hands (experience of ultrasound of schwannomas), targeted ultrasound can be a useful adjunct in regard to the investigation of pain related to such lesions.

Recommendations		Strength
Rec. 1	For tumour surveillance or screening MRI **should** be used. PET scanning **should not** be used for diagnosis or surveillance of schwannomas.	moderate
Rec. 2	A baseline assessment including full craniospinal MRI and/or whole-body MRI **should** be carried out as soon after diagnosis as the MRIs can be conducted without general anaesthetic (typically late childhood; 12-14 years) and should be repeated in early adulthood or if symptoms evolve.	moderate
Rec. 3	The frequency of repeat MRI **should** be determined by clinical judgement guided by the presence of changing symptoms.	moderate
Rec. 4	It is expected that routine repeat MRI are conducted at intervals of 2-3 years. More frequent MRI **should not** be conducted unless the person's symptoms change.	moderate

Rec. 5	In patients with localised pain and/or associated neurologic focal deficit, without an obvious schwannoma localised MRI **should** be performed using thin slices (<3mm) in order to detect very small but functionally significant schwannomas.	moderate
Rec. 6	For targeted investigation of pain, ultrasound (in the hands of someone experienced at imaging schwannomas) may be a useful problem-solving modality.	weak
References: (Jaremko et al. 2012, Merker et al. 2012, Plotkin et al. 2012, Fayad et al. 2013, Merker et al. 2014, Ahlawat et al. 2016, Smith et al. 2017, Plotkin et al. 2018, Ahlawat et al. 2020)		

7.4. Summary of evidence and guideline Recommendations for Genotype Specific Imaging Surveillance

The imaging paradigm for both baseline assessment as well as follow-up in the genetic subtypes of *SMARCB1* and *LZTR1* are aligned. As suggested in the guidelines for imaging assessment in schwannomatosis as a whole, initial imaging must include adequate assessment of the IAMs as described above. In addition, at baseline, in both genotypes, WB-MRI is recommended in addition to cranio-spinal specific MRI assessment to quantify baseline tumour load.

Again, in both subtypes, routine imaging follow-up in asymptomatic patients, can be extended to a three-year interval (including patients in which baseline imaging has demonstrated tumours). Similarly, in both instances spinal MRI may be alternated with WB-MRI in asymptomatic or clinically stable patients.

In both instances a change in symptoms, especially neurological or pain, mandates earlier imaging assessment with targeted MRI, which should include fine cut pre- and post-contrast imaging as well as consideration for the use of physiological sequences such as diffusion-weighted assessment. Ultrasound, in skilled hands, may again be of benefit in this regard.

Recommendations		Strength
Rec. 1	*SMARCB1*: the following baseline investigation **should** be performed at diagnosis: MRI brain and spine, and whole-body MRI.	moderate
Rec. 2	*LZTR1:* the following baseline investigation **should** be performed at diagnosis:	moderate

	1). High-resolution brain MRI with fine cuts (<3 mm) through the internal auditory canal and spine MRI 2). Whole body MRI. * *Note people with *LZTR1* pathogenic variants detected incidentally with no personal or family history of schwannomas and no pain or other schwannoma symptoms should not undergo MRI imaging to detect schwannomas as their risks are likely well below 1%.	
Rec. 3	If tumours are present at baseline MRI imaging, imaging **should** be repeated every 2-3 years, unless there is a change in symptoms or if tumours are present on brain imaging in which case an MRI at 12 months is indicated. Small (less than 1 cm) asymptomatic non-CNS tumours detected on whole body MRI particularly in the limbs **may not** require repeat imaging if no symptoms or signs develop.	moderate
Rec. 4	If there is a change in symptoms, localised MRI **should** be performed according to clinical manifestations, and **should** be repeated at an increased frequency as determined by the clinical presentation.	moderate

7.5. Summary of evidence and guideline Recommendations for Annual Clinical Assessment

Schwannomatosis is an increasingly recognised tumour predisposition syndrome leading to the development of predominantly painful non-dermal schwannomas (benign peripheral nerve sheath tumours) that, in contrast to neurofibromatosis 2 (NF2), spare the 8th cranial nerve.

Schwannomatosis is characterised by the presence of two or more non-intradermal schwannomas with at least one confirmed on histology, no evidence of vestibular tumour on high quality MRI scan and no known constitutional NF2 pathogenic variant in a subject over 30-years. The risk of malignancy is uncertain, but malignant peripheral nerve sheath tumours (MPNST) and other malignancies have been reported.

Initial evaluation of patients who have or are at a risk of schwannomatosis should include:

- Genetic testing to confirm a diagnosis.
- A complete medical history including questions about pain (full assessment of pain history is mandatory), auditory and vestibular functions, focal neurologic symptoms, skin tumours or hyperpigmented lesions, seizures, headache, and visual symptoms.

- A complete family history exploring unexplained neurologic, dermatological, and audiological symptoms in all first-degree relatives. Given the incomplete penetrance of schwannomatosis, a lack of symptoms in first-degree relatives cannot be assumed to indicate that these individuals do not carry a causative germline mutation.
- Full neurological examination.
- Assessment of Quality of Life using validated questionnaires.
- Based on the 2016 American Association for Cancer Research Childhood Cancer Predisposition Workshop, surveillance guidelines have been proposed (Evans et al. 2017).

SMARCB1-related schwannomatosis

- Baseline MRI examination of the brain (with thin cuts < 3 mm and no interslice gap) through the IACs, to exclude bilateral VS and distinguish this entity form NF2) and spine at diagnosis, then every two to three years beginning at age ten years.
- Consideration of whole-body MRI examination and increasing surveillance frequency if symptomatic.
- An adequate Genetic Counselling Process should be granted.

LZTR1-related schwannomatosis (Merker et al. 2014, Evans et al. 2017)

- Baseline MRI examination of the brain and spine at diagnosis, then every two to three years beginning at age 15 to 19 years
- Consideration of whole-body MRI examination and increasing surveillance frequency if symptomatic
- An adequate Genetic Counselling Process should be granted.

Recommendations		Strength
Rec. 1	At each review visit there should be: • Full assessment of pain history • Full neurological examination • Assessment of Quality of Life using a recognised tool e.g. EQ-5D • Assessment of psychological needs of the patient	strong
References: (Merker et al. 2014, Evans et al. 2017)		

7.6. Summary of evidence and guideline Recommendations for Non-Surgical Pain Management

Pain represents one of the most common features in schwannomatosis. Its management can be challenging due to the pain becoming debilitating and refractory. The pain associated with schwannomatosis may be localised to the tumour area or more widespread. While the tumour itself can be painful, pain may be widespread and diffuse. There is a correlation with pain and tumour burden but not location (Lu-Emerson et al. 2009, Gonzalvo et al. 2011, Merker et al. 2012, Merker et al. 2014, Li et al. 2016, Ostrow et al. 2017). These associations may suggest a genetic component that may correlate with increased pain in certain genotypes (Jordan et al. 2018, Ostrow et al. 2019). In addition to mechanical compression, tumours may contribute to pain by secreting trophic and inflammatory substances such as TNF-α and Nerve Growth Factor.

The International Association for the Study of Pain has defined pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." This reflects that pain is more than just a pure sensory phenomenon and is an individual, personal experience resulting from biological, psychological and social factors.

The pain may have both neuropathic and nociceptive components and the proportions of these will alter the therapeutic approach. Scholz et al have classified the variety of pain states, and as such the pain from schwannomatosis is commonly classified as chronic neuropathic pain but there may be some elements of chronic primary pain as well (Scholz et al. 2019).

The cornerstone of successful pain management involves a multidisciplinary approach involving many diverse types healthcare professionals. This ensures correct assessment of the pain and the management of pain-related disability with the intention of maximising symptomatic relief. It is important in the assessment of pain to cover not only the pain itself but also pain-related disability, functional loss and psychological distress as a result of pain. In addition, these measures may be magnified by non-medical issues such as the patient's social circumstances and adverse psychological conditions. The strength of a multidisciplinary approach facilitates such a comprehensive assessment that would be challenging for a lone clinician.

Pain management in schwannomatosis aims to help and support patients in dealing with both pain and the disability that result from their symptoms. The goal should focus on functional restoration, as symptom relief from pain is not always possible.

It is common to trial pharmacological analgesics to reduce the pain intensity of schwannomatosis. As neuropathic pain often forms a considerable proportion of the pain syndrome, it is important to identify when pain has a significant neuropathic component. A variety of screening tools can be useful, but the assessment remains predominantly clinical. A variety of anti-neuropathic agents can be used in neuropathic pain (Finnerup et al. 2015) but care must be undertaken to recognise their efficacy compared to the potential side effects. Analgesics should not be continued unless demonstrable benefit has been shown. Opioids are no longer recommended in chronic pain and should be reserved only for short term use.

For patients with significant pain related disability, a multidisciplinary approach to pain management involving allied health professionals such as physiotherapy, psychology and occupational therapists can help in dealing with pain-related disability, psychological distress and activities of daily living (Attal et al. 2010, Chaparro et al. 2012, Bates et al. 2019).

Emerging technologies such as neuromodulation in the form of spinal cord stimulation may become more commonly used as the electrical stimulation at the spinal cord and dorsal root ganglion may be effective in focal neuropathic pain(Joosten et al. 2020). These devices are now MRI-compatible up to 1.5T and allow ongoing imaging surveillance.

Overall, non-surgical pain management in schwannomatosis aims to help patients manage both symptoms and their pain-related disability and quality of life. Focus should not be on a single modality and a multidisciplinary approach should be considered for those whom pain has affected their physical function and psychological well-being.

