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ERN GENTURIS Tumour Management in Neurofibromatosis Type 1 Guideline

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1. ABSTRACT

Neurofibromatosis type 1 (NF1) is a genetic disorder that predisposes people to the development of benign and malignant peripheral nerve sheath tumours and other malignancies. It is a disease that cuts across multiple disciplines. Given the potential for tumour development, long-term surveillance is important, and should be performed by clinicians who understand the condition and can provide lifelong care. New proposals for care of individuals with NF1 have been developed but need to be integrated with routine care. It is important not to delay assessment for patients who are at risk of serious complications. Monitoring, surveillance and management of NF1 individuals requires a multidisciplinary approach and specific guidance adapted to the specific risks and natural history of the disease.

In Europe, patients with NF1 may not all have access to the same level of care and treatment differs across different institutions. This guideline aims to improve quality of care by presenting evidence-based information to assist health care professionals in tumour surveillance and further management of individuals with NF1 in Europe.

Methods: The European Reference Network GENTURIS NF1 Tumour Management Guideline Group was established by experts in NF1 encompassing the clinical care of the wide disease spectrum (n=32) as well as patient representatives (n=6) from 11 countries. To overcome the issue of variability in recommendations for specific national health care settings and to account for the recommendations based on indirect (scarce) evidence, we applied a modified Delphi procedure. Experts in this exercise included the members of the NF1 Tumour Management Guideline Group, as well as an additional 60 external experts identified by the Guideline Group. The survey consisted of three rounds.

Results: Recommendations in this guideline are divided into 14 sections: general approach, optic pathway glioma, other low grade or high grade brain or spine glioma (non-OPG) in children, non-OPG in adults, malignant peripheral nerve sheath tumour and atypical neurofibromatous neoplasm with uncertain biologic potential, orbital & periorbital plexiform neurofibroma, plexiform neurofibroma, cutaneous neurofibroma, gastrointestinal stromal tumours, phaeochromocytoma, breast cancer, glomus tumours of the digits, juvenile myelomonocytic leukaemia, and psychosocial needs. For all manifestations, we discussed i) what clinical screening is appropriate for detecting tumours, ii) what imaging screening is useful for detecting tumours and how does this differ in NF1 from the general population, iii) what is the method and monitoring interval if a tumour is diagnosed (if applicable); iv) what is the indication for treatment and is the type of

treatment different in NF1 from the general population. In addition, we discuss and advise on the role of optical coherence tomography and whole body MRI in NF1 management. Finally, we address what type of psychosocial support is useful in people with NF1 and discuss the issues of living with the uncertainty of whether a tumour will develop or uncertainty during the monitoring and management of a tumour.

Conclusions: In this guideline, we defined recommendations for tumour management in NF1 in a personalised and targeted approach, balancing appropriate care for those in need versus reducing unnecessary investigations for those without complications. We also incorporated tumour-related psychosocial and quality of life aspects. The guideline is meant for member states of the EU and the UK as they reflect the current standard of care for NF1 in Europe. They are not meant to be prescriptive and may be adjusted given local available resources at the treating centre. The recommendations take local/national differences within EU countries into account if relevant, but these recommendations can also be used in other countries. Given the low prevalence of the condition, its potential manifestations and low prevalence of some complications, decisions about management should include discussion by NF1 experts and local multidisciplinary teams with the patient and/or her/his family.

2. GUIDELINE SUMMARY

This guideline for tumour management in Neurofibromatosis type 1 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.

Table 1. Summary of the surveillance protocol for tumour screening/identification in individuals with NF1.

	Surveillance	Interval	Age (years) / Indication	Strength [a]	If manifestation is found, please refer to the following chapters in the guideline for management and treatment of observed manifestation
Optic pathway glioma	Clinical assessment: 1. Visual assessment 2. Fundoscopy 3. Visual fields 4. Optic coherence tomography	1-3: At least yearly 4: When feasible	0 - 8	1. Strong 2. Strong 3. Moderate 4. Moderate	7.2 & 9.2 (rec. 1-4)
	Visual screening	Yearly	8 – transition adolescence to adult	Moderate	7.2 & 9.2 (rec. 5-6)
Brain or spine glioma	Patient history / Examination signs of brain tumours	Every visit	All ages	Moderate	7.3 & 9.3 for children 7.4 & 9.4 for adults
Plexiform neurofibroma	Clinical examination	Every visit	All ages	Moderate	7.5 & 9.5 (rec. 1-2)
	Whole body MRI	Once	Transition adolescence -adult	Weak	7.5 & 9.5 (rec. 3-4)
Malignant peripheral nerve sheath tumour + Atypical	Clinical examination + history taking	Every visit	All ages	Strong	7.6 & 9.6 (rec. 1-2)

neurofibromatous neoplasm with uncertain biologic potential	Regional MRI combined with ^{18}FDG PET MRI or ^{18}FDG PET CT	On indication	Suspicion for malignancy	Moderate	7.6 & 9.6 (rec. 3)
Orbital & Periorbital Plexiform neurofibroma	Clinical assessment, refraction error, vision fields, ocular motility	Every visit	All ages	Strong	7.7 & 9.7 (rec. 1)
Cutaneous neurofibroma	Clinical examination	Every visit	All ages	Strong	7.8 & 9.8 (rec. 1)
Gastrointestinal stromal tumour	Clinical examination + history taking	Every visit	Adolescence and adults	Moderate	7.9 & 9.9 (rec. 1-2)
	Abdominal MRI or CT	On indication	Clinical suspicion of presence based on symptoms	Moderate	7.9 & 9.9 (rec. 4)
Phaeochromocytoma and paraganglioma	Biochemical screening	On indication	Raised blood pressure	Moderate	7.10 & 9.10 (rec. 2)
	Biochemical screening	On indication	Pregnant women Consider if elective surgery requiring general anaesthesia	Weak	7.10 & 9.10 (rec. 1 and 3)
Breast cancer	MRI	Yearly	30 - 50	Moderate	7.11 & 9.11 (rec. 2-3)
	Breast screening per national guideline for the general population		> 50	Moderate	7.11 & 9.11 (rec. 2-3)

Glomus tumours of the digits	Screening for symptoms and visual inspection	Every visit	All ages, clinical suspicion	Moderate (Age, weak)	7.12 & 9.12 (rec. 1-3)
Juvenile myelomonocytic leukaemia	As part of normal clinical routine: patient history and physical examination	Every visit	<12	Moderate	7.13 & 9.13 (rec. 1-2)
Psychosocial needs	Psychosocial wellbeing and neuropsychological functioning	Every visit	All ages	Weak	7.14 & 9.14 (rec.1-3)

[a] 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 within the Core Working Group.

3. INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with an annual incidence of 1 in 2000-2500 (Uusitalo et al. 2015). Approximately half of the patients with NF1 have inherited the disorder from their parents, while the other half have acquired a de novo pathogenic variation in the *NF1* gene. NF1 can be diagnosed using the revised diagnostic criteria which include the presence of café-au-lait-macules, skinfold freckling, neurofibromas, optic pathway gliomas (OPG), Lisch nodules or choroidal abnormalities, bone dysplasia, the presence of a heterozygous pathogenic *NF1* variant and the presence of a parent with NF1 (Legius et al. 2021).

NF1 is a genetic disorder that predisposes to the development of nerve sheath tumours (Ferner 2007). These tumours are mostly benign, but have a risk of malignant transformation. They can cause significant neurological morbidity due to their size and/or location and potential encroachment on bone or surrounding soft tissue. More than 95% of the adult NF1 population presents with cutaneous neurofibromas and subcutaneous neurofibromas affect at least 20% of the NF1 population (Cannon et al. 2018). Approximately 40-60% of patients with NF1 develop plexiform neurofibromas (Mautner et al. 2008, Nguyen et al. 2011, Plotkin et al. 2012). Another common manifestation associated with NF1 is neurocognitive impairment, including attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), behavioural problems, and specific learning difficulties and learning disability (Ferner et al. 1996, Acosta et al. 2006, Hyman et al. 2006, Descheemaeker et al. 2013, Payne et al. 2019). NF1 individuals are also prone to develop generalised and neurovascular changes (including Moyamoya (Barreto-Duarte et al. 2021), renal artery stenosis (Kaas et al. 2013)), and skeletal defects such as congenital bowing of the tibia (7.2%), pseudarthrosis (2-3.6%), osteoporosis, short stature, macrocephaly, sphenoid bone dysplasia and scoliosis (Boulanger et al. 2005, Heerva et al. 2012, Monroe et al. 2017). Non-ossifying fibromas (Stewart et al. 2014, Vannelli et al. 2020) and giant cell granulomas (Friedrich et al. 2016a) occur in NF1. Although non-ossifying fibromas can be mistaken for sarcomas, they are benign, but may present with symptoms of pain and fracture.

Furthermore, NF1 individuals have an increased risk of developing a wide range of tumours such as glomus tumours of the digits, gastrointestinal stromal tumours (GISTs), phaeochromocytoma, OPGs, other low-grade (LGG) and high-grade brain or spine gliomas (HGG) (in this guideline recommendations referred to as 'non-OPG'), juvenile myelomonocytic leukaemia (JMML), and breast cancer in women younger than 50 years (Bergqvist et al. 2020). In addition, rare neuro-endocrine tumours do occur, such as carcinoids (Fernandez et al. 2021). Patients with NF1 have a high risk for nervous system malignancies which are uncommon in the general population. Some NF1-related malignancies present at younger age than in the

general population (Uusitalo et al. 2016, Lobbous et al. 2020). A majority of other NF1-related neoplasias, such as OPG, have a much better prognosis compared to sporadic cases with an often indolent disease course, although a subgroup of patients with OPG presents with progressive disease and functional impairment requiring treatment (Helfferich et al. 2016). Patients with NF1 have a 8-16% lifetime risk of developing malignant peripheral nerve sheath tumours (MPNSTs) (Evans et al. 2002, Uusitalo et al. 2016). The life expectancy of patients with NF1 is 8-15 years shorter, due to malignancies and vascular complications (Zoller et al. 1995, Rasmussen et al. 2001, Duong et al. 2011b). Although these cancers occur also in non-NF1 individuals, monitoring/surveillance and management of NF1 individuals requires specific guidance.

4. COMPOSITION OF THE GUIDELINE GROUP

The European Reference Network (ERN) GENTURIS Guideline Group for NF1 (NF1 Tumour Management Guideline Group) was established by experts in NF1 encompassing the clinical care for the wide disease spectrum as well as patient representatives. The NF1 Tumour Management Guideline Group was supported by a Core Working Group which comprised ERN GENTURIS healthcare provider members from different Member States and other experts who are recognised experts and specialised in clinical practice and/or in the diagnosis and tumour management of NF1. The Core Working Group met online monthly and drafted the guideline scope, clinical questions, recommendations and guideline document and asked feedback from the NF1 Tumour Management Guideline Group. The recommendations were finalised in a modified Delphi approach in which the Core Working Group, NF1 Tumour Management Guideline Group (including patient representatives) and additional experts participated (see chapter 8).

Approach to secure views and preference of target population

ERN GENTURIS NF1 Tumour Management Guideline Group was supported by a Patient Advisory Group of six patient representatives who have experience with NF1. One patient representative was part of the Core Working Group and present during these meetings.

Involving the patient representatives in the development of these guidelines and in the NF1 Tumour Management 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 focused outcomes are identified and prioritised

- the balance of the benefits and harms related to the intervention are 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 review the findings of the literature and recommendations.

5. CONFLICT OF INTERESTS

All members of the ERN GENTURIS NF1 Tumour Management 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, Eric Legius, Ignacio Blanco, Hector Salvador Hernandez, Rosalie Ferner, Amedeo Azizi, Enrico Opocher, Conxi Lázaro, Joan Brunet and Thorsten Rosenbaum and Rianne Oostenbrink report receipt of honoraria or consultation fees from AstraZeneca. Said Farschtschi reports receipt of consulting fees and honoraria from AstraZeneca/Alexion. Gareth Evans, and Eric Legius report receipt of honoraria or consultation fees from Springworks Therapeutics. Claas Röhl and Walter Taal report grants and research support from Novartis. Claas Röhl reports grants and research support from AstraZeneca, Roche, and Pfizer, and receipt of honoraria or consultation fees from Novartis, Pfizer, Boehringer, Ingelheim. Vera Lipkovskaya, Vanessa Martin and Ana Elisabete Pires report grant from AstraZeneca. Rosalie Ferner also reports grants and research support from AstraZeneca. Hector Salvador Hernandez reports participation on a data safety monitoring board or advisory board from AstraZeneca. Amedeo Azizi reports receipt of honoraria or consultation fees from Hofmann, LaRoche. Thomas Pletschko reports a grant from Pfizer. Eamonn Maher reports participation in a company sponsored speaker's bureau: Illumina and MSD. Thorsten Rosenbaum reports a spouse working at Lonza AG. Charlotte Carton, Eric Legius, and Rianne Oostenbrink participate in EU Patient-centric clinical trial platform (EU-PEARL). EU-PEARL has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 853966. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and EFPIA and Children's Tumor Foundation, Global Alliance for TB Drug Development non-profit organization, Springworks Therapeutics Inc.

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6. PURPOSE AND SCOPE OF THIS GUIDELINE

6.1. WHY WAS THIS GUIDELINE PRODUCED?

NF1 is a genetic disorder that predisposes to the development of both benign and malignant tumours. Although most nerve sheath tumours are benign, NF1 patients have a lifetime risk of 8-16% for developing MPNSTs. This malignancy confers a poor prognosis in NF1 patients and a low 5-year overall survival rate. On the other hand, benign peripheral nerve sheath tumours can cause significant neurological morbidity due to their size and/or location.

Besides the risk for developing MPNSTs, NF1 individuals are at risk for developing several types of cancers. Although these cancers occur also in non-NF1 individuals, some malignant tumours may occur with higher incidence and have an early onset in NF1 patients. As a consequence, monitoring/surveillance and management of NF1 individuals requires specific guidance adapted to the NF1 specific risks and natural history.

Therefore, this guideline aims specifically to integrate available information to assist healthcare professionals in evidence-based surveillance of individuals with a confirmed germline pathogenic variant in the *NF1* gene. It addresses surveillance for the different tumour types associated with NF1, offers guidance on the imaging modality that should be used for surveillance, on the age at which to start surveillance for each tumour type, and on the interval of subsequent monitoring if applicable. Moreover, when developing these guidelines, we recognised the neurocognitive deficits and psychosocial needs associated with NF1 and included specific approaches/guidelines required for NF1 patients.

The scope of this guideline was set to assess what is currently known about the efficacy, frequency and potential methods for surveillance for the different tumour types in NF1.

6.2. WHO IS THE GUIDELINE FOR?

This guideline is intended to address tumour surveillance of individuals with NF1 and has been elaborated by members of ERN GENTURIS. The guideline is meant for clinicians in many fields of medicine, for patients and to inform on potential risks of developing tumours in NF1 and to raise awareness to facilitate early detection. However, given the low prevalence of the condition, its potential manifestations and low prevalence of some complications, decisions about management should be taken/discussed with NF1 experts and multidisciplinary teams.

The guideline aims to summarise the optimal approach for surveillance and management of NF1 related tumours. The guideline is meant for member states of the EU as they reflect the current standard of care for NF1 in Europe. They are not prescriptive and may be adjusted to the available resources in the local treatment centre. They could also be used in other countries. Recommendations are adapted to local/national differences within EU countries, if relevant.

6.3. WHAT IS THE GUIDELINE ABOUT?

6.3.1 SCOPE

The scope of this guideline is surveillance, follow-up and management of tumours in people with neurofibromatosis type 1.

NF1 as a cancer syndrome predisposes the affected individuals to several types of cancers. Tumours of central and peripheral nervous system are most characteristic for NF1 while breast cancer, GIST, glomus tumours of the digits, phaeochromocytoma, and JMML can also be considered as NF1-related neoplasias. In addition, there are increased standardised incidence ratios (SIR) for several types of other malignancies, such as rhabdomyosarcoma, thyroid, lung and ovarian carcinomas, and melanoma in NF1 (Seminog et al. 2013, Uusitalo et al. 2016). This guideline is however committed to tumours with highest risk associated with NF1, namely tumours of nervous system, breast cancer, GIST, glomus tumours of the digits, phaeochromocytoma, and JMML.

CLINICAL SCOPE

NF1 is a multi-organ disease, with variable expression and manifestations presenting at different ages (Ferner 2007). Although NF1 is a condition that presents as a continuum from early childhood through adulthood and advanced age, local organisation of care is often age-specific. Children with NF1 will be managed mostly by paediatricians, paediatric neurologists or paediatric oncologists (Miller et al. 2019); for adults this likely to be neurologists, clinical geneticists or dermatologists amongst others (Hirbe et al. 2014, Stewart et al. 2018). Transition of care from childhood to adulthood is not always formalised, but the need to have a formal pathway is recognised (Rietman et al. 2018) .

Although in general the occurrence of manifestations in NF1 seems unpredictable, some pathogenic variants in the *NF1* gene have been identified that are associated with prognosis. A 3-bp in-frame deletion is correlated with a particular clinical phenotype without cutaneous neurofibromas or plexiform neurofibromas (Upadhyaya et al. 2007). Microdeletions of the *NF1* gene and flanking regions have been associated with a more severe phenotype such as increased tumour burden or tumour growth (Well et al. 2021). The loss of *SUZ12* (tumour suppressor gene), for instance, potentiates the development of cancer in these patients (De Raedt et al. 2014). In addition, missense mutations in the *NF1* region affecting amino acids 844-848 confer a higher risk of developing malignancies compared with the general NF1-affected population (Koczkowska et al. 2018). Also individuals with NF1 and a high internal tumour load or an atypical neurofibromatous neoplasm with uncertain biologic potential (ANNUBP) have a higher risk for MPNST (Higham et al. 2018), as well as individuals with NF1 and a family history of MPNST. These genetic risk profiles should be considered to help identify patients with increased risks for the development of malignancies in NF1, and may be referred to in several recommendations in this guideline.

Similar to other lifelong conditions, the impact of NF1 on quality of life and mental health is large (Cohen et al. 2015, Vranceanu et al. 2015, Ferner et al. 2017, Gutmann et al. 2017, Lai et al. 2019, Hamoy-Jimenez et al. 2020). It may be related to specific tumour-related issues but also to the fear of increased tumour burden or malignancy risk and its many interventions (Granström et al. 2012, Smith et al. 2013, Rietman et al. 2018, Bellampalli et al. 2019). The psychosocial effects are not determined by the specific tumour type or diagnosis per se; given the paucity of NF1-specific research on psychosocial effects and interventions, recommendations in this area are proposed in a general separate paragraph rather than addressed to in the specific tumour sections.

6.3.2 Health Questions

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

- In people with NF1, what clinical screening is beneficial for detecting tumours? What, when and how often?
- In people with NF1, what imaging screening (and surveillance?) is useful for detecting tumours?
- If a specific tumour is diagnosed, is the indication for treatment or surveillance in NF1 different from the general population?
- What is the method and interval of surveillance? What is the indication for treatment in NF1?
- Is treatment different in NF1? If YES , what is the NF1-specific treatment?
- What type of psychosocial support do people with NF1 benefit from? What are the issues in living with uncertainty of developing a tumour or in the management of a diagnosed tumour?

The following tumour types were reviewed individually: OPG, other low- and high grade brain or spine glioma (in the guideline referred to as 'non-OPG'), plexiform neurofibroma, MPNST and ANNUBP, orbital & periorbital plexiform neurofibroma, cutaneous neurofibroma, GIST, phaeochromocytoma and paraganglioma, breast cancer, glomus tumours of the digits and JMML.

6.3.3 Population

The guideline applies to all individuals with NF1. Where appropriate we adapted recommendations to different age groups, types of pathogenic variants in *NF1* or to pre-existing medical history that might influence risks for different tumour types in NF1.

Given particular age-dependent risks, specific recommendations for children or adults may appear in the guideline. Next, evidence for age specific recommendations is based on the underlying patient populations in studies, rather than on a clearly defined threshold. We will use term 'children' or 'childhood' for ages 0-16 years and 'adults' or 'adulthood' for ages of 18 and older, with a variable transition from child to adulthood between 16-18 years as applicable for local health care settings.

6.3.4 Care setting

This guideline is intended to address tumour surveillance of individuals with NF1 and has been elaborated by members of the ERN for GENTURIS. The guideline is meant for clinicians in many fields of medicine and patients to inform on potential risks of developing tumours in NF1 and to raise awareness for early detection. However, given the low prevalence of the condition and its rare, potential manifestations, decisions about management should be taken/discussed with NF1 experts and multidisciplinary team.

The guideline aims to summarise the optimal approach for surveillance and management of NF1 related tumours. The guideline is meant for member states of the EU as they reflect the current standard of care for NF1 in Europe. They are not prescriptive and may be adjusted to the available resources in the local treatment centre. They could also be used in other countries. Recommendations are adapted to local/national differences within EU countries, if relevant.

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. A more fragmented, but rather more tangible approach will be to disseminate this guideline via professional and patient societies.

6.3.5 Epidemiology & Aetiology

Epidemiology:

NF1 (Mendelian Inheritance in Man, 162200) is a cancer predisposition syndrome with an annual incidence of 1:2000 as reported in Finland and a prevalence of 1:2000–4000 (Evans et al. 2010, Uusitalo et al. 2015, Kallionpaa et al. 2018). Patients with NF1 are predisposed to develop benign as well as malignant tumours. The overall lifetime risk of any cancer was 59.6% in NF1 cases compared with 30.8% in the general Finnish population (Uusitalo et al. 2016). More than 95% of the adult NF1 population presents with cutaneous neurofibroma. NF1-associated nervous system malignancies such as MPNSTs and gliomas are uncommon in the general population (Seminog et al. 2013, Uusitalo et al. 2016). Central nervous system (CNS) tumours have been reported in approximately 20% of patients with NF1 and OPGs are usually detected in early childhood (Listernick et al. 1994, Mahdi et al. 2017). OPGs account for about 70% of all CNS tumours in children with NF1, with an incidence of OPG in NF1 as high as 15–20%. They usually develop before the age of eight years (Listernick et al. 2007). Other brain or spine tumours in NF1 children are less frequent, with a SIR of 59.1 (95% CI 39.3 to 89.0) (Peltonen et al. 2019). Adults with NF1 develop gliomas of the brain with a frequency of about 4% (Nix et al. 2020). The second most common brain tumour is brainstem glioma, representing about 17% of all CNS tumours (Guillamo et al. 2003, Mahdi et al. 2017). In addition to optic nerve and brain stem tumours, low-grade pilocytic astrocytomas and HGG occur also in other locations of the CNS in NF1 (Mahdi et al. 2020, Packer et al. 2020). Non-CNS NF1 tumours include MPNST, which is an aggressive tumour and accounts for 38–45% of the cancer deaths of all NF1 patients (Evans et al. 2011, Uusitalo et al. 2016). MPNST in the general population is a rare tumour with a median age at

diagnosis of approximately 43 years (age range of 5–81). The lifetime risk of developing MPNSTs in NF1 amounts to 8-16% (Evans et al. 2002, Uusitalo et al. 2016, Watson et al. 2017). Although MPNST may develop at any age, it is usually diagnosed between the age of 20-40 years and the cumulative risk of an MPNST by age 20 years is 2.7% (95% CI 1.4% to 5.3%) (Ducatman et al. 1986, Evans et al. 2002, Ferner et al. 2002, Evans et al. 2012, Uusitalo et al. 2016, Higham et al. 2018, Peltonen et al. 2019). These NF1-associated MPNSTs develop predominantly from pre-existing plexiform neurofibroma, but can occur de novo. Plexiform neurofibromas are visible or palpable in ~30% and internal plexiform neurofibromas are reported in 40-60% on whole body MRI (Mautner et al. 2008, Nguyen et al. 2012, Plotkin et al. 2012). They may also be located in orbita and periorbital regions (Avery et al. 2017). Plexiform neurofibromas are considered as congenital tumours which usually show the highest growth potential during early childhood, slowing down in adolescence, and growing slowly in adulthood.

NF1 patients are also at increased risk for developing other tumours such as breast cancer (Uusitalo et al. 2017), phaeochromocytoma and paraganglioma (Gruber et al. 2017), GISTs (Nishida et al. 2016), neuroendocrine tumours of the intestine (duodenal carcinoids), rhabdomyosarcoma, glomus tumours of the digits (Brems et al. 2009) and JMML (Niemeyer et al. 2019). The cumulative risk for breast cancer in NF1 patients by the age of 40 years is 4.7 % which is over 10 times that of the general population (Uusitalo et al. 2017). The risk for a second breast cancer in NF1 patients is 26% during the first 20 years after the first breast cancer (Evans et al. 2020b, Evans et al. 2020a). Phaeochromocytoma and paraganglioma are also associated with NF1, with a reported prevalence of approximately 3%, which is higher than in the general population; and is mainly a concern in adulthood (Gruber et al. 2017). The reported prevalence of NF1-GIST amounts to 6-7% and 1-2% of all GISTs are NF1-GISTs (Zoller et al. 1997, Nishida et al. 2016). However, this could be an underestimation since the diagnosis and registration of small and asymptomatic GISTs may be incomplete and some autopsy studies showed that in one of three NF1 patients GISTs were present (Andersson et al. 2005). In contrast to the sporadic GISTs, the NF1-GISTs often occur in younger patients (mean age 52.8 years). Up to 5% of adult NF1 patients were estimated to be affected with glomus tumours of the fingers (Stewart et al. 2010). Harrison et al. demonstrated that 29% of all patients with glomus tumours were diagnosed with NF1 (Harrison et al. 2013); thus, NF1-associated glomus tumours are more common than previously suspected. The estimated overall annual incidence of JMML in NF1 is 1.2 per million children aged 0–11 with 95% of all cases diagnosed before the age of 6 years (Niemeyer et al. 2008, Proytcheva 2011). Several studies support the over-representation of NF1 patients with Chronic Myelomonocytic Leukaemia

(CMML), with an estimated 200-fold increase in incidence of CMML compared to the general population (Bader et al. 1977, Stiller et al. 1994, Niemeyer et al. 1997).

Aetiology:

The *NF1* gene is localised on chromosome 17, it encompasses 61 exons and encodes for the large protein neurofibromin (2818 amino acids) (Viskochil et al. 1990, M. R. Wallace et al. 1990). All pathogenic alterations of the *NF1* gene inactivate neurofibromin. Most pathogenic alterations of the *NF1* gene are caused by small variations in the *NF1* gene (base substitutions, small deletions, insertions or duplications). A large deletion encompassing in the *NF1* gene and neighbouring genes (so-called '*NF1* microdeletion') is observed in 5-10% of NF1 patients (Messiaen et al. 2000, Wimmer et al. 2011, Vogt et al. 2014, Kehrer-Sawatzki et al. 2017). *NF1* is a tumour suppressor gene following the Knudson two-hit hypothesis (Legius et al. 1993). The first hit is a germline inactivation of *NF1*. The second hit (intragenic *NF1* pathogenic variation or loss of heterozygosity) causes the complete inactivation of neurofibromin, which can lead to the unregulated proliferation of the affected cells. A biallelic inactivation of *NF1* has been identified in both NF1-related tumours and in non-tumour manifestations such as café-au-lait-macules s and pseudarthrosis tissue (Stevenson et al. 2006, Maertens et al. 2007, De Schepper et al. 2008, Sant et al. 2015, Brekelmans et al. 2019).

Neurofibromin, the protein encoded by *NF1*, is a negative regulator of rat sarcoma virus (RAS) (Bollag et al. 1996). The activation of RAS will activate the downstream mitogen-activated protein kinase (MAPK) pathway involved in cell proliferation and differentiation (Simanshu et al. 2017). Neurofibromin can bind to RAS and stimulates this intrinsic guanosine triphosphatase activity, which in turn inactivates RAS signalling. Loss of function of neurofibromin results in the loss of inactivation of RAS and causes an increased signalling through the RAS-MAPK pathway (Lock et al. 2015). The biallelic loss of *NF1* is required to initiate the development of NF1-related tumours such as neurofibromas, glomus tumours of the digits, GISTs, phaeochromocytoma, and gliomas. However, the abundance of other regulatory systems will limit the growth of these tumours by inducing the process of cell senescence and thereby inhibit further progression (Lock et al. 2015). When sufficient additional alterations have been accumulated, plexiform neurofibromas could undergo a transformation to MPNSTs (Brems et al. 2009, Beert et al. 2011). Sometimes these lesions pass through an identifiable intermediate stage called ANNUBP (Miettinen et al. 2017). A comparable process of accumulation of additional genetic abnormalities has been reported for the transition of LGG to HGG (D'Angelo et al. 2019).

NF1 is characterised by a variable expression between patients and even between affected members of the same family. In approximately 10% of the patients with NF1 there is a genotype-phenotype association. For the other 90%, no predictions on the progression of the disease can be made based on the pathogenic *NF1* alterations. A number of patients fulfilling the revised diagnostic criteria are misdiagnosed with NF1, while having Legius syndrome, NF1 mosaicism, Noonan syndrome with multiple lentigines or constitutive mismatch repair deficiency due to similar, overlapping phenotypes (see table) (Digilio et al. 2002, Legius et al. 2002, Maertens et al. 2007, Pandit et al. 2007, Brems et al. 2013, Suerink et al. 2019, Denayer et al. 2020, Koczkowska et al. 2020). Some of these disorders also predispose the patients to malignancies, but with different risk requiring different management strategies (Kratz et al. 2011, Villani et al. 2017, Marwaha et al. 2018, Hagizawa et al. 2020, Aronson et al. 2022 Apr). This should be considered in NF1-like presentations that are not confirmed genetically. Although NF1 complications are relatively infrequent in mosaic or segmental NF1, plexiform neurofibromas and MPNSTs have been found in these patients and the recommendations in this guideline apply (Marwaha et al. 2018, Hagizawa et al. 2020).

Table: Conditions with a similar phenotype to NF1

Condition	Genes affected	Phenotype
NF1	*NF1*	Café-au-lait-macules, freckling, malignancies.
Legius syndrome	*SPRED1*	Café-au-lait-macules and axillary freckling; no tumoral complications.
NF1 mosaicism	*NF1*, mosaicism for the *NF1* pathogenic variation	Mild generalised NF1 phenotype, or skin manifestations / internal neurofibroma in a restricted segment of the body.
Noonan syndrome with multiple lentigines	*PTPN11, RAF1*	Lentigines which resemble small café-au-lait-macules (in paediatric patients), electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of the genitalia, retarded growth, and deafness (sensorineural).
Constitutive mismatch repair deficiency	*MLH1, MSH6, PMS2, MSH2*	Highly prone to develop childhood malignancies and 50% have multiple café-au-lait-macules.

7. KEY FINDINGS & RECOMMENDATIONS

Recommendations in this guideline are divided into 14 sections: general approach, optic pathway glioma, non-optic pathway glioma (including low and high grade brain and spine glioma) in children, non-optic pathway glioma (including low and high grade brain and spine glioma) in adults, plexiform neurofibroma, malignant peripheral nerve sheath tumour and atypical neurofibromatous neoplasm with uncertain biologic potential, orbital and periorbital plexiform neurofibroma, cutaneous neurofibroma, gastrointestinal stromal tumours, phaeochromocytoma and paraganglioma, breast cancer, glomus tumours of the digits, juvenile myelomonocytic leukaemia, and psychosocial needs.