Recommendations		Strength
Rec. 1	Multidisciplinary pain management focusing on symptom management and targeting pain related disability using a bio-psychosocial approach **should** be used.	moderate
Rec. 2	Radiotherapy is likely to increase the risk of malignant transformation in people with schwannomatosis. Radiotherapy **should** only be considered in growing schwannomas that cannot be treated surgically or by other therapies.	strong
Rec. 3	Painful schwannomas have a significant neuropathic component, drugs such as tricyclic antidepressants and gabapentinoids **should** be used first line, and SSRI or other ASD (Topiramate, Carbamazepine, Oxcarbazepine) second line.	moderate

Rec. 4	Chronic use of opioids **is not** recommended due to their poor effect on neuropathic pain and associated tolerance, dependency and hyperalgesia.	strong
Rec. 5	Transient Receptor Potential Vanilloid 1 (TRPV1) antagonists [capsaicin and some cannabinoid receptor ligands] **may be** effective in intractable pain because of Schwann cell expression of nerve growth factor.	weak
References: (Lu-Emerson et al. 2009, Attal et al. 2010, Gonzalvo et al. 2011, Chaparro et al. 2012, Merker et al. 2012, Merker et al. 2014, Finnerup et al. 2015, Li et al. 2016, Ostrow et al. 2017, Jordan et al. 2018, Bates et al. 2019, Ostrow et al. 2019, Scholz et al. 2019, Joosten et al. 2020)		

7.7. Summary of evidence and guideline Recommendations for Surgical Intervention

Central nervous system schwannomas

The most common indication for surgical intervention for central nervous system tumours in schwannomatosis is in spinal schwannomas presenting with pain and/or progressive loss of neurological function. The indications for surgery to vestibular schwannomas (VS) in LZTR1 schwannomatosis and meningiomas in SMARCB1 schwannomatosis are unaltered from their management outside of schwannomatosis. Importantly, bilateral VS is not a feature of schwannomatosis and therefore surgical considerations for the treatment of a VS in this condition should be the same as those of a sporadic/isolated VS rather than NF2 VS. The same applies to non-VS cranial nerve schwannomas.

Despite the widely accepted and quoted (Plotkin et al. 2013) view of these indications for surgery, particularly in spinal schwannomas, there is a paucity of evidence in the literature with only retrospective institutional series (Huang et al. 2004, Javalkar et al. 2007, Gonzalvo et al. 2011, Merker et al. 2012, Li et al. 2016, Ansari et al. 2018) and case reports (Birch et al. 1996, Hakan et al. 2008, Brennan et al. 2011, Reddy et al. 2013, Lee et al. 2015, Baruah et al. 2016, Radek et al. 2016, Toms et al. 2016). Those papers that do exist tend to differentiate between peripheral schwannomas and intra-spinal schwannomas, although there is cross-over, notably extra-spinal nerve root tumours (Ansari et al. 2018). That said, it is consistent in recommending surgery for the indications described.

In 2011, Gonzalvo et al (Gonzalvo et al. 2011) reported 158 patients who underwent the excision of 216 schwannomas, of whom 14 were described as having schwannomatosis. Of the 14 schwannomatosis cases, 6 were sporadic/isolated cases and 6 familial. Eight (57%) of the 14 patients presented with at least 1 tumour in the spinal canal. The 6 sporadic/isolated cases underwent 14 operations for the excision of 40 lesions. Five

individuals had uncomplicated macroscopically completed tumour excision, whereas 1 patient experienced anaesthesia dolorosa after subtotal resection of a trigeminal nerve schwannoma. The 8 patients with familial schwannomatosis underwent 25 operations for the excision of 43 lesions. Among the 32 tumours excised at the author centre, the resection was macroscopically complete, and the functionality of nerves affected by the tumours was unchanged or improved during follow-up in 30 cases.

They concluded that the indication for the excision of schwannomas in people with schwannomatosis followed the same principles as the management of sporadic/isolated schwannomas, namely operating on only symptomatic tumours or those demonstrating enlargement during the follow-up and noted that this principle was shared by several previous authors (Bhattacharyya et al. 2004, Huang et al. 2004, Javalkar et al. 2007, Westhout et al. 2007).

A year later, Merker et al (Merker et al. 2012) published a single centre series of 86 patients who underwent 217 surgeries for schwannoma resection (median number of surgeries per patient, 2; range, 1–9). Forty patients underwent a total of 72 spinal surgeries. The remaining surgeries were on peripheral lesions. In contrast to other almost universally positive conclusions as to the benefits of surgery, almost half of the patients (18 of 40, 45%) experienced persistent postoperative deficits, including sensory abnormalities in 13 patients, weakness in four patients, painful kyphosis or kyphoscoliosis in three patients, and bladder dysfunction in three patients.

More recently, Li et al (Li et al. 2016) carried out a retrospective review of 831 patients with solitary schwannomas, 65 with schwannomatosis, and 102 with NF2. In terms of surgical outcome, the patients in the 3 groups obtained similar benefits from the operation with the recovery rates in the patients with solitary schwannomas, NF2, and schwannomatosis were 50.1%, 38.0%, and 53.9%, respectively. The prognosis varied among spinal schwannomas in the people with schwannomatosis. Among 65 patients with this condition, the result of surgical intervention was recovery in 35 (53.9%), improvement in 23 (35.4%), stable in 5 (7.7%), and worsened in 2 (3.1%). Note is specifically made that the postoperative outcome appeared to correlate with the patient's preoperative neurological condition. In terms of numbers of operations undergone by the patients, most had undergone a single spinal operation (81.5%), but 12 patients (18.5%) had undergone multiple operations.

In conclusion, the evidence base for surgical intervention supports the case for its role in painful and/or growing tumours but is reliant on retrospective single centre series and case reports.

Peripheral nervous system schwannomas

Surgery for peripheral nerve schwannomatosis spans cases from the very simplest of small non-critical peripheral nerve disease all the way up to complex, unresectable, poly-fascicular disease (Plotkin et al. 2018). The former can be managed by local surgeons who are familiar with the disease with minor risk of significant morbidity. The latter requires discussion between members of a broad multidisciplinary team, considering the following information – clinical symptoms and signs, review of imaging, histology if available, medication review and genetics. Ultimate management may include watchful wait, specialist pain management, immunotherapy, radiotherapy or surgery or a combination of these. Psychological therapies may also be helpful.

Schwannomatosis is perhaps unusual in that small schwannomas can cause significant symptoms, mainly pain, which is out of proportion to the apparent clinical or radiological size of the lesion. A lump, which may be tender to touch and with or without positive percussion symptoms (Tinel's sign) are alternative presenting features (Tinel 1915). Sensory disturbance may be present associated with a lump or not (Oberle et al. 1997, Padua et al. 2006), and motor symptoms may exist, although more rarely (Ganju et al. 2001, Josty et al. 2001). Surgery can be helpful in patients exhibiting these symptoms. Whilst MRI is the mainstay of radiological investigation, ultrasound localisation of the schwannoma may help define the area for surgery, and this can be performed contemporaneously in the operating room(Senchenkov et al. 2005).

It should be noted, as commented above under central nervous system lesions, that surgical considerations in sporadic/isolated schwannomas and schwannomatosis-related schwannomas are similar and much of the literature does not separate them when discussing outcomes. A well-circumscribed schwannoma affecting an accessible peripheral nerve offers the patient and surgeon the opportunity for a favourable outcome. Surgery aims to incise the pseudo-capsule of the schwannoma, away from the healthy nerve fascicles, and carefully dissect the schwannoma from its bed (Kalamarides et al. 2019). This process has been described as enucleation. Similarly, an intra-capsular approach is reported by Date et al. as giving a lower risk of permanent neurological deficit post operatively, compared to an extracapsular dissection (0/16 (0%) vs 4/20 (20%) respectively) (Date et al. 2012). Operative microscopy, nerve stimulation, intravenous fluorescein and intraoperative nerve monitoring help minimise the risk to nerve function (Huang et al. 2004, Li et al. 2019, Pedro et al. 2019). Post-operative risks include sensory and/or motor disturbance, which usually recovers, but this may be slow or incomplete. Pre-existing neuropathic pain may persist or new pain may develop. In 2001 Ganju et al reported 111 nerve sheath tumours of the brachial plexus, of which 36 were schwannomas. No comment is made as to whether these represent cases in schwannomatosis. The surgical outcomes in the 23 cases who presented with pain showed no worsening in 3 cases and symptomatic

improvement in 15 (overall 78%), and in those presenting with motor weakness, weakness improved or was unaltered in 16 (70%) (Ganju et al. 2001). Li et al describe 92 schwannomas resected with a temporary postoperative neurological deficit in 18 (20%) and a permanent neurological deficit rate in just 3/92 (3%) (Li et al. 2019). Suitable preoperative counselling considering preoperative pain and any neurological deficit, and radiological appearances, will mitigate the disappointment of a less than perfect outcome. Clinically significant recurrence of the underlying schwannoma is rare in well-circumscribed disease. In a series of 71 schwannoma cases treated surgically at the Mayo Clinic, 19 were in peripheral sites, these had a recurrence rate of 0% in the study period (Casadei et al. 1995). Levi et al reported on a series of schwannomas operated in Miami over a 17-year period. 87 schwannomas had no recurrences in the follow-up period and the postoperative neurological deficit rate was 10% in those who had not undergone preoperative biopsy. The deficit rate was 41% in those who had undergone preoperative biopsy, suggesting there is a negative association and morbidity to this investigation (Levi et al. 2010). Chick et al report six cases of multiple schwannomas in cases of sporadic/isolated schwannomatosis, with recurrence rates of 0% in the study period after resection of an average of 4.7 tumours per patient (Chick et al. 2017). In a population of patients with schwannomas (both sporadic/isolated and with schwannomatosis) Guha et al report a rate of permanent neurological change of 10/133 for sensory symptoms, 6/133 for motor symptoms and 1/133 for pain. The recurrence rate following schwannoma excision was 5.3% overall, increasing to 14.3% in schwannomatosis patients. (Guha et al. 2018)

In people with multiple schwannomas which have been demonstrated on imaging, surgical resection should be restricted to symptomatic lesions. Correlation between imaging and Tinel's sign on clinical testing can help localise clinically significant lesions (Tinel 1915).