Recommendations in this guideline address surveillance, follow-up and management of tumours in people with NF1. During the Delphi-survey we noticed that the ***definition of surveillance is not always clear*** *as it can mean to identify tumours in high-risk patients as well as to perform follow-up for individuals with tumours. We therefore decided to use the term clinical assessment or imaging screening throughout the document.* ***Clinical assessment*** *is part of long-term surveillance and includes history taking and physical examination by a qualified clinician with expertise according to the state of art.* ***Imaging screening*** *implies searching for complications that are not yet known to be present.* ***Monitoring*** *is used for complications/manifestations that are known to be present, but may have a variable course and do not need immediate treatment.*

7.1. General approach Recommendation

Recommendations		Strength
Rec. 1	Based on the risk of occurrence of tumour complications in NF1, systematic clinical assessment by NF1 experts at regular intervals is advised: - with a minimum of annually in children up to 10 years - with a minimum of once every two years in children older than 10 years - with a minimum of once every 3 years in adults. During transition from adolescence to adulthood more frequent systematic clinical assessment (than the above mentioned) may be warranted.	weak

7.2. Optic Pathway Glioma (OPG) Recommendations

Recommendations		Strength
Rec. 1	Clinical assessment for OPG should begin immediately after diagnosis or suspicion of NF1 in childhood. Baseline ophthalmology assessment should be done at presentation whatever the age	strong
Rec. 2	Clinical assessment for OPG should take the form of examination by trained paediatric ophthalmologists or neuro-ophthalmologists or equivalent with experience in the assessment of NF1 related visual changes.	strong
Rec. 3	Clinical assessment for OPG should include age-appropriate assessment of visual acuity, visual fields, pupillary testing, eye movements, and optic disc appearance.	strong
Rec. 4	Assessment of retinal nerve fibre layer and retinal ganglion cell layer by optic coherence tomography is helpful and should be conducted whenever.	moderate
Rec. 5	For children until the age of 8 years without known OPG, ophthalmological assessment (see recommendation 1-3) should be repeated at least every year (every six months if feasible).	moderate
Rec. 6	In children > 8 years without known OPG formal annual visual screening is advised until adulthood. Diagnostic evaluation by an ophthalmologist is also indicated in those with new visual symptoms.	moderate
Rec. 7	Imaging for OPG with MRI should be performed in people where ophthalmological examination is suggestive for OPG and in children older than 2 years with repeated inconclusive or unreliable ophthalmological exam, e.g. due to age or attention deficit. Abnormal, inconclusive or unreliable ophthalmological exam should be repeated within a short timeframe.	strong
Rec. 8	Any patient with NF1 diagnosed with an asymptomatic OPG should receive a referral to a unit with expertise (e.g. paediatric, ophthalmology, and/or neuro-oncology) in the monitoring and management of NF1-OPG.	moderate
Rec. 9	Any patient with NF1 diagnosed with a symptomatic OPG should receive an urgent referral to a unit with expertise (e.g. paediatric, ophthalmology, and/or neuro-oncology) in the management of NF1-OPG.	strong

7.3. Non-optic pathway glioma (non-OPG: low or high grade brain or spine glioma) in Children Recommendations

Recommendations		Strength
Rec. 1	Families with children with NF1 should be educated about possible symptoms and signs of brain tumours.	moderate
Rec. 2	Clinical assessment should take the form of patient history taking and examination for signs of brain tumours (amongst others new onset or change in seizures, unusual or concerning headache, endocrine problems related to hypothalamic dysfunction, focal neurological deficits, neuropsychological deficits) and should be repeated at every clinical visit from diagnosis.	moderate
Rec. 3	Routine diagnostic imaging screening for non-OPG, in children who are well (see previous recommendation), is not indicated. However, in a child with clinical concern for a brain tumour, e.g. in the presence of symptoms or endocrine dysfunction, then investigative imaging should be recommended.	moderate
Rec. 4	Symptomatic non-OPG in children with NF1 should be treated by the same care pathway as sporadic non-OPG in children without NF1. A multidisciplinary team should guide on appropriate therapeutic agents in the setting of NF1. Radiotherapy should be avoided, if at all possible, and is not indicated in low-grade glioma, whilst recognising that it may be required as an important treatment option in the setting of high-grade glioma.	moderate

7.4. Non-optic pathway glioma (non-OPG: low or high grade brain or spine glioma) in Adults Recommendations

Recommendations		Strength
Rec. 1	Patients with NF1, their carers and primary care physicians should be educated about possible symptoms and signs of brain tumours in a manner appropriate to the individual patient.	moderate
Rec. 2	Clinical assessment should take the form of examination for signs of brain tumours (amongst others new onset or change in seizures, new onset, unusual or concerning headache, endocrine problems related to hypothalamic dysfunction, focal neurological deficits, neuropsychological deficits) at every clinical visit.	moderate
Rec. 3	Imaging screening for gliomas should be considered at the age of transition from childhood to adulthood for all patients with NF1 and should take the form of brain MRI with contrast. Imaging investigation should also be undertaken after new associated symptoms (amongst others new onset or change in seizures, new onset,	moderate

	unusual or concerning headache, endocrine problems related to hypothalamic dysfunction, focal neurological deficits, neuropsychological deficits) or positive physical examination findings.	
Rec. 4	Incidental detected gliomas should be followed up with imaging like sporadic incidental detected gliomas, with a first interval of 3 months, and if stable asymptomatic disease, intervals can be prolonged.	weak
Rec. 5	Non-OPG in adults with NF1 should be managed and treated through the same care pathways as sporadic non-OPG. A multidisciplinary team should guide on appropriate therapeutic agents in the setting of NF1. Radiotherapy should be avoided if at all possible, and is not indicated in low-grade glioma, whilst recognising that it may be required as an important treatment option in the setting of high-grade glioma.	strong

7.5. Plexiform neurofibroma Recommendations

Recommendations		Strength
Rec. 1	Clinical assessment should be by observation, palpation and neurological examination and should be performed by clinicians with NF1 expertise. Photography or video of the plexiform neurofibroma can be useful adjuncts.	moderate
Rec. 2	Clinical assessment for plexiform neurofibroma should start at diagnosis or birth and should be carried out at every clinical visit.	moderate
Rec. 3	Imaging by whole body MRI (WB-MRI) to monitor for plexiform neurofibromas should be performed at least at transition from childhood to adulthood to evaluate internal tumour burden as a predictor for the development of malignant peripheral nerve sheath tumour (MPNST) risk. WB-MRI assessment at higher frequency may be considered for patients at high risk for MPNST.	weak
Rec. 4	The frequency of repeat imaging should be determined on an individual basis guided by the multidisciplinary team assessment of the level of risk for the individual. Increased assessment may be considered for patients with high risk for MPNST. In absence of internal neurofibromas at WB-MRI at transition age to adulthood clinical assessment only is required.	moderate
Rec. 5	Clinical monitoring of plexiform neurofibromas should start when first detected and repeated during each visit.	moderate
Rec. 6	Symptomatic plexiform neurofibromas require increased monitoring at shorter intervals for ANNUBP/MPNST. With careful judgement, it is appropriate to use ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT (if ^{18}FDG PET MRI is not available) combined with	moderate

	clinical assessment and MRI in the diagnostic process, prior to discussing the need for biopsy.	
Rec. 7	For symptomatic plexiform neurofibroma#, surgery is the only treatment that can potentially cure the tumour. Plexiform neurofibroma surgery should be considered.	moderate
Rec. 8	If part of standard national care, MEK-inhibitors may be considered as treatment option for symptomatic plexiform neurofibroma#, and inoperable symptomatic plexiform neurofibromas.	moderate
Rec. 9	Management of plexiform neurofibroma should be decided upon and performed by a multidisciplinary team with expertise in NF1.	weak
Rec. 10	Given the burden of having a potential risk of malignancy and visible manifestation in NF1 patients with plexiform neurofibroma, people with plexiform neurofibromas should be offered psychological support in decisions of management (please see recommendations in the psychosocial needs section 7.14 & 9.14).	weak

Footnote:

symptomatic plexiform neurofibromas are: persistent pain not responsive to treatment in regional pain centre, disfigurement, functional deficit or potential deficit including neurological deficit, bladder, bowel, respiratory or swallowing problems or haemorrhage.

7.6. MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR (MPNST) AND ATYPICAL NEUROFIBROMATOUS NEOPLASM WITH UNCERTAIN BIOLOGIC POTENTIAL (ANNUBP) RECOMMENDATIONS

Recommendations		Strength
Rec. 1	The following groups of people with NF1 should be considered at high risk of MPNST: • *NF1* microdeletion affecting *SUZ12* • missense variants affecting codons 844-848 • previous atypical neurofibromatous neoplasm with uncertain biologic potential (ANNUBP) • high internal tumour load on whole body MRI (WB-MRI) or large or multiple plexiform neurofibroma in absence of WB-MRI • neurofibromatous neuropathy • previous radiotherapy • a relative with NF1 and MPNST	strong
Rec. 2	Clinical assessment for MPNST should consist of assessing the following: • Tumour growth: a rapid increase in the size or a change in growth rate or of an existing plexiform neurofibroma.	strong

	• Pain: new and persistent, nocturnal, substantial pain / pain that is difficult to control. • New motor deficit, sensory deficit associated with any neurofibroma or peripheral nerve. This includes bladder function, bowel disturbance, swallowing problems and breathing difficulty. • Tumour consistency: development of hard nodule in a previously soft plexiform neurofibroma. People with NF1 and any of the above should be investigated for MPNST.	
Rec. 3	When clinical signs and symptoms point towards malignancy (suspicious tumours), investigation should begin with regional MRI. Prior to surgery, MRI should be carried out and ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT (if ^{18}FDG PET MRI is not available) undertaken, using visual assessment and semiquantitative assessments with a cut-off standardised uptake value.	moderate
Rec. 4	In case of a suspected ANNUBP or MPNST, primary resection is recommended if it is safe and feasible. Otherwise, radiologically (preferably ^{18}FDG PET MRI) guided diagnostic biopsy should be performed. This biopsy should be taken at the discretion of a (sarcoma) multidisciplinary team, as tumours can be heterogeneous, with the potential for a false negative result by missing malignant parts of the tumour.	strong
Rec. 5	There is no place for watchful waiting in MPNST and urgent surgical resection should be the mainstay for treatment (if possible), with post-operative assessment for recurrence.	strong
Rec. 6	Treatment decisions, on initial surgery and/or (neo)adjuvant chemo- or radiotherapy should be guided by an experienced multidisciplinary team.	moderate
Rec. 7	If a diagnosis of ANNUBP is proven by biopsy then surgery should be the primary treatment option, if this is possible with acceptable morbidity.	strong
Rec. 8	If an ANNUBP cannot be resected with acceptable morbidity, initial screening with MRI should be conducted at least every 6 months. In case of tumour growth or increase in symptoms, screening should include ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT (if ^{18}FDG PET MRI is not available). After an initial clinical assessment, the follow-up interval should be determined by the characteristics of the tumour.	moderate

7.7. Orbital & Periorbital Plexiform neurofibroma Recommendations

Recommendations		Strength
Rec. 1	The clinical assessment of NF1 patients suspected of having an orbital and periorbital plexiform neurofibroma, should be physical examination looking for blepharoptosis, proptosis, eyelid oedema, orbital dysplasia and/or dystopia, distortion of the (peri)orbital skeleton, pulsation of the eye, and strabismus. Clinical testing of vision and refractive error, visual field, ocular motility and alignment, and evaluation of the optic disc to exclude glaucoma or optic neuropathy should be basic steps in the examination of NF1 patients who are suspected of having an orbital and periorbital plexiform neurofibroma.	strong
Rec. 2	MRI of the brain and orbits should be performed in all children with a suspected orbital and periorbital plexiform neurofibroma. High-resolution MRI sequences with and without contrast should be acquired through the orbit, face, and cavernous sinus. Whenever possible the radiation exposure from CT scans should be avoided in all children with NF1.	strong
Rec. 3	Symptomatic clinical progression, of known orbital and periorbital plexiform neurofibromas, and new findings should be the primary indication for imaging assessment and follow-up, and this should be by MRI.	strong
Rec. 4	Given the burden of visible manifestation in NF1 patients with orbital and periorbital plexiform neurofibroma, people with orbital and periorbital plexiform neurofibroma should be offered psychological support in decisions of management (please see recommendations in the psychosocial needs section 7.14 & 9.14).	weak

7.8. Cutaneous neurofibroma Recommendations

Recommendations		Strength
Rec. 1	Clinical assessment consisting of visual inspection and palpation should begin when NF1 is diagnosed and should be repeated at every clinical visit.	strong
Rec. 2	Discomfort for the patient should be the primary indication for treatment. With regard to aesthetic considerations the impacts are unique to each individual and each health system has its own criteria and thresholds for intervention, so this should be considered on a case-by-case with discussion between the treating team and person with NF1.	weak

Rec. 3	Removal should be by laser, surgery, electrodesiccation or radiofrequency ablation. If multiple tumours are removed, histological assessment of all clinically obvious small cutaneous neurofibroma is not necessary.	moderate
Rec 4	Given the burden of the visible manifestations in NF1 with cutaneous neurofibroma, patients with cutaneous neurofibroma should be offered psychological support (please see recommendations in the psychosocial needs section 7.14 & 9.14).	weak

7.9. GASTROINTESTINAL STROMAL TUMORS (GIST) RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Investigation for GIST should only be conducted if there is clinical suspicion.	moderate
Rec. 2	Clinical suspicion should be raised in the presence of gastrointestinal discomfort, weight loss, anaemia, gastrointestinal bleeding, abdominal pain, palpable abdominal mass, or intestinal obstruction.	moderate
Rec. 3	Resection should be considered for at least large (>2cm) or symptomatic tumours as there is a risk for bleeding and rupture and risk for malignancy with metastasis.	strong
Rec. 4	People with an incidentally detected GIST that is asymptomatic AND <2 cm diameter should be monitored at least once a year with abdominal MRI (or CT abdomen if an MRI not possible), for at least 5 years, and thereafter to be performed every 2 years.	moderate

7.10. PHAEOCHROMOCYTOMA AND PARAGANGLIOMA RECOMMENDATIONS

Recommendations		Strength
Rec. 1	Routine biochemical screening for phaeochromocytoma and paraganglioma is not recommended in people with NF1 except for all women with NF1 who are contemplating pregnancy or are already pregnant.	moderate
Rec. 2	Biochemical testing for phaeochromocytoma and paraganglioma should be conducted in any person with NF1 who has raised blood pressure unexplained by other medical reason.	moderate
Rec. 3	Biochemical testing for phaeochromocytoma and paraganglioma might be considered prior to any elective surgical procedures requiring general anaesthesia in adult patients with NF1.	weak

Rec. 4	As in any phaeochromocytoma and paraganglioma predisposition syndrome surgery should be considered for symptomatic or biochemically active lesions.	strong
Rec. 5	A cortical-sparing adrenalectomy should be the preferred approach due to the risk of metachronous contralateral adrenal tumour.	moderate

7.11. Breast cancer Recommendations

Recommendations		Strength
Rec. 1	Despite there being no evidence of outcome benefits from clinical assessment, education about breast self-examination probably should be conducted as it raises awareness and engagement with clinical centres.	weak
Rec. 2	Screening with annual breast MRI should be the primary approach, mammography being second best alternative when MRI is not available. Age at commencement of screening in NF1 should begin as soon after the age of 30 years as feasible in the local health system context.	moderate
Rec. 3	Screening should continue until 50 years after which time, screening should be according to national guidelines for the general population.	moderate
Rec. 4	Risk-reducing bilateral mastectomy for woman without breast cancer should not be performed in NF1 patients unless there are substantial additional risk factors such as a family history of breast cancer that would elevate risk into a high-risk category.	moderate

7.12. Glomus tumours of the digits Recommendations

Recommendations		Strength
Rec. 1	Glomus tumours of the digits are easily missed and therefore clinical suspicion is essential to make a diagnosis of glomus tumours of the digits. Clinical diagnosis should be based on patient reported typical symptoms (see recommendation 2) and on visual examination of the nail beds and palpation.	moderate
Rec. 2	The majority of people will have at least two of the following symptoms: localised tenderness, severe paroxysmal (lancinating, similar to being hit on the nailbed) pain and sensitivity to cold. Visual inspection may show purplish discolouring of the nailbed.	moderate

Rec. 3	Glomus tumours of the digits occur mostly in adulthood, but should also be considered in children/adolescents with typical symptoms.	weak
Rec. 4	Surgical excision should be considered for painful glomus tumours of the digits.	moderate

7.13. JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML) RECOMMENDATIONS

Recommendations		Strength
Rec. 1	At this time the increased risk for JMML in NF1 is not clear, and is almost certainly <1%. As such specific clinical assessment probably should not be conducted.	moderate
Rec. 2	Observing juvenile xanthogranulomas in children with NF1 may raise awareness to actively search for other alarming signs of JMML (amongst others hepatosplenomegaly, paleness, abnormal lymph nodes), but should not be considered reason enough for extensive investigations for JMML.	weak

7.14. PSYCHOSOCIAL NEEDS RECOMMENDATIONS

Recommendations		Strength
Rec. 1	NF1 has a significant effect on psychosocial and neuropsychological functioning and impacts on quality of life. It is strongly advised to have a psychologist as a member of the multidisciplinary team, to support patients and families when making decisions about diagnosis, management and treatment.	weak
Rec. 2	Psychosocial wellbeing and neuropsychological functioning should be addressed at each clinic visit. These may include assessing e.g. anxiety and depression, coping mechanisms and patient reported outcomes.	weak
Rec. 3	The information and guidance for NF1 patients and family members should be age-appropriate and tailored to the needs of the individual, potential interventions to reduce the impact of NF1 on psychosocial functioning and quality of life should be included.	weak

8. METHODS FOR GUIDELINE DEVELOPMENT

8.1. FORMULATING AND GRADING STATEMENTS AND CONSENSUS BUILDING

Literature search

The guideline was based on an existing literature review of Bergqvist et al. (Bergqvist et al. 2020). As this review contained literature up to 2013, additional searches were performed for each section of this guideline using the following terms in Pubmed: (Neurofibromatosis Type 1[title/abstract] OR NF1 [title/abstract]) AND optic pathway glioma [title/abstract] OR non-optic glioma [title/abstract] OR malignant peripheral nerve sheath tumour [title/abstract] OR orbital plexiform neurofibroma [title/abstract] OR periorbital plexiform neurofibroma [title/abstract] OR plexiform neurofibroma [title/abstract] OR cutaneous neurofibroma [title/abstract] OR gastrointestinal stromal tumours [title/abstract] OR phaeochromocytoma [title/abstract] OR breast cancer [title/abstract] OR glomus tumours of the digits [title/abstract] OR juvenile myelomonocytic leukaemia [title/abstract]. After collecting additional references and excluding papers not relevant to surveillance, follow-up and management of tumours in people with NF1 a total of 484 published articles 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 mostly 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 follow this recommendation

- Should Probably & Should Probably Not, were taken to mean: the majority of informed people would follow this recommendation, 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 GRADE (Grading of Recommendations Assessment, Development and Evaluation).

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 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 Delphi survey

To overcome the issue of variability in recommendations for specific (national) health care settings and to account for the recommendations based on indirect (scarce) evidence, we applied a modified Delphi procedure. This is a consensus building exercise and 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. The goal is to reach consensus after several rounds of questionnaires.

Experts included in this exercise included the members the NF1 Tumour Management Guideline Group (including the Core Working Group and the Patient Advisory Group) as well as other (external) experts identified by the Guideline Group.

The survey existed of three 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 optional in a free text format. Even if consensus was met, recommendations were still modified if a higher consensus was thought achievable from written responses.

The Delphi participants were asked to indicate their expertise per tumour type and only grade the recommendations in which they had indicated expertise. All recommendations (n=70) developed by the ERN GENTURIS NF1 Tumour Management Core Working 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 but one recommendation passed the threshold for consensus in the first round.

The Core Working Group discussed the anonymised summary of comments given to all recommendations in the first round and decided to delete three recommendations, add four recommendations (general approach and psychological recommendations in plexiform neurofibroma, orbital and periorbital plexiform neurofibroma and cutaneous neurofibroma) and adjust 45 recommendations for the second round. These were subjected to the experts' opinion in the second round of the survey. In the second round 49 recommendations were included for review. 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. The facilitator of the Delphi survey provided an anonymised summary of the experts' decisions from the second round as well as the reasons they provided for their judgements. The new recommendations all passed the threshold for consensus. All but one of the changed recommendations reached similar or higher percentage of agreement. However, the Core Working Group discussed the need of removing 4 recommendations and adapting 15 recommendations, which were submitted to a third round of the Delphi. All recommendations reached similar or higher percentage of agreement. As a results of the modified Delphi, 67 recommendations are included in this manuscript.

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

Name	Speciality / Role	Healthcare provider
Monique Anten, MD, PhD	Neurologist	Maastricht University Medical Center+, Maastricht, the Netherlands
Britt-Marie Anderlid, MD, PhD	Geneticist	Karolinska University Hospital, Stockholm, Sweden
Dr. Juan Luis Becerra	Neurologist	Hospital Germans Trias I Pujol, Barcelona, Spain
Anna Sophie Berghoff, MD, PhD	Oncologist	Medical University of Vienna, Vienna, Austria
Didier Bessis, MD, PhD	Dermatology	University hospital of Montpellier, Montpellier, France
Dr. Isabel Bielsa	Dermatology	Universitat Autònoma de Barcelona, Barcelona, Spain
Ana Blatnik, MD, PhD	Geneticist	University of Ljubljana, Ljubljana, Slovenia
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Judith Eelloo	NF clinical nurse specialist	Guy's and St Thomas', NHS Foundation Trust, London, United Kingdom
Dr. Shruti Garg	(child) Psychiatrist	The University of Manchester, NHS Foundation Trust Manchester, United Kingdom
Prof. Chris Hammond	Ophthalmologist	Kings College Hospital, London, United Kingdom
Dr. Helen Hanson	Geneticist	St George's University Hospitals, NHS Foundation Trust, London, United Kingdom
Arvid Heiberg, MD, PhD	Geneticist	Oslo University Hospital, Oslo, Norway
Pablo Hernaiz Driever, MD, PhD	Neuro-oncologist, paediatric	Charité - Universitätsmedizin, Berlin, Germany
Jose Hinojosa, MD, PhD	Neurosurgeon, paediatric	Sant Joan de Deu hospital, Barcelona, Spain
Prof. dr. Daphne Hompes	Surgeon	UZ Leuven, Leuven, Belgium
Dr. Christina Hostalot	Neurosurgeon	Hospital Germans Trias I Pujol, Barcelona, Spain
Katja Hukkinen, MD, PhD	Radiologist	The University of Helsinki, Helsinki, Finland.
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Dr. Nicole Naus	Ophthalmologist	Erasmus MC, Rotterdam, the Netherlands
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Prof. Juha Peltonen, MD, PhD		University of Turku, Turku, Finland
Assoc. Prof. Dr. Berthold Pemp	(neuro-) Ophthalmologist	Medical University of Vienna, Vienna, Austria
Dr. Hannes Platzgummer		Medical University of Vienna, Vienna, Austria
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8.2. 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.

In addition, the NF1 Tumour Management Guideline Group engaged with EClinicalMedicine as an independent review of the guideline.

ERN GENTURIS first published the Guideline for the surveillance, follow-up and management of tumours in people with NF1 on 16 January 2022.

8.3. Timeline and procedure for updating the guideline

Any new evidence that has been published will be updated by 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.

8.4. Funding and Financial support

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9. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS

9.1. SUMMARY OF EVIDENCE AND GUIDELINE RECOMMENDATIONS FOR GENERAL APPROACH

NF1 is a tumour suppressor disease and the potential complications are manifold and vary in their severity. Furthermore, the timing of the clinical manifestations is unpredictable for a specific patient. A limited number of NF1 genotype–phenotype correlations are known and can be clinically useful in some cases to guide management (Upadhyaya et al. 2007, Mautner et al. 2010, Koczkowska et al. 2020). However, it is notable that the spectrum of severity of the NF1 phenotype varies, even within a family.

Although in retrospect a majority of individuals with NF1 have been managed well through the support of their local clinicians, community services and family, it is essential that complications or unusual NF1 phenotypes, disease manifestations that are potentially life threatening or cause significant morbidity are detected and managed. Therefore, we advise that all NF1 patients require a multidisciplinary approach, in a national centre with NF1 expertise in order to optimise outcomes (Ferner et al. 2007, Stewart et al. 2018, Ahlawat et al. 2020). Key players in expert centres (although not complete) are (paediatric) neurologist, paediatrician, ophthalmologist, (neuro-)oncologist, geneticist, and other subspecialty experts for specific manifestations. Patient education should focus on signs and symptoms suggestive of MPNST, including persistent pain, rapid growth, hard texture or new unexplained impaired function. Patients should be alert to the possible symptoms of brain and spine tumours (in the guideline referred to as non-OPG), and phaeochromocytoma and paraganglioma (Stewart et al. 2018). In addition, clinicians should ensure continuity of care during transition from childhood to adulthood and be mindful of different clinical needs and manifestations (Rietman et al. 2018).

Recommendations	Strength
Based on the risk of occurrence of tumour complications in NF1, systematic clinical assessment by NF1 experts at regular intervals is advised: - with a minimum of annually in children up to 10 years - with a minimum of once every two years in children older than 10 years - with a minimum of once every 3 years in adults. During transition from adolescence to adulthood more frequent systematic clinical assessment (than the above mentioned) may be warranted.	weak

9.2. Summary of evidence and guideline recommendations for optic pathway glioma (OPG)

In OPG the tumoural extension may be uni- or bilateral and may be restricted to the optic nerves (=pure optic nerve glioma), the optic chiasm or the optic tracts or involve some or all of these structures at the same time or impact on the hypothalamus (Taylor et al. 2008). The course of NF1-associated OPGs are more favourable than that of sporadic cases. Diagnosis is most often neuroradiological. If biopsied, the histological evaluation most often reveals pilocytic astrocytoma (Campen et al. 2018, D'Angelo et al. 2019, Packer et al. 2020).

Approximately 40-50% of children with OPG develop symptoms due to their OPG, whereas the remaining patients stay clinically silent despite presence of a tumour of the optic system (Guillamo et al. 2003, Friedrich et al. 2016b). Symptoms may include visual signs such as reduced visual acuity, squint, abnormal visual behaviour, proptosis, papilledema and nystagmus as well as other symptoms such as neurological or endocrine manifestations or symptoms of raised intracranial pressure (Azizi et al. 2021).

About 20% of all children with an OPG will undergo oncological treatment (Nicolin et al. 2009, Friedrich et al. 2016b). Reasons for treatment include either ophthalmologic symptoms such as documented deterioration of vision, poor visual acuity (VA) with "threat to vision" or proptosis / exophthalmos or progression of tumour size of more than 25% (Gnekow et al. 2019). Progression of tumour size is measured as change in tumour volume from annotated images (Gnekow et al. 2019).

Standard of care in the treatment of NF1 associated OPG is chemotherapy with carboplatin and vincristine (Packer et al. 1997, Gnekow et al. 2004). An alternative drug treatment is weekly vinblastine (Lassaletta et al. 2016). Recently treatment with MEK inhibitor selumetinib has shown to be effective in progressive NF1 associated LGG including OPG (Fangusaro et al. 2019). Radiological progression free survival with standard chemotherapy is higher than in children with sporadic OPG. Functional outcome does not correlate with radiological response, i.e. a tumour might shrink while vision is deteriorating or remain stable while VA improves (Mitchell et al. 2001, Fisher et al. 2012, Kelly et al. 2012, Kalin-Hajdu et al. 2014, Azizi et al. 2021). Overall, more than a quarter of patients show improvement of vision, more than a third remain stable, while the remaining show deterioration of vision despite therapy (Mitchell et al. 2001, Fisher et al. 2012, Kelly et al. 2012, Kalin-Hajdu et al. 2014, Azizi et al. 2021).

Risk factors for a poor functional outcome have not prospectively been assessed. According to analysis of historical data, following factors have been associated with poor outcome (yet concordance between studies is limited): extension to the optic tracts, young age, optic atrophy, multiple visual symptoms at diagnosis and

female sex (Balcer et al. 2001, Dalla Via et al. 2007, Fisher et al. 2012, Diggs-Andrews et al. 2014, Azizi et al. 2021).

The knowledge about genotype-phenotype correlations is limited and results are yet conflicting (Sharif et al. 2011, Bolcekova et al. 2013, Xu et al. 2018, Melloni et al. 2019, Fisher et al. 2021).

Regular ophthalmological examinations are performed to detect signs of OPG and evaluate visual function (Cassiman et al. 2013). VA is the most reliable and reproducible measurement and is seen as parameter of choice for visual assessment over time (Cassiman et al. 2013, Fisher et al. 2013). Age-appropriate testing methods as well as age over spanning methods (such as Teller Acuity Cards 2) should be used for the quantitative evaluation of VA (Cassiman et al. 2013, Fisher et al. 2013). Factors such as visual maturation must be taken into account when interpreting VA. OCT has emerged to detect changes in retinal nerve fibre layer and retinal ganglion cell layer thickness and as these have been associated with reduction in VA (de Blank et al. 2017). OCT may be considered as a potential biomarker for visual dys-function. Yet, OCT is not readily available yet, is not consistent across different machines and requires optimal cooperation (for fixed devices) or even sometimes sedation (for handheld devices) in young children.

MRI of the brain is clearly indicated in children with visual symptoms, but also in case of endocrine dysfunction (e.g. precocious puberty, diencephalic syndrome) (Listernick et al. 2007, de Blank et al. 2017). In case when valid ophthalmologic assessment (in order to achieve measurable and quantifiable VA) is not feasible (e.g. due to lacking compliance of young children with NF1 and attention deficit) the presence of OPG has to be excluded by MRI (Listernick et al. 2007, de Blank et al. 2017). At the present time specific imaging sequence parameters with regard to NF1 brain imaging have not been published. However, guidance can be sought by combining recommended SIOPE brain imaging guidelines (Avula et al. 2021) and RAPNO guidance for imaging of low-grade tumours, including imaging of the optic tract (Fangusaro et al. 2020) as discussed further in the document.

There is ongoing debate on the role of screening MRI. Generally, present guidelines do not recommend routine MRI screening (Caen et al. 2015, Cassina et al. 2019, Bergqvist et al. 2020). In a French series there was no clinical benefit in screening by MRI, as only symptomatic children were treated (Blanchard et al. 2016). Yet, other centres report that early detection of OPG by MRI may prevent or minimise visual damage (Blazo et al. 2004, Prada et al. 2015). Furthermore, novel MRI sequences like diffusion tensor imaging and volumetric analysis of the optic pathway may play a role in the future to predict visual outcome or future vision loss (de Blank et al. 2017). A recent multicentre analysis of risk factors associated with visual outcome in NF1-OPG

suggests MRI screening as a factor associated with a favourable visual outcome (Azizi et al. 2021). This may be explained by a closer monitoring and shorter delay before initiation of treatment and a selection of more benign cases that would not have been identified by ophthalmological screening. The decisions about more frequent surveillance or the use of diagnostic imaging in asymptomatic children are best made by clinicians and ophthalmologists following these patients (Miller et al. 2019).

Late initiation of treatment, i.e. presence of multiple and severe visual symptoms and damage to the optic nerve (visualised by optic atrophy) seems to decrease the possibility to salvage vision (Azizi et al. 2021). It is key to identify patients at risk for visual deterioration in order to spare patients with low visual risk the possible toxicity of chemotherapy but allow the earliest possible treatment initiation in patients at high risk of vision loss.