The decision to operate on lesions which are harder to access, are larger, or fall across multiple nerve roots is more complex. Careful consideration should be given to the potential morbidity of continued conservative management balanced against the risk of adverse outcome either due to direct nerve injury, or damage to adjacent structures e.g. injury to thoracic duct, phrenic, vagus or spinal accessory nerves or vascular injury. Alternative treatment modalities may be considered.

Nerve grafting is rarely required in schwannoma resection, as the absolute pathological fascicular involvement is small. During surgery intraoperative neurophysiological monitoring can aid the surgeon as to the potential deficit if a given lesion is resected. Intra-neural dissection down to the nerve fibre of origin will usually demonstrate a non-functioning fascicle on intraoperative testing (Guha et al. 2018, Li et al.

2019). Patients with larger complex schwannomas may be considered to have surgically resectable disease which will inevitably result in sacrifice of one or more major peripheral nerves or nerve roots. In these circumstances, the effects of the resection can be mitigated by preoperative planning of direct nerve treatments such as nerve grafting, or the use of distal neurotisation or tendon transfers procedures. These modalities are outside the scope of this guidance but are well covered in the scientific literature.

Recommendations		Strength
Rec. 1	For those with painful schwannomas, if surgery is possible without neurological deficit, then early surgical intervention **should** be offered.	strong
Rec. 2	If surgery is performed on symptomatic schwannomas, it **should** be by surgeons with experience resecting nerve sheath tumours.	strong
Rec. 3	Some lesions are not surgically removable, and operations are linked to increased morbidity. So, assessment of the likelihood of success and the risks of neurological deficit **should** include assessment by a surgeon with significant experience resecting nerve sheath tumours	strong
Rec. 4	The use of intraoperative neurophysiological monitoring **should** be considered and is essential for surgery on critical nerves.	moderate
Rec. 5	If surgery fails to relieve local pain or symptoms, repeated surgeries to the same symptomatic area **should** be avoided as they offer diminishing benefit to pain control and may contribute to worsening of the schwannomatosis pain syndrome.	moderate
Rec. 6	Use of spinal cord stimulation is an emerging therapeutic option and **should** be considered by multidisciplinary teams on an individual basis.	weak
References: (Casadei et al. 1995, Birch et al. 1996, Oberle et al. 1997, Ganju et al. 2001, Josty et al. 2001, Bhattacharyya et al. 2004, Huang et al. 2004, Senchenkov et al. 2005, Padua et al. 2006, Javalkar et al. 2007, Westhout et al. 2007, Hakan et al. 2008, Levi et al. 2010, Brennan et al. 2011, Gonzalvo et al. 2011, Date et al. 2012, Merker et al. 2012, Plotkin et al. 2013, Reddy et al. 2013, Lee et al. 2015, Baruah et al. 2016, Li et al. 2016, Radek et al. 2016, Toms et al. 2016, Chick et al. 2017, Ansari et al. 2018, Guha et al. 2018, Li et al. 2019)		

7.8. Summary of evidence and guideline Recommendations for Non-Surgical Intervention

Schwannomatosis is characterised by the development of typically painful benign nerve sheath tumours (schwannomas) on the spinal and peripheral nerves around the body (Dhamija et al. 1993, Evans et al. 2018). The overriding feature in individuals with schwannomatosis is pain which contributes to a reduced quality of life (QoL) in these individuals. Removal of schwannomas often results in complete resolution of pain symptoms (Dhamija et al. 1993). However, this is not always possible, and a proactive and aggressive non-surgical pain management is recommended. Proactive monitoring and aggressive treatment of pain with pharmacologic, surgical, and complementary and alternative medicine interventions in people with schwannomatosis is required. Additionally, there is a need for a comprehensive approach to treatment that goes beyond tumour-focused therapies and includes psychosocial interventions to improve all domains of QOL more effectively in these patients (Merker et al. 2014). We recommend a multidisciplinary pain management focusing on symptom management and targeting pain related disability using a bio-psychosocial approach. Mind-Body Therapies have been proven useful in patients with NF1 and NF2 and other chronic pain diseases (Vranceanu et al. 2016, Funes et al. 2019).

Mansouri and colleagues (Mansouri et al. 2020) showed the presence of the SH3PXD2A-HTRA1 gene fusion for the first time in schwannomatosis or sporadic schwannomas (SWNTS-SWNs) and also showed that its prevalence is significantly associated with germline *LZTR1* mutations and tumour-associated pain. LZTR1 plays an important role in regulating the activation of the oncogenic RAS/MAPK signalling pathway. Additionally, it is well documented that MAPK activation plays a role in peripheral and central nervous system sensitisation to extensive noxious stimuli. Given the direct therapeutic significance of the fusion, Mansouri and colleagues suggest the opportunity for use of MEK inhibitors as a therapeutic strategy for pain management in familial schwannomatosis.

Painful SWNTS-SWNs and tumours from extremities also show distinct upregulation of mTOR, a pathway with an established role in the initiation and maintenance of chronic pain. Importantly, they also found activation of angiogenesis-regulating pathways including PIGF, VEGF, and RAF in painful tumours, suggesting that already existing drugs, such as the anti-angiogenic drug Avastin or compounds targeting PIGF, can be used for management of pain or to modulate tumour size in SWNTS (Finnerup et al. 2015).

There is concern of a higher risk for malignancy in people with schwannomatosis, in particular for MPNSTs and atypical teratoid/rhabdoid tumours (Eelloo et al. 2019). Furthermore, radiotherapy might increase the

risk of malignant transformation especially in people with SMARCB1 schwannomatosis. Taking this into account, radiotherapy should only be considered in growing schwannomas that cannot be treated surgically.

Pain in the context of schwannomatosis has a significant neuropathic component. Drugs such as tricyclic antidepressants and gabapentinoids should be used first line, and SSRI antidepressants (or other ASD) (Topiramate, Carbamazepine, Oxcarbazepine) as a second line.

Strong opioids (particularly oxycodone and morphine) and Botulinum Toxin-A (BTX-A) (specialist use for peripheral neuropathic pain and presumed local pain generator) have weak GRADE recommendations for use and are recommended as third line of treatment of neuropathic pain. Chronic use of opioids in schwannomatosis is not recommended due to its poor effect on neuropathic pain and associated tolerance, and the risk of dependency and hyperalgesia.

The transient receptor potential vanilloid-1 (TRPV1) is a non-specific cation channel known for its sensitivity to pungent vanilloid compound (i.e. capsaicin) and noxious stimuli, including heat, low pH or inflammatory mediators. TRPV1 is found in the somatosensory system, particularly primary afferent neurons that respond to damaging or potentially damaging stimuli (nociceptors). Pharmacological and genetic studies have validated TRPV1 as a therapeutic target in several preclinical models of chronic pain, including cancer, neuropathic, postoperative and musculoskeletal pain (Iftinca et al. 2020). TRPV1 antagonists [capsaicin and some cannabinoid receptor ligands] may be effective in intractable pain because of Schwann cell expression of Nerve Growth Factor (Iorno et al. 2018).

There has been very limited evidence of benefit of the VEGf inhibitor antibody bevacizumab in schwannomatosis. This is limited to a single case report in the published literature (Blakeley et al. 2014). However, members of the guideline group are aware of other schwannomatosis patients who have gained benefit both in terms of tumour shrinkage and pain relief. There is also very strong evidence in treating schwannomas in NF2 patients that the majority respond to treatment and that side effects are relatively mild or absent in most patients (Forde et al. 2020). As all schwannomas in schwannomatosis are thought to involve inactivation of the *NF2* gene, it is likely that schwannomatosis patients at least those caused by a 22q mechanism including *LZTR1* and *SMARCB1* may benefit if they have a growing schwannoma that is not amenable to other management options.

Recommendation		Strength
Rec. 1	Bevacizumab **probably should** be actively considered along with all other treatment options in the multidisciplinary team review, specifically in patients with multiple rapidly enlarging tumours, which are symptomatic in terms of pain and/or neurological deficit, and for those which are inoperable.	weak
References: (Dhamija et al. 1993, Finnerup et al. 2015, Evans et al. 2018, Iorno et al. 2018, Eelloo et al. 2019, Iftinca et al. 2020, Mansouri et al. 2020)		

8. PSYCHOLOGICAL NEEDS

While the physical manifestations of schwannomatosis are objective and describable, it is important to consider the impact of schwannomatosis on patients' cognitive, psychological, emotional and social well-being. Psychological distress can be caused by pain, fatigue, having to undergo multiple surgeries, uncertainties about disease progression, and fears related to family planning. Studies in Neurofibromatosis patients have shown that significant psychological distress occurs in up to one third of all patients and recognising this distress can improve overall outcomes (Carillo et al. 2018, Quarmby et al. 2019). Evidence of psychological distress in other chronic disease has been well recognised and it is becoming of increasing importance (Mouridsen et al. 1995, de Ridder et al. 2008, Granstrom et al. 2012, Carillo et al. 2018, Quarmby et al. 2019, Bottesi et al. 2020).