Recommendations		Strength
Rec. 1	Clinical assessment for OPG should begin immediately after diagnosis or suspicion of NF1 in childhood. Baseline ophthalmology assessment should be done at presentation whatever the age	strong
Rec. 2	Clinical assessment for OPG should take the form of examination by trained paediatric ophthalmologists or neuro-ophthalmologists or equivalent with experience in the assessment of NF1 related visual changes.	strong
Rec. 3	Clinical assessment for OPG should include age-appropriate assessment of visual acuity, visual fields, pupillary testing, eye movements, and optic disc appearance.	strong
Rec. 4	Assessment of retinal nerve fibre layer and retinal ganglion cell layer by optic coherence tomography is helpful and should be conducted whenever.	moderate
Rec. 5	For children until the age of 8 years without known OPG, ophthalmological assessment (see recommendation 1-3) should be repeated at least every year (every six months if feasible).	moderate
Rec. 6	In children > 8 years without known OPG formal annual visual screening is advised until adulthood. Diagnostic evaluation by an ophthalmologist is also indicated in those with new visual symptoms.	moderate
Rec. 7	Imaging for OPG with MRI should be performed in people where ophthalmological examination is suggestive for OPG and in children older than 2 years with repeated inconclusive or unreliable ophthalmological exam, e.g. due to age or attention deficit. Abnormal, inconclusive or unreliable ophthalmological exam should be repeated within a short timeframe.	strong

Rec. 8	Any patient with NF1 diagnosed with an asymptomatic OPG should receive a referral to a unit with expertise (e.g. paediatric, ophthalmology, and/or neuro-oncology) in the monitoring and management of NF1-OPG.	moderate
Rec. 9	Any patient with NF1 diagnosed with a symptomatic OPG should receive an urgent referral to a unit with expertise (e.g. paediatric, ophthalmology, and/or neuro-oncology) in the management of NF1-OPG.	strong

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **OPG**?	Ophthalmological screening (by trained paediatric ophthalmologists / optometrists) is uniformly accepted in order to identify ophthalmological signs of OPG, as (slow) changes in VA - especially in young children - may remain unrecognised until severe symptoms occur. The interval of screening and the methodology remain under debate. Recent publications suggest 6-12 monthly ophthalmological examinations until the age of 6 years (Caen et al. 2015) or annually until 8 years (de Blank et al. 2017). This should be followed by yearly or every 2-year screening until adulthood (Caen et al. 2015, de Blank et al. 2017).
What methods of clinical surveillance?	The Response Evaluation in Neurofibromatosis and Schwannomatosis guidelines for unifying ophthalmological assessment in children with OPG (Fisher et al. 2013, de Blank et al. 2017, Bergqvist et al. 2020). VA assessment and fundoscopy (e.g. optic disc pallor) are the most feasible and comparable and should be considered the minimum. VA should be measured with consistent quantitative testing methods, proposing Teller acuity cards and HOTV cards (or comparable) as soon as feasible (i.e. age appropriate) (Avery et al. 2011a, Cassiman et al. 2013, Evans et al. 2017). VA should be reported in logarithm of the minimum angle of resolution (Fisher et al. 2013). Despite limited by compliance with testing methods, and lack of objective measures, visual fields assessment represents another important aspect of the overall visual function assessment in children with OPG and should be attempted when feasible, especially in children older than 5 years of age (Fisher et al. 2013). OCT has proven to be an important tool in the evaluation of NF1-OPG (Avery et al. 2011b, Fard et al. 2013, Avery et al. 2015, de Blank et al. 2017). Retinal nerve fibre layer as objective measurement was reported to correlate with VA (Fard et al. 2013, de Blank et al. 2017, Parrozzani et al. 2018, Cassina et al. 2019). Whereas some groups report feasibility even in very young children during routine ophthalmological examinations (Cassina et al. 2019), sedation is often necessary in this population (Avery et al. 2015). Retinal nerve fibre layer and retinal ganglion cell layer measurement by OCT should be attempted, whenever feasible and available without the use of sedation (Gu et al. 2014, Hepokur et al. 2018, Sahinoglu-Keskek et al. 2018, Cassina et al. 2019). It may play a future role in the early detection of OPG in children with NF1 (Vagge et al. 2020).

When should surveillance start?	Immediately after NF1 diagnosis. Surveillance prior to diagnosis in young children with suspected NF1 not yet fulfilling the revised criteria (Legius et al. 2021) should also be considered (Miller et al. 2019).
How often should surveillance be repeated?	All children diagnosed with NF1 should undergo ophthalmological screening by trained paediatric ophthalmologists / optometrists /neuro-ophthalmologists. Recent publications suggest 6 monthly ophthalmological examinations until at least the age of 6 years (Caen et al. 2015) or annually until 8 years (de Blank et al. 2017). This should be followed by yearly or every 2 years screening until adulthood (Caen et al. 2015, de Blank et al. 2017). Ophthalmological exam should be repeated or performed more often in case of concern or doubt (Miller et al. 2019). As OPG may (and be it rarely) become symptomatic after the age of 8 years and rarely even progress into adulthood, the screening should be performed until adulthood. Thereafter only in case of visual symptoms (Hernáiz Driever et al. 2010, Friedrich et al. 2016b).
Q.2 In people with NF1, what imaging surveillance is beneficial for detecting **OPG**?	Systematic screening for OPG by brain MRI in young children with NF1 without symptoms is controversial. Generally, present guidelines do not recommend routine MRI screening (Caen et al. 2015, Cassina et al. 2019, Bergqvist et al. 2020). In a French and an Italian series there was no clinical benefit in screening by MRI, as only symptomatic children were treated (Blanchard et al. 2016, Trevisson et al. 2017). Yet, other centres report that early detection of OPG by MRI may prevent or minimise visual damage (Blazo et al. 2004, Prada et al. 2015). A recent multicentre analysis of risk factors associated with visual outcome in NF1-OPG suggests MRI screening as factor associated with a favourable visual outcome (Azizi et al. 2021). This may be explained by a closer monitoring and shorter delay before initiation of treatment, but also with a selection of asymptomatic children who might develop an indolent OPG. Clear indications for MRI are (Listernick et al. 2007): - ophthalmological examination suggestive for symptomatic OPG including VA below age-based norms, visual field loss, optic atrophy, optic nerve swelling, proptosis, squint, etc. - inconclusive or unreliable ophthalmological exam in young children (e.g. due to age or attention deficit) - an abnormal OCT does not (yet) constitute sufficient criteria for screening MRI in the absence of other visual symptoms, e.g. VA loss. The decisions about surveillance frequency, or the use of screening MRI in asymptomatic children are best made by clinicians and ophthalmologists following these patients (Miller et al. 2019) and should be weighted balancing the benefit of an early diagnosis vs. the risk of unnecessary Investigation. Finally, there are currently no MRI specific technical recommendations in regards to the imaging sequences to employ in such imaging. However, guidance can be sought by combining recommended SIOPE brain imaging guidelines (Avula et al. 2021) and RAPNO guidance for imaging

	of low-grade tumours (Fangusaro et al. 2020), including imaging of the optic track as discussed below.
What modality of imaging for surveillance?	MRI of the brain should be adherent to the SIOPE MRI guidelines for imaging patients with central nervous system tumours (Avula et al. 2021). This will include T2/FLAIR and T1 with or without contrast administration and also a high resolution isotropic T1 weighted sequence to enable accurate assessment and tumour measurement if required. Full sequence parameters can be found within reference (Avula et al. 2021). When following up OPG, orbital MRI should also be employed with adherence to the RAPNO paediatric recommendations for LGG which include sequence parameters for orbital imaging (Fangusaro et al. 2020). Given the overlap between both recommendations, it is mainly the addition of fat saturated post contrast T1 weighted imaging, to the SIOPE brain imaging guidelines, that is of importance in ensuring adequate assessment of the orbits in addition to the brain.
When should imaging surveillance start?	At any age when ophthalmological exam is suggestive for an OPG or if the ophthalmological exam is not reliable in providing quantitative age-appropriate VA. (Listernick et al. 2007, Cassina et al. 2019) Centres with positive experience in early detection of NF1 associated OPG may discuss this approach with individual families (Miller et al. 2019).
How often should imaging surveillance be repeated?	There is consensus that children with newly diagnosed NF1-OPG need both ophthalmology and MRI follow-up. If an OPG is detected on the initial MRI, imaging should be repeated every 3 months for the first year, followed by every 6 months for the next two years. If the imaging and ophthalmological examination are stable, then annual imaging may be appropriate. Alterations to the above schedule can be considered based on the entire clinical picture and suspected risk of vision loss (de Blank et al. 2017). Because vision in NF1-OPGs generally is stable after 18 years of age, surveillance of known NF1-OPG may be discontinued after that age if clinically stable (de Blank et al. 2017). Baseline MRI without follow-up is of minimal value, as a negative baseline MRI does not exclude future development (Listernick et al. 2007, Cassina et al. 2019). Follow-up intervals in centres that screen by MRI vary (Blazo et al. 2004, Prada et al. 2015, Blanchard et al. 2016). Novel MRI sequences and prediction of visual outcome may change the view on MRI screening (de Blank et al. 2017).
Q3. If an **OPG** is diagnosed is the indication for monitoring different in NF1? And if yes, what is	Children with sporadic OPG present almost exclusively when they become symptomatic (i.e. without prior screening) and will therefore very likely receive treatment at diagnosis or in the first 3-6 months of follow-up therefore MRI and ophthalmological review is often required every 3 months (S. Singhal et al. 2002, Czyzyk et al. 2003, Robert-Boire et al. 2017, Hamideh et al. 2018). In patients with NF1 associated OPG the decision between treatment and observation has to be made and repeated over time. Possible risk factors for visual deterioration (e.g. young age, posterior involvement, female sex) have been described but need to be evaluated (de Blank et al. 2017, Cassina et al. 2019, Azizi et al. 2021).

content of monitoring (mode, interval).	The aim is to prevent unnecessary treatment but to initiate treatment if needed in order to prevent (further) visual deterioration. The decision is influenced by various factors including severity of visual deficit and bilateral threat to vision at presentation or during follow-up and VA changes over time. In a number of patients, the decision between treatment and observation remains difficult (de Blank et al. 2017, D. A. Walker et al. 2017). Monitoring of newly diagnosed OPG in patients with NF1 (even where there is no indication to treat) is necessary and any patient diagnosed with OPG should receive a referral to a paediatric (neuro-oncology) unit with expertise in the management of NF1-OPG. These patients should receive: - 3 monthly eye examination (Listernick et al. 2007, de Blank et al. 2017, Cassina et al. 2019) - 3 monthly MRIs for the first year after diagnosis, with increasing intervals thereafter (Listernick et al. 2007, de Blank et al. 2017, Cassina et al. 2019) - MRIs every 6 months for two years, then annually until the age of 8 (de Blank et al. 2017). Thereafter, annual eye exams until the age of 18 and annual MRIs for 3 to 5 years (if stable). If the tumour involves the chiasm and/or hypothalamus attention to auxology (i.e. growth and weight gain) and endocrine symptoms (e.g. symptoms of growth hormone excess or precocious puberty) a referral to a paediatric endocrinologist should be considered.
Q4. If an **OPG** is diagnosed, is the indication for treatment different in NF1? And if YES on, what is the indication for treatment in NF1?	No. (Gnekow et al. 2019) The decision on treatment of an OPG has to be made at an experienced centre by an multidisciplinary team taking into account clinical, ophthalmological and radiological findings. The ophthalmologic indications for treatment in NF1 are (Gnekow et al. 2019): • New onset or progressive vision loss not due to other ophthalmological causes (i.e. amblyopia, refractive error, etc) • Definitive history of loss of vision loss • Borderline vision ("Threat to vision") • Reduction of residual low-level vision/visual field • Nystagmus subsequent to visual impairment in infants (once any other cause of nystagmus is excluded) • Any visual loss in the second eye when the first eye is blind Other indications include (Gnekow et al. 2019): • New onset neurologic symptoms related to the tumour • Change in tumour volume of >25% from annotated images • diencephalic syndrome (once other causes of weight loss are excluded) The best timepoint for therapy needs yet to be determined (e.g. role of pre-emptive therapy; prevention of deterioration vs. trying to improve vision) (Azizi et al. 2021). The aim is to prevent unnecessary treatment (i.e. to treat OPG in patients where visual function and / or tumour might have remained stable) but, at the same time, not to delay treatment if needed in order to prevent

	(further) visual deterioration. Yet, in a number of patients, the decision between treatment vs. observation remains difficult (de Blank et al. 2017).
Q5. Is treatment different in NF1? And if YES, what is the NF1 specific treatment?	No, first line treatment is similarly based on systemic chemotherapy with vincristine/carboplatin combination as the current standard of care (Packer et al. 1997, Gnekow et al. 2004, Ater et al. 2016, Packer et al. 2020). Treatment is necessary in patients who develop symptomatic tumours with clinically significant growth and progressive visual loss, this is usually a small percentage of patients. Various chemotherapeutic agents have been used successfully and include carboplatin +/– vincristine (the combination being considered as standard of care), , bevacizumab alone or in combination with other chemotherapy agents (Packer et al. 1997, Walter et al. 2000, Lancaster et al. 2003, Gnekow et al. 2004, Jahraus et al. 2006, Ater et al. 2012, Lassaletta et al. 2016). Radiological progression free survival with standard chemotherapy is higher than in children with sporadic OPG. Functional outcome does not correlate with radiological response, i.e. a tumour might shrink while vision is deteriorating or remain stable while VA improves (Mitchell et al. 2001, Fisher et al. 2012, Kelly et al. 2012, Kalin-Hajdu et al. 2014, Azizi et al. 2021). Overall, more than a quarter of patients showed improved vision after therapy, more than a third remain stable, while the remaining show deterioration of vision despite therapy (Mitchell et al. 2001, Fisher et al. 2012, Kelly et al. 2012, Kalin-Hajdu et al. 2014, Azizi et al. 2021) . The emerging role of MEK inhibitors (e.g. selumetinib, trametinib) has raised interest in this NF1 population, in view of the positive results from NF1 plexiform neurofibroma and preliminary data from a phase II study in relapsed LGG including NF1-LGG (Fangusaro et al. 2019). Radiological and clinical effectiveness of MEK inhibitors compared to Carboplatin / Vincristine is currently being evaluated in a Children's Oncology Group clinical trial in newly diagnosed NF1-LGG with indication to treat. Surgery has a very limited indication in the treatment of OPG as it can lead to permanent neurological damage (Listernick et al. 2007). However, surgery can be used to remove large orbital tumours mainly for aesthetic purposes when there is no useful vision (Listernick et al. 2007) and severe proptosis. Surgical decompression of chiasmal gliomas or of a large cystic component is occasionally required especially in the context of third ventricular compression with secondary hydrocephalus. But usually a ventriculostomy or a ventricular shunt is preferred (Listernick et al. 2007). <u>Radiotherapy treatment of OPG is not recommended for children with NF1</u> due to the increased likelihood of developing secondary malignancies, either gliomas or MPNST (Sharif et al. 2006, Bhatia et al. 2019); as well as developing neurovascular complications such as Moyamoya syndrome (Ullrich et al. 2007), endocrine and neuropsychological problems (Guillamo et al. 2003, Listernick et al. 2007, Oh et al. 2011).
Q6. What psychosocial support do people with NF1 benefit from,	Survivors of childhood glioma with NF1 were more likely to report psychosocial impairments, neurocognitive deficits, and socio-economic difficulties compared with glioma survivors without NF1 (Avery et al. 2014, de Blank et al. 2020). Poorer socio-economic outcomes suggest that survivors with NF1 may have fewer resources than non-NF1 survivors or siblings. Understanding

specifically in living with the uncertainty of **OPG** or in the management of a diagnosed **OPG**?	these risks may help guide surveillance and early intervention efforts to improve outcomes in glioma survivors with NF1 (de Blank et al. 2020). Psychological functioning and quality of life is decreased in people with NF1 (Cipolletta et al. 2018), resulting in higher emotional and social stress in patients with NF1 and OPG. The time of observance and uncertainty of therapy appears to be the main burden for the families. Expert psychosocial guidance is needed to address social care needs, educational access, and employment rights. Psychological intervention is helpful to reduce anxiety and to improve self-esteem, to stabilise the family and to prepare the children for different medical assessments. During their stay at the hospital many medical assessments and procedure may be necessary. Studies show that age-appropriate preparation of children and adolescents for upcoming investigations promotes disease processing (Andrews et al. 2012, Loucas et al. 2017). Interventions, aiming at preparing children for medical procedures, can serve to facilitate coping strategies and improve long-term adjustment during specific treatments (Loucas et al. 2017, Perez et al. 2019). Through psycho-educational measures and active involvement of the children and adolescents their self-esteem can be improved. Extensive multidisciplinary intervention is needed to prepare children and adolescents for medical procedures and thereby avoid long-term consequences. At the same time self-esteem is strengthened, adherence to medical advice is enhanced, and the acquired knowledge promotes health literacy. By means of anxiety-reducing measures secondary mental illnesses can be prevented and coping strategies can be the focus. The multidisciplinary team's responsibility is to provide the best possible age-appropriate care and support for the families with age appropriate information. The inclusion of patient organisations and a psychosocial team in the hospital are key positions in supporting the families and guarantee high quality of life during and after therapy.
References used:	(Packer et al. 1997, Walter et al. 2000, Mitchell et al. 2001, S. Singhal et al. 2002, Czyzyk et al. 2003, Guillamo et al. 2003, Lancaster et al. 2003, Blazo et al. 2004, Gnekow et al. 2004, Jahraus et al. 2006, Sharif et al. 2006, Listernick et al. 2007, Ullrich et al. 2007, Hernáiz Driever et al. 2010, Avery et al. 2011a, Avery et al. 2011b, Oh et al. 2011, Andrews et al. 2012, Ater et al. 2012, Fisher et al. 2012, Kelly et al. 2012, Cassiman et al. 2013, Fard et al. 2013, Fisher et al. 2013, Avery et al. 2014, Gu et al. 2014, Kalin-Hajdu et al. 2014, Avery et al. 2015, Caen et al. 2015, Prada et al. 2015, Ater et al. 2016, Blanchard et al. 2016, Friedrich et al. 2016b, Lassaletta et al. 2016, de Blank et al. 2017, Evans et al. 2017, Loucas et al. 2017, Robert-Boire et al. 2017, Trevisson et al. 2017, D. A. Walker et al. 2017, Cipolletta et al. 2018, Hamideh et al. 2018, Hepokur et al. 2018, Parrozzani et al. 2018, Sahinoglu-Keskek et al. 2018, Bhatia et al. 2019, Cassina et al. 2019, Fangusaro et al. 2019, Gnekow et al. 2019, Miller et al. 2019, Perez et al. 2019, Bergqvist et al. 2020, de Blank et al. 2020, Fangusaro et al. 2020, Packer et al. 2020, Vagge et al. 2020, Avula et al. 2021, Azizi et al. 2021, Legius et al. 2021)

9.3. Summary of evidence and guideline Recommendations for non-Optic Pathway Glioma in Children

The age at diagnosis of non-OPG tumours (low- (LGG) and high-grade (HGG) brain and spinal glioma) in children is later than for OPGs (median age between 6-10 years, range 0.8-18 years) with no significant differences with respect to sex, location or family history (Mahdi et al. 2020). The vast majority are LGG, although other malignant tumours have been described, such as HGG of brain and spinal cord, primitive neuroectodermal tumour, or dysembryoplastic neuroepithelial tumour. At the current time there are no consistent guidelines for identifying or monitoring non-OPG tumours in patients with NF1.

Childhood NF1-related non-OPGs are primarily located in the brainstem (commonest location) basal ganglia, thalamus, and, cerebellum but also described in the cerebral hemispheres and spinal cord (Byrne et al. 2017, Peltonen et al. 2019, Mahdi et al. 2020). They can be discovered incidentally on neuroimaging studies obtained for other reasons (e.g. pre-existing OPG assessment) or due to symptomatology, such as acute (hydrocephalus) or more subtle or progressive neurological manifestations.

Non-OPGs are often seen concurrently with OPG in children (50-60%). However, unlike OPG, the incidence of symptomatic non-OPG tumours that require intervention is lower than in OPGs (25-34% at diagnosis, although be aware that this number increases because of tumour progression to 35-40%) (Mahdi et al. 2020, Santoro et al. 2020). Patients with multiple lesions tend to be younger at diagnosis and their lesions tend to progress earlier (Santoro et al. 2020).

There is a correlation between radiographic progression, clinical progression and further need for treatment. According to Mahdi et al., the average time to initial change in size on MRI was 16 months across all locations, with a range of 1–125 months. However, the majority of progressive non-OPG tumours stop growing on their own or secondary to treatment in 2-3 years, arguing that neuroimaging surveillance is unnecessary after some years of tumour stabilization (Mahdi et al. 2020).

According to Byrne et al. (Byrne et al. 2017), the requirement for surgical intervention was much higher in the cohort of patients who had a scan because of glioma-related symptoms at presentation compared to those who had an MRI for screening or other reasons (71% vs. 19%). Symptomatic reasons for surgical intervention included seizures, raised intracranial pressure, rapid increase in size of tumour, and hemiparesis. Some predictors with regard to the requirement for treatment include: symptomatic tumours at diagnosis tumour; thalamic, cerebellar and frontal location; multiple and diffuse lesions (usually related to younger patients).

Conversely, some locations are related to a much lower risk, e.g. the basal ganglia and brainstem (Byrne et al. 2017, Mahdi et al. 2020, Santoro et al. 2020).

Surgery remains the best therapeutic option in symptomatic LGG, with the aim of achieving complete resection when feasible. In those with mild symptoms or where a full resection is not feasible, a watch-and-wait approach may be appropriate. For the remaining inoperable symptomatic gliomas, standard treatment is chemotherapy. Although the role of other emerging treatments is to be considered (see OPG section). For NF1-associated malignant CNS tumours the approach should be the same as for non-NF1 malignant CNS tumours.

The overall survival of children with non-OPG tumours does not significantly differ between those with or without NF1, with a survival profile of HR 0.64, 95%CI 0.23 – 1.76 (Peltonen et al. 2019). The survival rate from diagnosis ranges from 85-95% at 5 years (Byrne et al. 2017, Santoro et al. 2020).

Recommendations		Strength
Rec. 1	Families with children with NF1 should be educated about possible symptoms and signs of brain tumours.	moderate
Rec. 2	Clinical assessment should take the form of patient history taking and examination for signs of brain tumours (amongst others new onset or change in seizures, unusual or concerning headache, endocrine problems related to hypothalamic dysfunction, focal neurological deficits, neuropsychological deficits) and should be repeated at every clinical visit from diagnosis.	moderate
Rec. 3	Routine diagnostic imaging screening for non-OPG, in children who are well (see previous recommendation), is not indicated. However, in a child with clinical concern for a brain tumour, e.g. in the presence of symptoms or endocrine dysfunction, then investigative imaging should be recommended.	moderate
Rec. 4	Symptomatic non-OPG in children with NF1 should be treated by the same care pathway as sporadic non-OPG in children without NF1. A multidisciplinary team should guide on appropriate therapeutic agents in the setting of NF1. Radiotherapy should be avoided, if at all possible, and is not indicated in low-grade glioma, whilst recognising that it may be required as an important treatment option in the setting of high-grade glioma.	moderate

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **non-OPGs**?	Neurological symptoms or signs seems to be the more efficient way of diagnosing (family education and neurological examination) (Mahdi et al. 2020).

What methods of clinical surveillance?	Neurological status examination in the form of patient history taking and examination for signs of brain tumours (which include amongst others, new onset or change in seizures, unusual or concerning headaches, endocrine problems related to hypothalamic dysfunction, focal neurological deficits, neuropsychological deficits)
When should surveillance start?	At the time of the NF1 diagnosis.
How often should surveillance be repeated?	At every clinical visit.
Q2. In people with NF1, what imaging surveillance is beneficial for detecting **non-OPGs**?	Imaging should be requested only if a non-OPG is suspected based on symptoms or signs, as per question 1 above (Guillamo et al. 2003, Griffith et al. 2018).
What modality of imaging for surveillance?	MRI
Q3. If a **non-OPG** is diagnosed is the indication for monitoring different in NF1?	No, the initial imaging timing will be the same as for suspected non-OPG in non-NF1 patients. However, once the diagnosis is confirmed then de facto stability may well have been established or otherwise. Monitoring of a stable paediatric NF1 glioma can have longer intervals between scans than children with the same tumour but without NF1 (Byrne et al. 2017, Mahdi et al. 2020, Santoro et al. 2020). The timing for imaging should take into account the initial histology (if surgery is performed) and possible high-risk sites: 1. Deep extensive tumours, although pathologically classified as LGG, show a more aggressive behaviour eventually leading to multiple rounds of treatments (Mahdi et al. 2020). Therefore, more frequent MRI monitoring (every 3 months) could be offered. 2. Thalamic tumours seems to exhibit a higher histological grade, a more aggressive behaviour and an increased risk of malignant transformation (Byrne et al. 2017), and they may also be assessed more often.
And if yes, what is content of monitoring (mode, interval)?	Non-OPG can potentially progress and require treatment, and this has been shown to occur generally in the first five years from diagnosis, especially the ones that are symptomatic at presentation or if multiple lesions are present. MRI should be performed for at least 5 years following initial diagnosis (Byrne et al. 2017) and in conjunction with local neuro-oncology multidisciplinary team decision making prior to transition to adult services.

Q4. If a **non-OPG**, is diagnosed, is the indication for treatment different in NF1? And if YES on, what is the indication for treatment in NF1?	No, surgery remains the best therapeutic option in symptomatic LGGs, with the aim of achieving complete resection when feasible, eventually followed by adjuvant chemotherapy (Gnekow et al. 2019). In case of cerebrospinal fluid (CSF) obstruction either endoscopic ventriculostomy or ventriculoperitoneal shunt should be considered (Campian et al. 2017, Roth et al. 2020). Otherwise for asymptomatic, incidentally found gliomas, a watch and wait policy remains appropriate (Byrne et al. 2017, Mahdi et al. 2020). There is a difference between brain stem gliomas in children with NF1 as they are usually benign (Mahdi et al. 2017) unlike sporadic diffuse intrinsic pontine gliomas, which represent a uniformly deadly malignant brain tumour in the majority of cases. Whilst the neuroradiological appearance is often different in the majority of cases, the possibility for a tumour in the setting of NF1, mimicking sporadic diffuse intrinsic pontine gliomas should be borne in mind and be considered. In case of unresectable, growing and symptomatic LGG as assessed by a multidisciplinary team, when adjuvant treatment is needed, chemotherapy is preferred and radiotherapy should be avoided.
Q5. Is treatment different in NF1?	Yes, as in childhood OPG, radiotherapy is not recommended for children with NF1 due to the increased likelihood of developing secondary malignancies, either gliomas or MPNST (Sharif et al. 2006, Bhatia et al. 2019); as well as developing neurovascular complications such as Moyamoya syndrome (Ullrich et al. 2007), endocrine and neuropsychological problems (Guillamo et al. 2003, Listernick et al. 2007, Oh et al. 2011).
And if YES, what is the NF1 specific treatment?	In LGG, radiotherapy should be avoided. The emerging role of MEK inhibitors (e.g. selumetinib, trametinib) has to be evaluated in upcoming clinical trials.
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **non-OPG** or in the management of a diagnosed **non-OPG**?	As per OPG in childhood paragraph.
References used:	(Guillamo et al. 2003, Sharif et al. 2006, Listernick et al. 2007, Ullrich et al. 2007, Oh et al. 2011, Byrne et al. 2017, Campian et al. 2017, Mahdi et al. 2017, Griffith et al. 2018, Bhatia et al. 2019, Gnekow et al. 2019, Mahdi et al. 2020, Roth et al. 2020, Santoro et al. 2020)

9.4. Summary of evidence and guideline Recommendations for Non-Optic Pathway Glioma in Adults

Adults with NF1 are more likely to develop both low or high grade brain or spine glioma (non-OPG), and even rarely glioblastomas (GBMs) (Costa et al. 2019). Despite their preponderant benign character, gliomas in general contribute to a higher mortality in patients with NF1 (Rasmussen et al. 2001, Evans et al. 2011).

Most tumours are low grade pilocytic astrocytomas by histology, which have a better prognosis than their sporadic counterparts (Korf 2000, Vinchon et al. 2000, Ullrich et al. 2007). These low grade pilocytic astrocytomas are rarely progressive over time (Helfferich et al. 2016), but higher histological grades (WHO grades II, III and IV) are also present in NF1 (Guillamo et al. 2003, Byrne et al. 2017, Campian et al. 2017) and are more likely when tumours are progressive in follow-up MRI or are located in the thalamus (Byrne et al. 2017).

As most of the pilocytic astrocytomas develop in childhood (mean age 7 years; (Molloy et al. 1995, Mahdi et al. 2020)), later developing neoplasms are more likely to be HGG (D'Angelo et al. 2019). In contrast to sporadic gliomas in adults, NF1 patients rarely develop cerebellar but most often hemispheric supratentorial tumours (D'Angelo et al. 2019, Lobbous et al. 2020); gliomas of the brainstem are associated with a less favourable prognosis. As focal areas of signal intensity can be a challenging differential diagnosis in children, new developing hemispherical lesions should always be considered to be HGG. Diffusely infiltrating astrocytomas encompasses up to 1/3 of cases (Rodriguez et al. 2008). Even if histology is the baseline for treatment regimen, there is a high variability in practice given the uncertain prognosis with low- and high-grade histology (Strowd et al. 2016).

Treatment strategies are variable and follow an individual risk assessment. When tumours are symptomatic or radiologically progressive, surgery and histological characterization should be considered. Although the impacts on management and outcome of biopsy results in patients with LGG is unclear mutational analysis of tumour specimen may be a future prognostic marker for risk stratification and differential therapy (Packer et al. 2020). In most cases the need for surgical intervention occurs within 5 years after detection and is predominantly associated with HGGs (Byrne et al. 2017). GBMs seem to require a similar treatment regimen as their sporadic counterparts (Albers et al. 2009). Observed age of occurrence (38y) is much younger than the mean for patients with sporadic GBMs (Gutmann et al. 2002, Lobbous et al. 2020). Additionally, despite the lack of good evidence, there are hints indicating a higher toxicity of the standard therapies (radiation, temozolomide based chemotherapy) in patients with NF1 (Stupp et al. 2005, Nakamura et al. 2011). The

pathophysiological mechanisms of NF1 with increased RAS activity and downstream signalling underline the need for targeted treatment strategies. Especially MEK inhibition and loss of e.g. CDKN2A or ATRX is in the focus of ongoing studies, but evidence is still lacking.

Recommendations		Strength
Rec. 1	Patients with NF1, their carers and primary care physicians should be educated about possible symptoms and signs of brain tumours in a manner appropriate to the individual patient.	moderate
Rec. 2	Clinical assessment should take the form of examination for signs of brain tumours (amongst others new onset or change in seizures, new onset, unusual or concerning headache, endocrine problems related to hypothalamic dysfunction, focal neurological deficits, neuropsychological deficits) at every clinical visit.	moderate
Rec. 3	Imaging screening for gliomas should be considered at the age of transition from childhood to adulthood for all patients with NF1 and should take the form of brain MRI with contrast. Imaging investigation should also be undertaken after new associated symptoms (amongst others new onset or change in seizures, new onset, unusual or concerning headache, endocrine problems related to hypothalamic dysfunction, focal neurological deficits, neuropsychological deficits) or positive physical examination findings.	moderate
Rec. 4	Incidental detected gliomas should be followed up with imaging like sporadic incidental detected gliomas, with a first interval of 3 months, and if stable asymptomatic disease, intervals can be prolonged.	weak
Rec. 5	Non-OPG in adults with NF1 should be managed and treated through the same care pathways as sporadic non-OPG. A multidisciplinary team should guide on appropriate therapeutic agents in the setting of NF1. Radiotherapy should be avoided if at all possible, and is not indicated in low-grade glioma, whilst recognising that it may be required as an important treatment option in the setting of high-grade glioma.	strong

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **non-OPG**?	It is important to educate patients about possible symptoms and signs tailored to the individual. Symptoms may occur between visits and surveillance scans and these tumours are very difficult to pick up clinically (Albers et al. 2009, Campian et al. 2017).
What methods of clinical surveillance?	Clinical monitoring for signs of non-OPG (seizures, headache, neurological deficits, neuropsychological deficits, etc.).

When should clinical surveillance start?	From 16-18y
How often should clinical surveillance be repeated?	Clinical monitoring in adulthood could be every one to two years, depending on patient's phenotype and request.
Q2. In people with NF1, is imaging surveillance beneficial for detecting **non-OPG**?	Yes, only ~25% of non-OPGs are symptomatic at diagnosis (Sellmer et al. 2017) and the rate of progression of non-OPGs per patient year of follow-up in the first 5 years after tumour diagnosis is 4.7% (Sellmer et al. 2017). Tumours which are symptomatic at initial diagnosis are more likely of higher grade and should be followed more frequently.
What modality of imaging for surveillance?	Brain MRI (with contrast enhancement if clinically justifiable)
When should imaging surveillance start?	A baseline MRI at age 18 is advisable. After any associated symptom (seizures, focal neurological deficit, pituitary endocrine abnormality) a brain MRI with contrast enhancement (gadolinium) should be performed.
How often should imaging surveillance be repeated?	After initial MRI without glioma imaging surveillance frequency is depending on clinical symptoms. In patients with asymptomatic/ LGG documented by MRI every 12 months. In patients with symptomatic gliomas documented by MRI every 3 to 6 months (Sellmer et al. 2017).
Q3. If **non-OPG** is diagnosed is the indication for monitoring different in NF1?	Yes. The rate of progressing non-OPG per patient year of follow-up in the first 5 years after tumour diagnosis was 4.7% (Byrne et al. 2017, Sellmer et al. 2017). GBMs seem to occur at younger ages than their sporadic counterparts.
And if yes, what is content of monitoring (mode, interval)?	Asymptomatic tumours (stable in growth and without symptoms) every 12 months in the first 5 years (Byrne et al. 2017). Symptomatic tumours every 3 – 12 months, depending on clinical parameters, potentially WHO grade etc.
Q4. If **non-OPG**, is diagnosed, is the indication for treatment different in NF1?	No, neurosurgery in case of tumour progression and/or clinical signs or symptoms, chemotherapy and radiation therapy additionally if tumour is not resectable. But toxicity of radiation may be higher in NF1 (Guillamo et al. 2003, Stupp et al. 2005, Albers et al. 2009, Nakamura et al. 2011, Helfferich et al. 2016, Campian et al. 2017, Costa et al. 2019) .
Q5. Is treatment different in NF1?	Maybe. Studies indicate a better outcome (S. Singhal et al. 2002, Guillamo et al. 2003, Rodriguez et al. 2008, Helfferich et al. 2016, Costa et al. 2019) , mostly due to the higher frequency of pilocytic astrocytomas (5-year survival rate minimum 85% (Rodriguez et al. 2008).