In order to achieve good long-term outcomes, it is crucial that psychological and social factors have a significant role in overall patient function and quality of life. Patients' beliefs about their medical condition can be extremely strong determinants in their response to therapy, long term management and overall disability. Severity of physical disease does not always correlate with emotional distress however pain was a significant factor in schwannomatosis (Wang et al. 2012). This is not surprising as pain has a well-recognised and significant psychosocial correlation.

Unfortunately, assessment of psychosocial factors may be left only after organic and physical approaches and management strategies have been exhausted. This can lead to unhelpful management beliefs and strategies that can be difficult to change in the long term.

Examples of psychological factors that may influence therapy and outcomes are:

1. Concerns about identity and body image
2. Depression
3. Anxiety
4. Lack of self-efficacy
5. Maladaptive coping strategies such as catastrophising and avoidance
6. Limited social support

A formal psychological assessment is unrealistic in all patients diagnosed with schwannomatosis but certain risk factors may alert the clinician to consider early psychological involvement and referral.

While psychological interventions are of value in chronic illness and pain, it is inferred that they will be still be useful in schwannomatosis. Future research would be useful in determining what types of psychological interventions are useful and what would be the optimum timing of such interventions.

9. WHAT DO OTHER GUIDELINES STATE?

There has only been one other guideline that gives recommendations for tumour surveillance. The guidance was developed by an expert group convened for an American Association of Cancer Research (AACR) meeting in 2016 (Evans et al. 2017) to discuss surveillance in children and young adults. For *SMARCB1* related schwannomatosis a baseline MRI brain and spine were recommended at diagnosis, then every 2 to 3 years, beginning at age 10. For *LZTR1* related schwannomatosis a baseline MRI brain and spine at diagnosis was also recommended, then every 2 to 3 years, beginning at age 15 to 19 years. The guideline also suggested considering whole-body MRI and increasing surveillance frequency if symptomatic for both types of schwannomatosis. A schwannomatosis workshop from 2011 gave recommendations for new diagnostic criteria as well as recommendations for surgical and other tumour management (Plotkin et al. 2013). This workshop proposed a molecular diagnosis for the first time related to the discovery of *SMARCB1* as the first schwannomatosis gene. Thus, a diagnosis could be made with: Two or more pathologically proved schwannomas or meningiomas AND genetic studies of at least two tumours with loss of heterozygosity (LOH) for chromosome 22 and two different *NF2* mutations OR if there is a common *SMARCB1* mutation, this defines SMARCB1-associated schwannomatosis. A molecular diagnosis could also be made with one pathologically proved schwannoma or meningioma AND a germline *SMARCB1* pathogenic variant. A clinical diagnosis still depended on the diagnosis of two or more non-intradermal schwannomas, one with pathological confirmation, including no bilateral vestibular schwannoma by high-quality MRI (detailed study of internal auditory canal with slices no more than 3 mm thick. It also excluded schwannomatosis if: there was a germline pathogenic NF2 variant, the patient fulfilled diagnostic criteria for NF2 or schwannomas had developed in a previous field of radiation therapy only.

The workshop made some recommendations for pain medications stating that: 'reasonable options include calcium channel alpha 2-delta ligands (e.g., gabapentin, pregabalin). In addition, several medications designated as antidepressants (e.g., amitriptyline, nortriptyline, duloxetine) can have potent anti-neuropathic pain effects. Medications used for mood stabilization (e.g., lamotrigine, valproate) can also be effective in chronic pain scenarios.' It also stated that 'surgery was the treatment of choice for symptomatic schwannomas and, in many patients, can relieve local pain or symptoms arising from compression of neighbouring tissues.' As for radiation therapy, most experts reserve the use of radiation for patients who require treatment for growing schwannomas that cannot be treated with surgery. The role of radiation for symptomatic (i.e., painful) schwannomas remains unclear.' It also expressed some reservations of use of radiotherapy because of potential malignancy risk. Chemotherapy options included a discussion of the

VEGF inhibitor bevacizumab as it had shown some benefit in pain control and improvement in function in two patients with life-threatening complications of schwannomatosis.

Since the workshop the *LZTR1* gene has been identified as a cause of schwannomatosis and an international consensus group (2018-2020) have developed new diagnostic criteria that include a molecular diagnosis with *LZTR1,* but these are not yet published at the time of writing.

10. SUGGESTIONS FOR FUTURE RESEARCH

(Genotype-specific) Imaging

Research on the mode and size of cut for whole body MRI and cranio MRI: Individuals with schwannomatosis require surveillance imaging to show the burden of disease and to detect symptomatic lesions. There is continuing debate about the timing of surveillance optimal imaging that is required. Whole body MRI (WBMRI) detects schwannomas in the body and limbs, but is not available in all hospitals, and is not useful for imaging the brain or internal meatus. This is important as SMARCB1 pathogenic variant is associated with brain meningiomas and LZTR1 with vestibular schwannomas. The slice thickness in WBMRI is greater than in brain and spine MR imaging and potentially, smaller lesions that are symptomatic may be missed. However, brain and spine imaging does not image the thorax, abdomen, pelvis and limbs adequately. Combining WBMRI with brain and spine imaging will result in longer duration of imaging for the patient, greater cost for the hospital and increased workload for the radiologist. More research is needed to determine the optimal imaging sequences for surveillance of schwannomatosis patients

There is no literature on genotype specific imaging, only general publications are available. Further research should include genotype-specific imaging and surveillance protocols.

Non-surgical pain management

Psychological and health impact of schwannomatosis: Although the psychological impact of chronic pain is well known from multiple studies, the impact of painful schwannomatosis on psychological is more limited. Quality of life, physical, psychological, social and other measures have been seen in NF1 and NF2, but are more limited in schwannomatosis and further investigation into this particular group would be welcome. There is a need for a comprehensive approach that goes beyond tumour-focused therapies and includes psychosocial interventions to improve all domains of QOL more effectively in these patients. The efficacy of different psycho-therapeutical approaches addressing numerous aspects across the QoL spectrum should be evaluated.

Patient reported outcome measures (PROMS) for schwannomatosis: The identification of specific patient reported outcomes measurement system for schwannomatosis will provide clinicians and researchers access to reliable, validated measures of physical, mental and social well-being, and it will facilitate comparisons among clinical subpopulations and with the European general population.

Understanding the cause of schwannomatosis-associated pain, the mechanisms of the disease and the possible treatments: Painful schwannomas show distinct upregulation of mTOR, and activation of angiogenesis-regulating pathways including PIGF, VEGF, and RAF. Possible treatments might therefore include PIGF, VEGF and RAF inhibitors. These and other new drugs should be evaluated in newly developed cellular and animal models to study schwannomatosis.

Neuromodulation: The role of spinal cord stimulation in managing neuropathic pain has been increasing in recent years. This is a result of improvements in implant technology and awareness among pain and neurosurgical specialists of its effectiveness in refractory neuropathic pain. Its role is in treating focal neuropathic pain rather than widespread pain as the stimulation can only cover a limited area. One limitation that has been overcome is their compatibility with magnetic resonance imaging. Older systems were not MRI compatible but current devices are MRI conditional up to 1.5T and they can be implanted without interfering with imaging. What is unknown is their effectiveness in patients with focal neuropathic pain in schwannomatosis. Not all neuropathic pain responds to spinal stimulation and patients with a mixed neuropathic and nociceptive or nociplastic pain may not respond.

Use of cannabis-based medications: Cannabis based medications for pain has become increasingly recognised in spite of the evidence base not demonstrating significant efficacy. Despite this, there are cases of significant pain relief with cannabis-based medications and questions about the balance of THC and CBD remain. The safety profile compares favourably with other analgesics and in refractory cases the use of cannabis-based medications for pain could be considered.

Cost effectiveness of multidisciplinary pain teams and interventions in schwannomatosis: Although multidisciplinary pain management teams have become well established as the standard of care, they are resource intensive and costly. The health economics of this method of delivering healthcare in schwannomatosis has not been established but given that medical therapy of painful schwannomas can be limited, and they can consume a disproportionate amount of healthcare resources it would be useful to objectively measure the role of a multidisciplinary pain team.

Topical capsaicin therapies: Capsaicin acts as a Transient Receptor Potential Vanilloid 1 receptor (TRPV1) agonist that is used topically. It is useful in patients who have cutaneous pain and hypersensitivity. Some patients with painful schwannomas have significant pain sensitivity and application of an 8% capsaicin patch every 3-6 months can reduce this sensitivity.

Infusion therapy of local anaesthetics for widespread neuropathic pain: Intravenous lidocaine has been established as a therapy for widespread neuropathic pain states despite a lack of high-quality evidence. As schwannomatosis can manifest as generalised widespread pain, infusing lidocaine can provide a short-term respite for these patients. It is unknown how effective these infusions can last and there remain safety concerns although the current experience is that serious adverse events are rare.

Sensory profiling in schwannomatosis: Quantitative sensory testing is a non-invasive method of determining mechanical and thermal thresholds in patients with chronic pain. While it is not diagnostic in itself, it can provide a more objective measurement of certain components of pain. This can assist in determining the effectiveness of therapies or other interventions.