	Transformation of pilocytic astrocytomas in higher grades is described (Brems et al. 2009, Rosenfeld et al. 2010), but infrequent (Parsa et al. 2008, Sellmer et al. 2017). Prognosis and treatment for HGG does not differ significantly from their sporadic counterparts (Albers et al. 2009, Bornhorst et al. 2016, Campian et al. 2017, Shibahara et al. 2018, Costa et al. 2019), larger studies on NF1 associated HGG are sparse (Blakeley et al. 2016, Uusitalo et al. 2016). New developing neoplasms in adults are more likely of higher grade, in these cases a stricter protocol of follow-up has to be followed (Vizcaíno et al. 2015, Nix et al. 2020).
And if YES, what is the NF1 specific treatment?	In general, the treatment regimen is the same as in sporadic gliomas (see above), although the pathogenetic mechanisms suggest some approaches for targeted therapies (Theeler et al. 2014, Ameratunga et al. 2016). For the latter evidence is lacking. Symptomatic gliomas: surgery when possible, chemotherapy in other cases. LGG should be resected if they become symptomatic. There is some evidence of increased toxicity of radiation in NF1-associated gliomas (see above). HGG are treated as their sporadic counterparts.
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **non-OPG** or in the management of a diagnosed **non-OPG**?	Certified brain tumour centres are obliged to offer psycho-oncological therapeutic programs which are connected with psychological support on an individual basis in the patient's home area (there are no guidelines for psychological support for patients who are at risk for the occurrence of brain tumours in NF1). The individual risk, prognosis and therapeutic options should be discussed on every regular visit and should go along with psychological support depending on individual need.
References used:	(S. Singhal et al. 2002, Guillamo et al. 2003, Stupp et al. 2005, Parsa et al. 2008, Rodriguez et al. 2008, Albers et al. 2009, Brems et al. 2009, Rosenfeld et al. 2010, Nakamura et al. 2011, Theeler et al. 2014, Vizcaíno et al. 2015, Ameratunga et al. 2016, Blakeley et al. 2016, Bornhorst et al. 2016, Helfferich et al. 2016, Uusitalo et al. 2016, Byrne et al. 2017, Campian et al. 2017, Sellmer et al. 2017, Shibahara et al. 2018, Costa et al. 2019, Nix et al. 2020)

9.5. Summary of evidence and guideline Recommendations for Plexiform neurofibroma

Plexiform neurofibroma are benign peripheral nerve sheath tumours that occur as either diffuse or nodular growths and are predominantly congenital in origin. There is an increased risk of developing malignant change, but benign plexiform neurofibroma are also associated with significant morbidity and even mortality, albeit infrequently. Aesthetic disfigurement is common and depending on the site of lesion, neurological deficit is reported, including weakness, sensory disturbance, bladder and bowel dysfunction, breathing and swallowing difficulty. Cord, cauda equina and bowel obstruction may occur due to a heavy disease burden and surgical intervention is not always curative. Individuals frequently experience intermittent or chronic pain that may require anti-inflammatories, anti-neuropathic medication or opioid analgesia and input from a regional pain service is recommended. plexiform neurofibroma are occasionally associated with haemorrhage, which may be severe and occur spontaneously. Some MEK inhibitors have been shown to reduce the size of symptomatic, inoperable tumours and in some individuals is associated with improved neurological function and reduced pain (Gross et al. 2020).

Recommendations		Strength
Rec. 1	Clinical assessment should be by observation, palpation and neurological examination and should be performed by clinicians with NF1 expertise. Photography or video of the plexiform neurofibroma can be useful adjuncts.	moderate
Rec. 2	Clinical assessment for plexiform neurofibroma should start at diagnosis or birth and should be carried out at every clinical visit.	moderate
Rec. 3	Imaging by whole body MRI (WB-MRI) to monitor for plexiform neurofibromas should be performed at least at transition from childhood to adulthood to evaluate internal tumour burden as a predictor for the development of malignant peripheral nerve sheath tumour (MPNST) risk. WB-MRI assessment at higher frequency may be considered for patients at high risk for MPNST.	weak
Rec. 4	The frequency of repeat imaging should be determined on an individual basis guided by the multidisciplinary team assessment of the level of risk for the individual. Increased assessment may be considered for patients with high risk for MPNST. In absence of internal neurofibromas at WB-MRI at transition age to adulthood clinical assessment only is required.	moderate
Rec. 5	Clinical monitoring of plexiform neurofibromas should start when first detected and repeated during each visit.	moderate

Rec. 6	Symptomatic plexiform neurofibromas require increased monitoring at shorter intervals for ANNUBP/MPNST. With careful judgement, it is appropriate to use ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT (if ^{18}FDG PET MRI is not available) combined with clinical assessment and MRI in the diagnostic process, prior to discussing the need for biopsy.	moderate
Rec. 7	For symptomatic plexiform neurofibroma#, surgery is the only treatment that can potentially cure the tumour. Plexiform neurofibroma surgery should be considered.	moderate
Rec. 8	If part of standard national care, MEK-inhibitors may be considered as treatment option for symptomatic plexiform neurofibroma#, and inoperable symptomatic plexiform neurofibromas.	moderate
Rec. 9	Management of plexiform neurofibroma should be decided upon and performed by a multidisciplinary team with expertise in NF1.	weak
Rec. 10	Given the burden of having a potential risk of malignancy and visible manifestation in NF1 patients with plexiform neurofibroma, people with plexiform neurofibromas should be offered psychological support in decisions of management (please see recommendations in the psychosocial needs section 7.14 & 9.14).	weak

Footnote:

symptomatic plexiform neurofibromas are: persistent pain not responsive to treatment in regional pain centre, disfigurement, functional deficit or potential deficit including neurological deficit, bladder, bowel, respiratory or swallowing problems or haemorrhage.

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **plexiform neurofibroma**?	Clinical signs of plexiform neurofibroma should be assessed at every visit from birth or the time of NF1 diagnosis. Asymmetry of the face, neck, limb or trunk area is suggestive of a plexiform neurofibroma. Plexiform neurofibromas may cause visible soft irregular mass in any body area. The skin overlying the tumour may be slightly more pigmented than the surrounding skin. A less pigmented halo may sometimes surround the pigmented area. Some plexiform neurofibroma are highly vascular and may be associated with a purplish or greenish blue hue; potentially these plexiform neurofibroma may be misdiagnosed as a vascular malformation or tumour of vascular origin (Nguyen et al. 2011).
What methods of clinical surveillance?	Clinical assessment is made by observation, palpation and neurological examination (Ferner 2007). Clinical photography and video are useful adjuncts.
When should surveillance start?	Clinical screening should start at birth or the time of diagnosis of NF1 (Gutmann et al. 2017)
How often should surveillance be repeated?	Clinical screening should be carried out at least yearly through childhood and throughout adulthood for assessment of known neurofibromas. New plexiform neurofibroma are very unusual in adulthood (Gutmann et al. 2017). More frequent

	imaging should be tailored to the individual with increased risk of malignancy or of neurological deficit.
Q2. In people with NF1, is imaging surveillance beneficial for detecting **plexiform neurofibroma**?	Yes, there is a clear role for the use of imaging in people with NF1 for the detection and assessment of plexiform neurofibromas.
What modality of imaging for surveillance?	There is a clear role for MRI in assessing the internal burden of NF1 plexiform neurofibroma (Mautner et al. 2008, Ahlawat et al. 2020). WB-MRI is the preferred screening tool. Once detected, a plexiform neurofibroma should be followed with regional MRI. There is no place for ^{18}FDG PET MRI or ^{18}FDG PET CT in surveillance of asymptomatic patients with plexiform neurofibromas that are not growing. Patients who require surgery for plexiform neurofibroma of the skull base and who require reconstruction after facial neurofibroma surgery will need fine cut CT scans. These should be done by specialist units (there is a radiation dose). In general CT scans should be avoided if possible, because of the radiation (see section on orbital and periorbital plexiform neurofibroma).
When should imaging surveillance start?	Imaging to look for plexiform neurofibromas should be at least performed at transition from childhood to adulthood. Patients with whole gene deletions should have WB-MRI at a younger age (potentially from 5-10 years) and depending on the tumour load, location and symptoms, annual WB-MRI should be considered. Plexiform neurofibroma have the highest volume rate increase during the first 10 years of age (Nguyen et al. 2013) and hormonal changes of puberty do not appear to accelerate plexiform neurofibroma growth (Dagalakis et al. 2014). Unlike cutaneous neurofibroma, pregnancy does not increase plexiform neurofibroma growth (Well et al. 2020). The reason for surveillance of plexiform neurofibromas is to minimise aesthetic disfigurement and neurological deficit and to facilitate detection of potential transformation into MPNST. This can occur in childhood but is rare (Evans et al. 2002, Valentin et al. 2016, Peltonen et al. 2019). Particular consideration should be given to individuals with whole gene deletion and early development of subcutaneous neurofibromas as they have a high tumour burden.
How often should surveillance be repeated?	If plexiform neurofibromas are detected, then monitoring should be commenced at least annually during childhood (see section above) and regularly due to clinical estimation (size, growth rate, symptoms, etc.) in adults. Otherwise baseline

	imaging to detect plexiform neurofibromas and overall tumour burden should be performed at latest at transition from childhood to adulthood.
Q3. If **plexiform neurofibroma** is diagnosed is the indication for monitoring different in NF1?	Not applicable, as all plexiform neurofibromas are related to either generalised or mosaic NF1 (Beert et al. 2012), the indication for monitoring in NF1 is therefore the same. Monitoring with regional MRI is required for symptomatic plexiform neurofibromas from infancy i.e. plexiform neurofibromas that cause disfigurement, pain, neurological deficit, breathing, swallowing, sphincter problems or bleeding. Monitoring of plexiform neurofibromas should start when first detected. Plexiform neurofibromas that are near vital structures may require more frequent MRI (e.g. spinal cord, trachea). Monitoring in NF1 is to minimise aesthetic disfigurement and neurological deficit and to facilitate early detect malignant transformation. ^{18}FDG PET is a sensitive and specific method for differentiating plexiform neurofibroma and MPNST in symptomatic patients with NF1 (Warbey et al. 2009, Azizi et al. 2018).
Q4. If **plexiform neurofibroma**, is diagnosed, is the indication for treatment different in NF1?	Not applicable, as all plexiform neurofibromas are related to either generalised or mosaic NF1 (Beert et al. 2012). Surveillance alone may be a reasonable option in some patients (Yepuri et al. 2018).
What is the indication for treatment?	For symptomatic plexiform neurofibroma, surgery is the first line of treatment in operable neurofibromas. Disfigurement, pain and functional impairment of threat to function are the major reasons for surgical intervention. Surgery can only completely resolve symptoms in a minority of patients and there is a risk of regrowth after surgery mainly in deep and diffuse tumours and paediatric patients (Needle et al. 1997). Early surgical intervention when the tumour is still small yet completely removable could be beneficial (Nguyen et al. 2013). MEK inhibitors could be considered for symptomatic, inoperable symptomatic plexiform neurofibromas in patients with NF1 (persistent pain not responsive to treatment in regional pain centre, disfigurement, neurological deficit or potential neurological deficit bladder, bowel, respiratory or swallowing problems) (Dombi et al. 2016, Avery et al. 2017).
Q5. What is the treatment different in NF1?	Surgery. MEK inhibitors could be considered (see section above).
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **plexiform neurofibroma** or in the	Patients need input from expert clinicians, psychology and psychiatry, and clinical nurse specialists. Treatment for anxiety and depression and cognitive behaviour therapy (CBT) or acceptance and commitment therapy are warranted in some cases as plexiform neurofibromas impact on quality of life and disease specific assessments should

management of a diagnosed **plexiform neurofibroma**?	be undertaken (Wolkenstein et al. 2001, Kodra et al. 2009, Wolkenstein et al. 2009, Ferner et al. 2017, Lai et al. 2019). Individuals in all age groups might have problems related to plexiform neurofibromas especially: pain, social function, physical function, and stigma. Adults place greater emphasis on plexiform neurofibromas adversely affecting relationships and providing psychoeducational resources to individuals with plexiform neurofibromas and their families is particularly important (Jensen et al. 2019).
References used:	(Needle et al. 1997, Wolkenstein et al. 2001, Evans et al. 2002, Ferner 2007, Mautner et al. 2008, Kodra et al. 2009, Warbey et al. 2009, Wolkenstein et al. 2009, Nguyen et al. 2011, Beert et al. 2012, Nguyen et al. 2013, Dagalakis et al. 2014, Dombi et al. 2016, Valentin et al. 2016, Avery et al. 2017, Ferner et al. 2017, Gutmann et al. 2017, Azizi et al. 2018, Yepuri et al. 2018, Jensen et al. 2019, Lai et al. 2019, Peltonen et al. 2019, Ahlawat et al. 2020, Well et al. 2020)

9.6. Summary of evidence and guideline Recommendations for Malignant peripheral nerve sheath tumor (MPNST) and Atypical neurofibromatous neoplasm with uncertain biologic potential (ANNUBP)

A hallmark manifestation of NF1 is the occurrence of neurofibromas. These arise from somatic alterations in the normal copy of the *NF1* gene in the Schwann cells from the peripheral nerve (Serra et al. 2000). Atypical neurofibromas are premalignant tumours, which are an intermediate stage between benign NFs and the malignant transformation to MPNST. In a study of Higham et al. atypical neurofibromas are mainly nodular lesions with the majority being deep seated (Higham et al. 2018). More than half of the atypical lesions were palpable and approximately 80% caused clinical symptoms, such as pain, growth and functional impairment (Higham et al. 2018). These symptoms are similar to those observed in patients with MPNST. ANNUBP is the current preferred name for these atypical neoplasms. It is remarkable that NF1 individuals with ANNUBPs frequently have more than one of these tumours and it has been estimated that in 50% of individuals with ANNUBPs eventually one of these tumours will progress to an MPNST before the age of 50 years (Higham et al. 2018). MPNSTs are difficult to diagnose in the context of NF1 as individuals frequently have multiple symptomatic lesions and the symptoms might overlap with those of ANNUBPs and benign plexiform neurofibroma. Symptoms that require investigation are new, unexplained persistent or nocturnal pain, rapid increase in size of a neurofibroma, change in texture and new or unexplained neurological deficit. Seventy percent of these tumours (MPNST) are high-grade and can metastasise widely with a poor prognosis (Ferner et al. 2002). The median survival is 18 months and the 5-year survival is 21% - 62%(Evans et al. 2002, Zehou et al. 2013a, Zehou et al. 2013b, Tovmassian et al. 2016, Reilly et al. 2017, Malbari et al. 2018, Bhat et al. 2019, Nelson et al. 2019, Schwabe et al. 2019, Tora et al. 2019, van Noesel et al. 2019, Meister et al. 2020). MPNSTs in NF1-patients seem to be associated with a lower overall survival, when compared to non NF1-patients (van Noesel et al. 2019).