Surgical research area

It is recognised that schwannomatosis predisposes to the development of MPNSTs. It is further recognised that clinical suspicion as to the possibility of an MPNST should be raised in the presence of a rapidly growing schwannoma. However, the reality in clinical practice is that is it not uncommon to have a rapidly growing schwannoma which on complete macroscopic surgical resection has concerning pathological features but does not meet the full criteria for MPNST. The definition of rapid growth may be suggested clinically or radiologically – with reference to either absolute measured increase in volume or description of growth rate as measured from consecutive scans over time. El Sayed et al suggest tumours with growth rates of >2cm^3/year or relative growth rate of >35%/year harboured rapid growth rate characteristics (El Sayed et al. 2020). Debate then occurs among the clinical teams, often including the sarcoma specialists, as to the role of adjuvant radiotherapy. Were it frankly malignant, radiotherapy would be the default treatment. This involves irradiating the adjacent neural structures, already with a predisposition to the development of malignant tumours, and therefore exposing the patient to the risk of second radiotherapy-induced malignancies and this in a patient with a complete macroscopic surgical resection. Conversely, to not irradiate an MPNST is to increase materially the risk of recurrence.

It would therefore be of great therapeutic benefit to identify further pathological markers present or absent in a rapidly growing schwannoma (in the context of schwannomatosis) that would define more precisely where the lesions sit on the spectrum of benign schwannoma to MPNST.

11. GLOSSARY

Schwannomas	typically painful benign nerve sheath tumours
Schwannomatosis	characterised by the development of schwannomas on the spinal and peripheral nerves around the body. Cranial nerves are affected to a lesser extent, as well as absence of intradermal schwannomas. tumour predisposition syndrome leading to the development of predominantly painful non-dermal schwannomas (benign peripheral nerve sheath tumours) that, in contrast to neurofibromatosis 2 (NF2), spare the 8th cranial nerve
Cranial schwannomas	characteristic lesions in neurofibromatosis 2, but not in schwannomatosis
Intradermal schwannomas	characteristic lesions in neurofibromatosis 2, but not in schwannomatosis
Meningiomas	typically a slow growing tumour that forms from the meninges, the membranous layers surrounding the brain and spinal cord.
Constitutional DNA	Tissue derived from reproductive cells (egg or sperm) that become incorporated into the DNA of every cell in the body of the offspring.
Penetrance	the extent to which a particular gene or set of genes is expressed in the phenotypes of individuals carrying it, measured by the proportion of carriers showing the characteristic phenotype (likelihood becoming symptomatically affected).
Prevalence	measures how much of a disease or condition there is in a population at a particular point in time.
Birth incidence	measures the rate of occurrence of new cases of a disease or condition at birth.

12. APPENDICES

APPENDIX - REFERENCES

Ahlawat, S., et al. (2016). "Multiparametric whole-body anatomic, functional, and metabolic imaging characteristics of peripheral lesions in patients with schwannomatosis." J Magn Reson Imaging **44**(4): 794-803.

Ahlawat, S., et al. (2020). "Current status and recommendations for imaging in neurofibromatosis type 1, neurofibromatosis type 2, and schwannomatosis." Skeletal Radiol **49**(2): 199-219.

Ahlawat, S., et al. (2016). "Current whole-body MRI applications in the neurofibromatoses: NF1, NF2, and schwannomatosis." Neurology **87**(7 Suppl 1): S31-39.

Alaidarous, A., et al. (2019). "Segmental schwannomatosis: characteristics in 12 patients." Orphanet J Rare Dis **14**(1): 207.

Ansari, I., et al. (2018). "Head and Neck Schwannomas: A Surgical Challenge-A Series of 5 Cases." Case Rep Otolaryngol **2018**: 4074905.

Antinheimo, J., et al. (2000). "Population-based analysis of sporadic and type 2 neurofibromatosis-associated meningiomas and schwannomas." Neurology **54**(1): 71-76.

Attal, N., et al. (2010). "EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision." Eur J Neurol **17**(9): 1113-e1188.

Baruah, R. K., et al. (2016). "Segmental Schwannomatosis of the Spine: Report of a Rare Case and Brief Review of Literature." Ortop Traumatol Rehabil **18**(1): 73-78.

Baser, M. E., et al. (2006). "Increasing the specificity of diagnostic criteria for schwannomatosis." Neurology **66**(5): 730-732.

Bates, D., et al. (2019). "A Comprehensive Algorithm for Management of Neuropathic Pain." Pain Med **20**(Suppl 1): S2-s12.

Bhattacharyya, A. K., et al. (2004). "Peripheral nerve tumors: management strategies and molecular insights." J Neurooncol **69**(1-3): 335-349.

Birch, B. D., et al. (1996). "Frequent type 2 neurofibromatosis gene transcript mutations in sporadic intramedullary spinal cord ependymomas." Neurosurgery **39**(1): 135-140.

Blakeley, J., et al. (2014). "Clinical response to bevacizumab in schwannomatosis." Neurology **83**(21): 1986-1987.

Bottesi, G., et al. (2020). "Dysfunctional coping is related to impaired skin-related quality of life and psychological distress in patients with neurofibromatosis type 1 with major skin involvement." Br J Dermatol **182**(6): 1449-1457.

Boyd, C., et al. (2008). "Alterations in the SMARCB1 (INI1) tumor suppressor gene in familial schwannomatosis." Clin Genet **74**(4): 358-366.

Brennan, P. M., et al. (2011). "Multiple schwannomatosis caused by the recently described INI1 gene--molecular pathology, and implications for prognosis." Br J Neurosurg **25**(3): 330-332.

Carillo, C., et al. (2018). "Psychological follow-up care of neurofibromatosis type 2 patients and their relatives." Neurochirurgie **64**(5): 381-385.

Casadei, G. P., et al. (1995). "Cellular schwannoma. A clinicopathologic, DNA flow cytometric, and proliferation marker study of 70 patients." Cancer **75**(5): 1109-1119.

Chaparro, L. E., et al. (2012). "Combination pharmacotherapy for the treatment of neuropathic pain in adults." Cochrane Database Syst Rev **2012**(7): Cd008943.

Chick, G., et al. (2017). "Six cases of sporadic schwannomatosis: Topographic distribution and outcomes of peripheral nerve tumors." Hand Surg Rehabil **36**(5): 378-383.

Christiaans, I., et al. (2011). "Germline SMARCB1 mutation and somatic NF2 mutations in familial multiple meningiomas." J Med Genet **48**(2): 93-97.

Date, R., et al. (2012). "Advantages of intra-capsular micro-enucleation of schwannoma arising from extremities." Acta Neurochir (Wien) **154**(1): 173-178; discussion 178.

de Ridder, D., et al. (2008). "Psychological adjustment to chronic disease." Lancet **372**(9634): 246-255.

Dhamija, R., et al. (1993). Schwannomatosis. GeneReviews((R)). M. P. Adam, H. H. Ardinger, R. A. Pagon et al. Seattle (WA), University of Washington, Seattle
University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

Eelloo, J. A., et al. (2019). "Multiple primary malignancies associated with a germline SMARCB1 pathogenic variant." Fam Cancer **18**(4): 445-449.

El Sayed, L., et al. (2020). "Natural history of peripheral nerve schwannomas." Acta Neurochir (Wien) **162**(8): 1883-1889.

Evans, D. G., et al. (2018). "Schwannomatosis: a genetic and epidemiological study." J Neurol Neurosurg Psychiatry **89**(11): 1215-1219.

Evans, D. G., et al. (2012). "Malignant peripheral nerve sheath tumours in inherited disease." Clin Sarcoma Res **2**(1): 17.

Evans, D. G., et al. (1992). "A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity." J Med Genet **29**(12): 841-846.

Evans, D. G., et al. (2019). "Identifying the deficiencies of current diagnostic criteria for neurofibromatosis 2 using databases of 2777 individuals with molecular testing." Genet Med **21**(7): 1525-1533.

Evans, D. G., et al. (1997). "Spinal and cutaneous schwannomatosis is a variant form of type 2 neurofibromatosis: a clinical and molecular study." J Neurol Neurosurg Psychiatry **62**(4): 361-366.

Evans, D. G., et al. (2021). "Typical 22q11.2 deletion syndrome appears to confer a reduced risk of schwannoma." Genet Med.

Evans, D. G. R., et al. (2017). "Cancer and Central Nervous System Tumor Surveillance in Pediatric Neurofibromatosis 2 and Related Disorders." Clin Cancer Res **23**(12): e54-e61.

Farschtschi, S., et al. (2016). "Multifocal nerve lesions and LZTR1 germline mutations in segmental schwannomatosis." Ann Neurol **80**(4): 625-628.

Fayad, L. M., et al. (2013). "Whole Body MRI at 3T with Quantitative Diffusion Weighted Imaging and Contrast-Enhanced Sequences for the Characterization of Peripheral Lesions in Patients with Neurofibromatosis Type 2 and Schwannomatosis." ISRN Radiol **2013**: 627932.

Finnerup, N. B., et al. (2015). "Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis." Lancet Neurol **14**(2): 162-173.

Forde, C., et al. (2020). "Disease course of Neurofibromatosis Type 2; a 30-year follow-up study of 353 patients seen at a single institution." Neuro Oncol.

Funes, C. J., et al. (2019). "First report of quality of life in adults with neurofibromatosis 2 who are deafened or have significant hearing loss: results of a live-video randomized control trial." J Neurooncol **143**(3): 505-513.

Ganju, A., et al. (2001). "Outcomes in a consecutive series of 111 surgically treated plexal tumors: a review of the experience at the Louisiana State University Health Sciences Center." J Neurosurg **95**(1): 51-60.

Gonzalvo, A., et al. (2011). "Schwannomatosis, sporadic schwannomatosis, and familial schwannomatosis: a surgical series with long-term follow-up. Clinical article." J Neurosurg **114**(3): 756-762.

Granstrom, S., et al. (2012). "Psychological burden in adult neurofibromatosis type 1 patients: impact of disease visibility on body image." Dermatology **224**(2): 160-167.

Guha, D., et al. (2018). "Management of peripheral nerve sheath tumors: 17 years of experience at Toronto Western Hospital." J Neurosurg **128**(4): 1226-1234.

Hadfield, K. D., et al. (2008). "Molecular characterisation of SMARCB1 and NF2 in familial and sporadic schwannomatosis." J Med Genet **45**(6): 332-339.

Hadfield, K. D., et al. (2010). "SMARCB1 mutations are not a common cause of multiple meningiomas." J Med Genet **47**(8): 567-568.

Hakan, T., et al. (2008). "Spinal schwannomatosis: case report of a rare condition." Turk Neurosurg **18**(3): 320-323.

Huang, J. H., et al. (2004). "Management of patients with schwannomatosis: report of six cases and review of the literature." Surg Neurol **62**(4): 353-361; discussion 361.

Hulsebos, T. J., et al. (2007). "Germline mutation of INI1/SMARCB1 in familial schwannomatosis." Am J Hum Genet **80**(4): 805-810.

Iftinca, M., et al. (2020). "TRPV1-Targeted Drugs in Development for Human Pain Conditions." Drugs.

Iorno, V., et al. (2018). "Including cannabinoids in the treatment of painful schwannomatosis." Brain Behav **8**(7): e01011.

Iwabuchi, S., et al. (1993). "Familial neurilemmomatosis: report of a case." Surg Today **23**(9): 816-819.

Jacoby, L. B., et al. (1997). "Molecular analysis of the NF2 tumor-suppressor gene in schwannomatosis." Am J Hum Genet **61**(6): 1293-1302.

Jaremko, J. L., et al. (2012). "Whole-body MRI in neurofibromatosis: incidental findings and prevalence of scoliosis." Skeletal Radiol **41**(8): 917-923.

Javalkar, V. K., et al. (2007). "Multiple schwannomas: report of two cases." Eur Spine J **16 Suppl 3**(Suppl 3): 287-292.

Joosten, E. A. and G. Franken (2020). "Spinal cord stimulation in chronic neuropathic pain: mechanisms of action, new locations, new paradigms." Pain **161 Suppl 1**: S104-S113.

Jordan, J. T., et al. (2018). "Pain correlates with germline mutation in schwannomatosis." Medicine (Baltimore) **97**(5): e9717.

Josty, I. C. and P. J. Sykes (2001). "An unusual schwannoma of the median nerve: effects on the motor branch." Br J Plast Surg **54**(1): 71-73.

Kalamarides, M., et al. (2019). "Extracapsular dissection in peripheral nerve schwannoma surgery using bright light and fluorescein sodium visualization: case series." Acta Neurochir (Wien) **161**(12): 2447-2452.

Kehrer-Sawatzki, H., et al. (2017). "The molecular pathogenesis of schwannomatosis, a paradigm for the co-involvement of multiple tumour suppressor genes in tumorigenesis." Hum Genet **136**(2): 129-148.

Kehrer-Sawatzki, H., et al. (2018). "Phenotypic and genotypic overlap between mosaic NF2 and schwannomatosis in patients with multiple non-intradermal schwannomas." Hum Genet **137**(6-7): 543-552.

Lee, S. H., et al. (2015). "Multiple Schwannomas of the Spine: Review of the Schwannomatosis or Congenital Neurilemmomatosis: A Case Report." Korean J Spine **12**(2): 91-94.

Levi, A. D., et al. (2010). "The surgical management of symptomatic peripheral nerve sheath tumors." Neurosurgery **66**(4): 833-840.

Li, P., et al. (2016). "Clinical features of spinal schwannomas in 65 patients with schwannomatosis compared with 831 with solitary schwannomas and 102 with neurofibromatosis Type 2: a retrospective study at a single institution." J Neurosurg Spine **24**(1): 145-154.

Li, X., et al. (2019). "Surgical strategies for peripheral nerve schwannoma based on the intraoperative neurophysiological monitoring." Laparoscopic, Endoscopic and Robotic Surgery **2**(3): 65-69.

Louvrier, C., et al. (2018). "Targeted next-generation sequencing for differential diagnosis of neurofibromatosis type 2, schwannomatosis, and meningiomatosis." Neuro Oncol **20**(7): 917-929.

Lu-Emerson, C. and S. R. Plotkin (2009). "The neurofibromatoses. Part 2: NF2 and schwannomatosis." Rev Neurol Dis **6**(3): E81-86.

MacCollin, M., et al. (2005). "Diagnostic criteria for schwannomatosis." Neurology **64**(11): 1838-1845.

MacCollin, M., et al. (2003). "Familial schwannomatosis: exclusion of the NF2 locus as the germline event." Neurology **60**(12): 1968-1974.

MacCollin, M., et al. (1996). "Schwannomatosis: a clinical and pathologic study." Neurology **46**(4): 1072-1079.

Mansouri, S., et al. (2020). "Epigenomic, genomic, and transcriptomic landscape of schwannomatosis." Acta Neuropathol.

Matsuo, A., et al. (1991). "[A case of schwannomatosis--clinical, pathological and biochemical studies]." Rinsho Shinkeigaku **31**(7): 742-745.

Merker, V. L., et al. (2014). "Relationship between whole-body tumor burden, clinical phenotype, and quality of life in patients with neurofibromatosis." Am J Med Genet A **164a**(6): 1431-1437.

Merker, V. L., et al. (2012). "Clinical features of schwannomatosis: a retrospective analysis of 87 patients." Oncologist **17**(10): 1317-1322.

Mouridsen, S. E. and S. A. Sorensen (1995). "Psychological aspects of von Recklinghausen neurofibromatosis (NF1)." J Med Genet **32**(12): 921-924.

Oberle, J., et al. (1997). "Peripheral nerve schwannomas--an analysis of 16 patients." Acta Neurochir (Wien) **139**(10): 949-953.

Ostrow, K. L., et al. (2017). "Creation of an international registry to support discovery in schwannomatosis." Am J Med Genet A **173**(2): 407-413.

Ostrow, K. L., et al. (2019). "The Secretomes of Painful Versus Nonpainful Human Schwannomatosis Tumor Cells Differentially Influence Sensory Neuron Gene Expression and Sensitivity." Sci Rep **9**(1): 13098.

Padua, L., et al. (2006). "Schwannoma of the median nerve (even outside the wrist) may mimic carpal tunnel syndrome." Neurol Sci **26**(6): 430-434.

Pathmanaban, O. N., et al. (2017). "Association of Genetic Predisposition With Solitary Schwannoma or Meningioma in Children and Young Adults." JAMA Neurol **74**(9): 1123-1129.

Pedro, M. T., et al. (2019). "Sodium Fluorescein-Guided Surgery in Peripheral Nerve Sheath Tumors: First Experience in 10 Cases of Schwannoma." World Neurosurg.

Piotrowski, A., et al. (2014). "Germline loss-of-function mutations in LZTR1 predispose to an inherited disorder of multiple schwannomas." Nat Genet **46**(2): 182-187.

Plotkin, S. R., et al. (2013). "Update from the 2011 International Schwannomatosis Workshop: From genetics to diagnostic criteria." Am J Med Genet A **161a**(3): 405-416.

Plotkin, S. R., et al. (2012). "Quantitative assessment of whole-body tumor burden in adult patients with neurofibromatosis." PLoS One **7**(4): e35711.

Plotkin, S. R. and A. Wick (2018). "Neurofibromatosis and Schwannomatosis." Semin Neurol **38**(1): 73-85.

Pulst, S. M., et al. (1997). "Spinal schwannomatosis." Neurology **48**(3): 787-788.

Quarmby, L. M., et al. (2019). "Screening and intervening: Psychological distress in neurofibromatosis type 2 (NF2)." Psychooncology **28**(7): 1583-1587.

Radek, M., et al. (2016). "Neurofibromatosis type 2 (NF 2) or schwannomatosis?--Case report study and diagnostic criteria." Neurol Neurochir Pol **50**(3): 219-225.

Reddy, R. G., et al. (2013). "A rare occurrence and management of familial schwannomatosis." BMJ Case Rep **2013**.

Rivera, B., et al. (2020). "DGCR8 microprocessor defect characterizes familial multinodular goiter with schwannomatosis." J Clin Invest **130**(3): 1479-1490.

Scholz, J., et al. (2019). "The IASP classification of chronic pain for ICD-11: chronic neuropathic pain." Pain **160**(1): 53-59.

Senchenkov, A., et al. (2005). "Use of intraoperative ultrasound in excision of multiple schwannomas of the thigh." J Clin Ultrasound **33**(7): 360-363.

Sestini, R., et al. (2008). "Evidence of a four-hit mechanism involving SMARCB1 and NF2 in schwannomatosis-associated schwannomas." Hum Mutat **29**(2): 227-231.

Smith, M. J., et al. (2020). "A deep intronic SMARCB1 variant associated with schwannomatosis." Clin Genet **97**(2): 376-377.

Smith, M. J., et al. (2017). "Revisiting neurofibromatosis type 2 diagnostic criteria to exclude LZTR1-related schwannomatosis." Neurology **88**(1): 87-92.

Smith, M. J., et al. (2015). "Mutations in LZTR1 add to the complex heterogeneity of schwannomatosis." Neurology **84**(2): 141-147.

Smith, M. J., et al. (2012). "Vestibular schwannomas occur in schwannomatosis and should not be considered an exclusion criterion for clinical diagnosis." Am J Med Genet A **158a**(1): 215-219.

Smith, M. J., et al. (2014). "SMARCB1 mutations in schwannomatosis and genotype correlations with rhabdoid tumors." Cancer Genet **207**(9): 373-378.

Tinel , J. (1915). "Le signe du fourmillement dans les lesions de nerfs peripheriques." Presse medicale **47**: 388-389.

Toms, J., et al. (2016). "An unusual case of schwannomatosis with bilateral maxillary sinus schwannomas and a novel SMARCB1 gene mutation." J Neurosurg Spine **24**(1): 160-166.

Vranceanu, A. M., et al. (2016). "Mind-body therapy via videoconferencing in patients with neurofibromatosis: An RCT." Neurology **87**(8): 806-814.

Wang, D. L., et al. (2012). "Emotional functioning of patients with neurofibromatosis tumor suppressor syndrome." Genet Med **14**(12): 977-982.

Westhout, F. D., et al. (2007). "Recognizing schwannomatosis and distinguishing it from neurofibromatosis type 1 or 2." J Spinal Disord Tech **20**(4): 329-332.

Wolkenstein, P., et al. (1997). "Schwannomatosis: a clinical entity distinct from neurofibromatosis type 2." Dermatology **195**(3): 228-231.

APPENDIX - EXPLICIT LINK BETWEEN EVIDENCE AND RECOMMENDATION

Clinical overview Recommendations		Strength
Rec. 1	Life expectancy in schwannomatosis **is not** usually affected, unlike NF2. Pain **is** a prominent feature, especially for people with a *LZTR1* germline pathogenic variant.	strong
Rec. 2	A changing tumour, in someone with *SMARCB1* germline pathogenic variant, especially one causing functional impairment, **should** prompt exclusion of malignant transformation.	strong
Rec. 3	*LZTR1* germline pathogenic variant is associated with higher risk of unilateral vestibular schwannomas; therefore these tumours **should not** be considered an exclusion criterion for the diagnosis of schwannomatosis.	strong

Paper	Design	Quality	Directness
(Baser et al. 2006)	Observational cohort	Single centre	direct
(Evans et al. 2012)	Observational cohort	Single centre	direct
(Smith et al. 2015)	Observational cohort	National multi-centre	direct
(Pathmanaban et al. 2017)	Observational cohort	Single centre	direct
(Smith et al. 2017)	Observational cohort	National multi-centre	direct
(Evans et al. 2018)	Observational cohort	National multi-centre	direct
(Evans et al. 2019)	Observational cohort	National multi-centre	direct
(Eelloo et al. 2019)	Case report	Single centre	direct
(Mansouri et al. 2020)	Observational cohort	International multi-centre	indirect

Diagnosis Recommendations		Strength
Rec. 1	Germline pathogenic variant in *SMARCB1* or *LZTR1* **should** be considered diagnostic of schwannomatosis in the presence of someone with a proven schwannoma.	strong
Rec. 2	Where possible, analysis of two tumours **should** be performed in sporadic cases to confirm or refute mosaic NF2. Schwannomatosis is characterised by multiple tumours harbouring independent somatic pathogenic variants in the NF2 gene which are not present in their constitutional DNA.	strong
Rec. 3	Baseline investigations to confirm schwannomatosis **should** include brain and internal auditory meati MRI with at least 3mm and preferably ≤1mm cuts through the internal auditory meatus to rule out bilateral vestibular schwannomas (NF2).	moderate
Rec. 4	In people in whom schwannomatosis is clinically suspected and without germline pathogenic variants in *SMARCB1* or *LZTR1*, and without the diagnostic characteristics of NF2, RNA testing **should** be considered (for instance, for deep intronic *SMARCB1* variant associated with schwannomatosis). Due to the increased malignancy risk in schwannomatosis associated with *SMARCB1* this additional step is important as when found it allows confirmation of the diagnosis and the ability to offer pre-symptomatic testing to relatives.	moderate
Rec. 5	In people with schwannomatosis at reproductive age or at transition, a discussion of the likely risks of transmission to offspring and the options for testing in pregnancy and pre-implantation diagnosis **should** be undertaken.	strong
Rec. 6	Affected people and at-risk offspring should be told the risk of transmission is 50% in those with germline inherited variants. In those isolated cases with no family history with negative testing of LZTR1 and SMARCB1 the transmission rate is <10%. Reduced penetrance in LZTR1 should be discussed.	strong

Paper	Design	Quality	Directness
(Kehrer-Sawatzki et al. 2017)	Review	Review	direct
(Evans et al. 2018)	Observational cohort	National multi-centre	direct

(Eelloo et al. 2019)	Case report	Single centre	direct
(Evans et al. 2019)	Observational cohort	National multi-centre	direct
(Rivera et al. 2020)	Family report	Single centre	direct
(Smith et al. 2020)	Family report	Single centre	direct

Imaging Recommendations		Strength
Rec. 1	For tumour surveillance or screening MRI **should** be used. PET scanning **should not** be used for diagnosis or surveillance of schwannomas.	moderate
Rec. 2	A baseline assessment including full craniospinal MRI and/or whole-body MRI **should** be carried out as soon after diagnosis as the MRIs can be conducted without general anaesthetic (typically late childhood; 12-14 years) and should be repeated in early adulthood or if symptoms evolve.	moderate
Rec. 3	The frequency of repeat MRI **should** be determined by clinical judgement guided by the presence of changing symptoms.	moderate
Rec. 4	It is expected that routine repeat MRI are conducted at intervals of 2-3 years. More frequent MRI **should not** be conducted unless the person's symptoms change.	moderate
Rec. 5	In patients with localised pain and/or associated neurologic focal deficit, without an obvious schwannoma localised MRI **should** be performed using thin slices (<3mm) in order to detect very small but functionally significant schwannomas.	moderate
Rec. 6	For targeted investigation of pain, ultrasound (in the hands of someone experienced at imaging schwannomas) may be a useful problem-solving modality.	weak

Paper	Design	Quality	Directness
(Jaremko et al. 2012)	Prospective study	247 patients prospective study at single centre	Direct

(Merker et al. 2012)	Case series / retrospective institutional series	Retrospective analysis, single centre. 87 patients	Indirect / direct
(Plotkin et al. 2012)	Prospective study	Dual site multi-national study. 247 patients in total with 1286 tumours identified in 145 of these patients	Direct
(Fayad et al. 2013)	Prospective study	11 patients only 1 with schwannomatosis	Direct/indirect
(Merker et al. 2014)	Patient survey	50 schwannomatosis patients	Direct
(Ahlawat et al. 2016)	Review	Review	Direct/Indirect
(Smith et al. 2017)	Observational cohort	National multi-centre	direct
(Plotkin et al. 2018)	Review	Review	Direct
(Ahlawat et al. 2020)	Review	Review	Indirect

Genotype Specific Imaging Surveillance Recommendations		Strength
Rec. 1	*SMARCB1*: the following baseline investigation **should** be performed at diagnosis: MRI brain and spine, and whole-body MRI.	moderate
Rec. 2	*LZTR1:* the following baseline investigation **should** be performed at diagnosis: 1). High-resolution brain MRI with fine cuts (<3 mm) through the internal auditory canal and spine MRI 2). Whole body MRI. * *Note people with *LZTR1* pathogenic variants detected incidentally with no personal or family history of schwannomas and no pain or other schwannoma	moderate

	symptoms should not undergo MRI imaging to detect schwannomas as their risks are likely well below 1%.	
Rec. 3	If tumours are present at baseline MRI imaging, imaging **should** be repeated every 2-3 years, unless there is a change in symptoms or if tumours are present on brain imaging in which case an MRI at 12 months is indicated. Small (less than 1 cm) asymptomatic non-CNS tumours detected on whole body MRI particularly in the limbs **may not** require repeat imaging if no symptoms or signs develop.	moderate
Rec. 4	If there is a change in symptoms, localised MRI **should** be performed according to clinical manifestations, and **should** be repeated at an increased frequency as determined by the clinical presentation.	moderate

Annual Clinical Assessment Recommendation		Strength
Rec. 1	At each review visit there should be: • Full assessment of pain history • Full neurological examination • Assessment of Quality of Life using a recognised tool e.g. EQ-5D • Assessment of psychological needs of the patient	strong

Paper	Design	Quality	Directness
(Merker et al. 2014)	Patient survey	50 schwannomatosis patients	Direct
(Evans et al. 2017)	Consensus guideline	review	indirect

Non-surgical pain management Recommendations		Strength
Rec. 1	Multidisciplinary pain management focusing on symptom management and targeting pain related disability using a bio-psychosocial approach **should** be used.	moderate
Rec. 2	Radiotherapy is likely to increase the risk of malignant transformation in people with schwannomatosis. Radiotherapy **should** only be considered in growing schwannomas that cannot be treated surgically or by other therapies.	strong
Rec. 3	Painful schwannomas have a significant neuropathic component, drugs such as tricyclic antidepressants and gabapentinoids **should** be used first line, and SSRI or other ASD (Topiramate, Carbamazepine, Oxcarbazepine) second line.	moderate
Rec. 4	Chronic use of opioids **is not** recommended due to their poor effect on neuropathic pain and associated tolerance, dependency and hyperalgesia.	strong
Rec. 5	Transient Receptor Potential Vanilloid 1 (TRPV1) antagonists [capsaicin and some cannabinoid receptor ligands] **may be** effective in intractable pain because of Schwann cell expression of nerve growth factor.	weak

Paper	Design	Quality	Directness
(Lu-Emerson et al. 2009)	Narrative review	review	indirect
(Gonzalvo et al. 2011)	Case series	Case Series, retrospective analysis of 158 patients	Indirect
(Merker et al. 2012)	Case series	Retrospective analysis, single centre. 87 patients	Indirect
(Merker et al. 2014)	Patient survey	50 schwannomatosis patients	Direct
(Li et al. 2016)	Case series	Single centre, 65 with schwannomatosis	Indirect

(Ostrow et al. 2017)	Registry study	International registry study	Indirect
(Jordan et al. 2018)	Cohort study	37 patients assessed for germline mutations	Direct
(Ostrow et al. 2019)	Laboratory study	Laboratory study of schwannoma cell lines from painful and non-painful tumours	Indirect
(Scholz et al. 2019)	International consensus classification guideline	ICD revision 11th ed. Comprehensive practice guideline statement	Indirect
(Finnerup et al. 2015)	Systematic review	Meta-analysis of 229 studies. No direct studies on schwannomatosis pain	Indirect
(Attal et al. 2010)	European Guideline	Consensus guideline	Indirect
(Chaparro et al. 2012)	Systematic review	Systematic review	Indirect
(Bates et al. 2019)	Review	Algorithm synthesized from multiple studies	Indirect
(Joosten et al. 2020)	Review	Narrative review	Indirect

Surgical intervention Recommendations		Strength
Rec. 1	For those with painful schwannomas, if surgery is possible without neurological deficit, then early surgical intervention **should** be offered.	strong
Rec. 2	If surgery is performed on symptomatic schwannomas, it **should** be by surgeons with experience resecting nerve sheath tumours.	strong
Rec. 3	Some lesions are not surgically removable, and operations are linked to increased morbidity. So, assessment of the likelihood of success and the risks of neurological deficit **should** include assessment by a surgeon with significant experience resecting nerve sheath tumours	strong
Rec. 4	The use of intraoperative neurophysiological monitoring **should** be considered and is essential for surgery on critical nerves.	moderate
Rec. 5	If surgery fails to relieve local pain or symptoms, repeated surgeries to the same symptomatic area **should** be avoided as they offer diminishing benefit to pain control and may contribute to worsening of the schwannomatosis pain syndrome.	moderate
Rec. 6	Use of spinal cord stimulation is an emerging therapeutic option and **should** be considered by multidisciplinary teams on an individual basis.	weak

Paper	Design	Quality	Directness
(Huang et al. 2004)	retrospective institutional series	Single Centre	Direct
(Javalkar et al. 2007)	retrospective institutional series	Single Centre	Direct
(Gonzalvo et al. 2011)	retrospective institutional series	Single Centre	Direct
(Merker et al. 2012)	retrospective institutional series	Single Centre	Direct
(Li et al. 2016)	retrospective institutional series	Single Centre	Direct

(Ansari et al. 2018)	retrospective institutional series	Single Centre	Direct
(Birch et al. 1996)	case reports	Single Centre	Direct
(Hakan et al. 2008)	case reports	Single Centre	Direct
(Brennan et al. 2011)	case reports	Single Centre	Direct
(Reddy et al. 2013)	case reports	Single Centre	Direct
(Lee et al. 2015)	case reports	Single Centre	Direct
(Baruah et al. 2016)	case reports	Single Centre	Direct
(Radek et al. 2016)	case reports	Single Centre	Direct
(Toms et al. 2016)	case reports	Single Centre	Direct
(Bhattacharyya et al. 2004)	review	Review	indirect
(Westhout et al. 2007)	Retrospective institutional series	Single Centre	direct
(Plotkin et al. 2013)	Meeting report	Meeting Report	indirect
(Ganju et al. 2001)	Retrospective case series 111 cases	Single centre	Direct
(Casadei et al. 1995)	Retrospective case series 70 cases	Single centre	Indirect – histological assessment
(Li et al. 2019)	Retrospective case series 92 cases	Single centre	Direct
(Senchenkov et al. 2005)	Case report	Single centre	Direct
(Chick et al. 2017)	Retrospective case series	Single series	Direct

	Six patients		
(Guha et al. 2018)	Retrospective case series 175 patients, 133 SWNs, or which 21 SCMTS-SWNs	Single centre	Direct
(Date et al. 2012)	Retrospective case series 36 SWNTS-SWNs in 35 patients	Single centre	Direct
(Levi et al. 2010)	Retrospective case series 87 schwannomas	Single Centre	Direct
(Oberle et al. 1997)	Case series	Single Centre	Direct
(Padua et al. 2006)	Case report	Single Centre	Direct
(Josty et al. 2001)	Case series	Single Centre	Direct

Non-surgical intervention Recommendation		**Strength**
Rec. 1	Bevacizumab **probably should** be actively considered along with all other treatment options in the multidisciplinary team review, specifically in patients with multiple rapidly enlarging tumours, which are symptomatic in terms of pain and/or neurological deficit, and for those which are inoperable.	weak

Paper	**Design**	**Quality**	**Directness**
(Dhamija et al. 1993)	Review	Narrative review	Indirect
(Evans et al. 2018)	Observational cohort	National multi-centre	direct
(Mansouri et al. 2020)	Observational cohort	International multi-centre	indirect
(Finnerup et al. 2015)	Systematic review	Meta-analysis of 229 studies. No direct	Indirect

		studies on schwannomatosis pain	
(Eelloo et al. 2019)	Case report	Single centre	direct
(Iftinca et al. 2020)	Review	Narrative review	indirect
(Iorno et al. 2018)	Case report	Single centre	direct

APPENDIX – PLAIN LANGUAGE SUMMARY

ERN GENTURIS Plain Language Summary:

CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS, TREATMENT, MANAGEMENT AND SURVEILLANCE OF PEOPLE WITH SCHWANNOMATOSIS

INTRODUCTION

Schwannomatosis is characterised by the development of typically painful, benign nerve sheath tumours (schwannomas) on the spinal and peripheral nerves around the body. Clinical care for people with schwannomatosis varies substantially, as there is no specific guideline on schwannomatosis yet.

GUIDELINE AIMS

The schwannomatosis guideline has been created to assist healthcare professionals to give the most up-to-date diagnosis, clinical management and surveillance of people with schwannomatosis. This guideline has been drawn from the best available evidence and the consensus of experts in caring for people with schwannomatosis and it will be regularly updated to reflect changes in evidence. The expectation is that clinicians will follow this guideline unless there is a compelling clinical reason specific to an individual patient not to.

SCOPE & PURPOSE OF THE GUIDELINE

The guideline is intended to define the optimal diagnosis, clinical management and surveillance of people with schwannomatosis.

GUIDELINE SUMMARY

Exam or surveillance		**Interval**	**Age to start**	**Strength***
Schwannomatosis	Clinical examination and assessment for pain and neurological examination	Annual	12-14	Moderate
Schwannomas	Brain and spine MRI	According to specific gene / age recommendations	Diagnosis or 12-14 years	Strong
	Whole-Body MRI	Baseline or soon after. Consider alternating with Craniospinal	Diagnosis or 12-14 years	Moderate
	Ultrasound	Consider for problem solving in limbs or intercostal	As appropriate	Moderate

*This grading is based on published articles and expert consensus.

KEY RECOMMENDATIONS

Clinical Overview	Life expectancy in schwannomatosis **is not** usually affected, unlike NF2. Pain **is** a prominent feature, especially for people with a *LZTR1* germline pathogenic variant.
Diagnosis	In people with schwannomatosis at reproductive age or at transition, a discussion of the likely risks of transmission to offspring and the options for testing in pregnancy and pre-implantation diagnosis **should** be undertaken.
Imaging	In patients with localised pain and/or associated neurologic focal deficit, without an obvious schwannoma localised MRI **should** be performed using thin slices (<3mm) in order to detect very small but functionally significant schwannomas.
	For targeted investigation of pain, ultrasound (in the hands of someone experienced at imaging schwannomas) **may be** a useful problem-solving modality.
Annual clinical assessment	At each review visit there **should** be: • Full assessment of pain history • Full neurological examination • Assessment of Quality of Life using a recognized tool e.g. EQ-5D • **Assessment of psychological needs of the patient**
Non-surgical pain management	Multidisciplinary pain management focusing on symptom management and targeting pain related disability using a bio-psychosocial approach **should** be used.
	Painful schwannomas have a significant neuropathic component, drugs such as tricyclic antidepressants and gabapentinoids **should** be used first line, and SSRI or other ASD (Topiramate, Carbamazepine, Oxcarbazepine) second line.
Surgical intervention	Some lesions are not surgically removable, and operations are linked to increased morbidity. So, assessment of the likelihood of success and the risks of neurological deficit **should** include assessment by a surgeon with significant experience resecting nerve sheath tumours

PSYCHOLOGICAL NEEDS

While the physical manifestations of schwannomatosis are objective and describable, **it is important to consider the impact of schwannomatosis on patients' cognitive, psychological, emotional and social well-being**. Psychological distress can be caused **by pain, fatigue**, having to undergo multiple surgeries, uncertainties about disease progression, and fears related to family planning.

Patients' beliefs about their medical condition can be extremely strong determinants in their response to therapy, long term management and overall disability. Severity of physical disease does not always correlate with emotional distress, however pain is a significant factor in schwannomatosis. This is not surprising as **pain has a well-recognised and significant psychosocial correlation**.

Realistically, a formal psychological assessment cannot be performed in all patients diagnosed with schwannomatosis. However, certain risk factors should alert the clinician to consider early psychological involvement and referral.

European Reference Networks

https://ec.europa.eu/health/ern

European Reference Network
for rare or low prevalence complex diseases

Network
Genetic Tumour Risk Syndromes (ERN GENTURIS)

www.genturis.eu

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