MRI is useful to delineate the site, extent, volume and growth pattern of nerve sheath tumours. However, it does not reliably differentiate between benign and malignant tumours in all situations. Histopathology can determine the stage of malignancy of these neoplasms. ANNUBPs are neurofibromatous tumours with hypercellularity, nuclear atypia, loss of neurofibroma architecture, and minimal mitotic activity (>1/50 high-power field and <3 high-power field) in the absence of necrosis (Miettinen et al. 2017). An increase in mitotic indices and the presence of necrosis is associated with malignant transformation to MPNSTs (Miettinen et al. 2017). However, blind biopsies can miss the malignant part of these heterogeneous tumours, resulting in an

erroneous diagnosis. Since malignant tumours are characterised by a large increase in glucose metabolism, this increase in glucose uptake will be represented on ^{18}FDG PET. Using this imaging method biopsies can be guided to the site of the highest glucose uptake or highest maximum standardised uptake value (SUV_{max}) (Ferner et al. 2008). Although there is an overlap between the SUV_{max} of benign plexiform neurofibroma, ANNUBPs and MPNSTs, the mean SUV_{max} of the group of ANNUBPs is higher compared to the group of benign plexiform neurofibroma and lower compared to MPNSTs (Ferner et al. 2008, Higham et al. 2018). Also, it is important to note that the SUV_{max} can vary as a result of the use of different protocols and machines, and between centres.

Previous research demonstrated that subtotal resection of ANNUBPs saves the function of the nerve and did not result in recurrence of the lesion (Bernthal et al. 2014, Nelson et al. 2019). Therefore, detection and resection (if possible) of these premalignant ANNUBPs is a possible strategy to prevent a transitioning to MPNSTs. The mainstay of treatment for MPNSTs is complete excision of the lesion with wide margins, but radiotherapy and chemotherapy may play a role in reducing the size of the tumour to facilitate surgery or for palliation. Risk factors for malignant transformation include prior MPNST, radiotherapy, a family history of MPNST, ANNUBP, neurofibromatous neuropathy, high internal load of NFs and individuals with an NF1 related whole gene deletion, or patients with a missense mutation affecting codons 844-848.

In 2011 Beert et al. demonstrated that ANNUBPs have recurrent copy number alterations in the *CDKN2A/CDKN2B* gene cluster (9p21.3), which is probably the first step towards a potential transformation (Beert et al. 2011). Malignant transformation into MPNSTs is associated with additional somatic alterations in genes involved in the cell cycle regulation such as *TP53* and components *EED* and *SUZ12* of the polycomb repressive complex 2 (PRC2) (Brems et al. 2009, De Raedt et al. 2014, Pemov et al. 2019). However, ANNUBPs do not show additional mutations in *TP53,* or *EED* and *SUZ12*, as seen in MPNSTs. Overall, these ANNUBPs present with a low mutation burden and few copy number aberrations (Pemov et al. 2019).

Recommendations		Strength
Rec. 1	The following groups of people with NF1 should be considered at high risk of MPNST: • *NF1* microdeletion affecting *SUZ12* • missense variants affecting codons 844-848 • previous atypical neurofibromatous neoplasm with uncertain biologic potential (ANNUBP) • high internal tumour load on whole body MRI (WB-MRI) or large or multiple plexiform neurofibroma in absence of WB-MRI	strong

	• neurofibromatous neuropathy • previous radiotherapy • a relative with NF1 and MPNST	
Rec. 2	Clinical assessment for MPNST should consist of assessing the following: • Tumour growth: a rapid increase in the size or a change in growth rate or of an existing plexiform neurofibroma. • Pain: new and persistent, nocturnal, substantial pain / pain that is difficult to control. • New motor deficit, sensory deficit associated with any neurofibroma or peripheral nerve. This includes bladder function, bowel disturbance, swallowing problems and breathing difficulty. • Tumour consistency: development of hard nodule in a previously soft plexiform neurofibroma. People with NF1 and any of the above should be investigated for MPNST.	strong
Rec. 3	When clinical signs and symptoms point towards malignancy (suspicious tumours), investigation should begin with regional MRI. Prior to surgery, MRI should be carried out and ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT (if ^{18}FDG PET MRI is not available) undertaken, using visual assessment and semiquantitative assessments with a cut-off standardised uptake value.	moderate
Rec. 4	In case of a suspected ANNUBP or MPNST, primary resection is recommended if it is safe and feasible. Otherwise, radiologically (preferably ^{18}FDG PET MRI) guided diagnostic biopsy should be performed. This biopsy should be taken at the discretion of a (sarcoma) multidisciplinary team, as tumours can be heterogeneous, with the potential for a false negative result by missing malignant parts of the tumour.	strong
Rec. 5	There is no place for watchful waiting in MPNST and urgent surgical resection should be the mainstay for treatment (if possible), with post-operative assessment for recurrence.	strong
Rec. 6	Treatment decisions, on initial surgery and/or (neo)adjuvant chemo- or radiotherapy should be guided by an experienced multidisciplinary team.	moderate
Rec. 7	If a diagnosis of ANNUBP is proven by biopsy then surgery should be the primary treatment option, if this is possible with acceptable morbidity.	strong
Rec. 8	If an ANNUBP cannot be resected with acceptable morbidity, initial screening with MRI should be conducted at least every 6 months. In case of tumour growth or increase in symptoms, screening should include ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT (if ^{18}FDG PET MRI is not available). After an initial clinical assessment, the follow-up interval should be determined by the characteristics of the tumour.	moderate

Q0. What people are at high risk for **MPNST**?	Defining people with NF1 at high risk of MPNST: • *NF1* microdeletion affecting *SUZ12* (De Raedt et al. 2014), • Missense variants affecting codons 844-848 (Koczkowska et al. 2018), • Previous ANNUBP (Higham et al. 2018), • High internal tumour load on whole body MRI (Nguyen et al. 2014), • neurofibromatous neuropathy • Previous radiotherapy (Nakamura et al. 2011, Watson et al. 2017, Yamanaka et al. 2017, Miao et al. 2019) • NF1 individuals with a relative with NF1 and MPNST (Malbari et al. 2018)
Q1. In people with NF1, what clinical surveillance is beneficial for detecting **MPNST**?	MPNST is a pathological diagnosis that is easy to overlook in clinical practice, so clinical suspicion and willingness to investigate must remain high especially in high-risk individuals. Symptoms most suggestive of MPNST are a new and persistent, substantial or difficult to control pain, new neurological deficit, a rapid increase in the size of an existing plexiform neurofibroma or alteration in its consistency from soft to hard (Ferner et al. 2002, Evans et al. 2017).
What methods of clinical surveillance?	Clinical surveillance consists of assessment for a change in clinical symptoms of growth, pain, motor deficit/weakness, sensory deficit associated with any neurofibroma. Annual growth rates >20% determined by volumetric analysis in adults are highly suspicious for MPNST (Nguyen et al. 2014).
When should surveillance start?	Although MPNST mainly occurs in adults, it can occur at younger ages. Therefore, clinical surveillance for MPNST should start from teenage on.
How often should clinical surveillance be repeated?	Clinical surveillance should be undertaken at each clinical visit.
Q.2 In people with NF1, what imaging surveillance is beneficial for detecting **MPNST** or **ANNUBPS**?	WB-MRI can detect tumours that could be MPNST or ANNUBPs (Evans et al. 2017, Higham et al. 2018). ^{18}FDG PET can discern potential malignant transformation even in asymptomatic patients (Tovmassian et al. 2016, Azizi et al. 2018).
What modality of imaging for surveillance?	WB-MRI can detect tumours that could be MPNST or ANNUBPs (Higham et al. 2018). In some radiology departments the distal parts of the extremities are not included in the WB-MRI and clinical examination of these regions are of importance to decide on targeted regional MRI. Suspicious tumours should be investigated further. The most sensitive and specific non-invasive indicator of malignant potential is ^{18}FDG PET using visual assessment and semiquantitative assessments with a cut-off SUV (Ferner et al. 2008, Warbey et al. 2009, Benz et al. 2010, Derlin et al. 2013).

Note on ^{18}**FDG PET CT**	SUVs cannot be compared between machines or institutions. For comparability, repeat SUVs must be conducted using identical protocols (Azizi et al. 2018).
When should imaging surveillance start?	A baseline WB-MRI is recommended at the transition age.
How often should imaging surveillance be repeated?	The frequency of repeat imaging should be determined on an individual basis guided by the multidisciplinary team assessment of the level of risk for the individual (Azizi et al. 2018). If no tumour suspected for MPNST or ANNUBP is detected by WB-MRI at the age of 16-18 years than no further specific imaging surveillance is needed. Yet, symptoms evocative of MPNST must lead to imaging evaluation, as not all MPNSTs arise from plexiform neurofibroma (Nguyen et al. 2014).
Notes on diagnosis of **MPNST** or **ANNUBP**	MRI helps define the size and location of the lesion but cannot always easily differentiate between benign and malignant tumours. ^{18}FDG PET and special MRI sequences (e.g. diffusion weighted imaging) may help to predict malignant transformation.
	Biopsy should be MRI-guided or ^{18}FDG PET guided as the heterogeneous nature of some MPNST makes it likely for blind biopsy to miss the area of malignant change in a tumour with mixed features (Ferner et al. 2002). Use of apparent diffusion coefficient improves the differential diagnosis between plexiform neurofibroma and MPNST (Demehri et al. 2014).
Q3a. If **MPNST** is diagnosed what is the indication for monitoring?	Monitoring MPNST following diagnosis is inappropriate, the best treatment option is the complete surgical resection of the MPNST with tumour-free margins (Dunn et al. 2013). After surgical resection monitoring is similar to non-NF1 MPNST. Expert opinion recommends following patients every 3 months for 3 years, then every 6 months for 2 years and then annually.
Q3b. If **ANNUBPs** is diagnosed what is the indication for monitoring?	If ANNUBP is suspected and proven by biopsy than surveillance with MRI is necessary if the tumour cannot be resected. MRI is an appropriate modality for monitoring ANNUBP and should be conducted every 6 months initially, will follow-up periods after that determined by the characteristics of the tumours. If the ANNUBP is growing, then a ^{18}FDG PET MRI (or ^{18}FDG PET CT if ^{18}FDG PET MRI is not available) should be repeated and if SUV is significantly increased the tumour should be resected or biopsy should be repeated. In stable tumours ^{18}FDG PET monitoring may be performed in longer intervals.
Q4a. If **MPNST**, is diagnosed, is the indication for treatment different in NF1?	In the clinical setting treatment is similar for both NF1 and non-NF1 MPNST. As radiotherapy may increase the risk of secondary malignancies in NF1 patients, novel radiotherapeutic regimens that more precisely target the tumour volume and spare healthy surrounding tissue should be evaluated (Nakamura et al. 2011, Watson et al. 2017, Yamanaka et al. 2017, Miao et al. 2019).

Q4b. If **ANNUBPs**, is diagnosed, what is the indication for treatment?	ANNUBP is specific for NF1 and it is considered to be a premalignant lesion (Beert et al. 2011, Röhrich et al. 2016). Indication for treatment can be twofold: 1) prevention of further evolution to MPNST in case the tumour can be relatively easily removed without damaging major nerve. 2) detection of early stage of transition to MPNST by ^{18}FDG PET and multiple biopsies.
Q5a. What is the treatment of **MPNST**?	The best treatment option is the complete surgical resection of the MPNST with tumour-free margins (resection margins lacking identifiable tumour within 1 mm from an inked surface of tissue) (Dunn et al. 2013, Tora et al. 2019, Prudner et al. 2020). Non-conservative surgery is associated with better local control but not with better survival in these patients (Zehou et al. 2013a, Zehou et al. 2013b) Radiotherapy provides local control and could delay the onset of recurrence but doesn't have an impact on the long-term survival (Ferner et al. 2002). Palliative radiotherapy can be used in patients with an incomplete resection or unresectable tumour. Therapeutic agents used for the treatment of MPNST follow usually those as included in the treatment protocols for sarcomas such as doxorubicin, trabectedin, ifosfamide, dacarbazine and pazopanib. Neoadjuvant chemotherapy can be administered to downstage tumours and facilitate surgical removal. It also could be considered in incomplete resected tumours, in large initial tumours > 5 cm, in G2-G3 tumours and in case of positive lymph nodes or distant metastases (van Noesel et al. 2019). However, this practice has not been widely adopted (Frustaci et al. 2001, Ferner et al. 2002, Kroep et al. 2011). Surgically excise of single lung metastases is applied following the latest consensus meeting (Reilly et al. 2017). Adjuvant chemotherapy also remains controversial (Carli et al. 2005). Single-agent approach may be used as front-line therapy for palliative care in patients with metastatic disease (Ferner et al. 2002, Kroep et al. 2011).There is little experience with targeted therapy for this indication (Prudner et al. 2020).
Q5a. what is the treatment of **ANNUBP**?	If an ANNUBP is suspected or diagnosed, surgery should be recommended if possible: Ideally fascicle-sparing gross-total, extracapsular resection of ANNUBP if possible with the use of intraoperative nerve stimulation and microdissection of nerve fascicles (Nelson et al. 2019). Local resection is sufficient even if incomplete in "intermediate" nerve sheath tumours (low-grade MPNST and ANNUBP). Case series suggest no patients developed metastatic disease nor died of disease despite a high rate of microscopically positive surgical margins (78%) (Bernthal et al. 2014). While positive margins do lead to increased rates of local recurrence, these data suggest that surgeons potentially can temper their zeal for negative surgical margins in the setting of low-grade MPNST and ANNUBP, as surgical morbidity may be more important than a presumed survival benefit of wide resection (Bernthal et al. 2014).
Q6a. What psychosocial support do people with NF1 benefit from, specifically in	Patients need psychological and/or psychiatric intervention which do not differ from general psychological care in the oncology field. Behavioural treatment, pharmacological intervention for anxiety and pain are warranted according to clinical requirement. Quality of life studies in MPNST in NF1 are missing and were only carried out for sporadic soft tissue sarcomas (Jones et al. 2018).

living with the uncertainty of **MPNST** or in the management of a diagnosed **MPNST**?	
Q6b. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **ANNUBP** or the management of a diagnosed **ANNUBP**?	People might be very anxious to know that they have a "premalignant" lesion (Beert et al. 2011) that might progress to a malignancy over time in case surveillance is chosen and not resection. Patients might also be concerned about nerve damage if the tumour is resected. Psychological support should be directed towards the individual's specific concerns.
References used - **MPNST**:	(Frustaci et al. 2001, Ferner et al. 2002, Carli et al. 2005, Ferner et al. 2008, Warbey et al. 2009, Benz et al. 2010, Kroep et al. 2011, Nakamura et al. 2011, Derlin et al. 2013, Dunn et al. 2013, Zehou et al. 2013a, Zehou et al. 2013b, De Raedt et al. 2014, Demehri et al. 2014, Nguyen et al. 2014, Tovmassian et al. 2016, Evans et al. 2017, Reilly et al. 2017, Watson et al. 2017, Yamanaka et al. 2017, Azizi et al. 2018, Higham et al. 2018, Jones et al. 2018, Koczkowska et al. 2018, Malbari et al. 2018, Miao et al. 2019, Tora et al. 2019, van Noesel et al. 2019, Prudner et al. 2020)
References used - **ANNUBP**:	(Beert et al. 2011, Bernthal et al. 2014, Röhrich et al. 2016, Tovmassian et al. 2016, Evans et al. 2017, Azizi et al. 2018, Higham et al. 2018, Nelson et al. 2019)

9.7. Summary of evidence and guideline Recommendations for Orbital & Periorbital Plexiform neurofibroma

Most orbital and periorbital plexiform neurofibromas are identified within the first few years of life. Small orbital and periorbital plexiform neurofibromas restricted to the eyelid may go unnoticed until later in childhood, especially if the ptosis is mild or unrecognized (Avery et al. 2017).

The NF1-associated alterations of the orbit and the periorbital area in connection with a plexiform neurofibroma are very diverse, e.g. orbital distortion, buphthalmos or temporal lobe herniation into orbit due to orbital roof defect (de Vries et al. 1998, Jacquemin et al. 2003, Lee et al. 2004, Marchac et al. 2005, Friedrich et al. 2010, Arrington et al. 2013, Latham et al. 2015, Avery et al. 2017). As a rule, it is necessary to consult the expertise of several medical disciplines in order to determine the potential disturbances in structure and functions of the tissues and organs located here. A major factor in tumour-associated morbidity in this region is the spread and biological behaviour of the plexiform neurofibroma (Fu et al. 2012). As a rule, the congenitally manifest, diffuse plexiform neurofibroma, grows during the postnatal phase leading to a slowly progressing destruction of the periorbital/orbital contents; however, infiltration of the eyeball is not mandatory. On the other hand, even very small neurofibromas can have significant pathogenic effects, for example in the case of intraocular neurofibroma causing increased intraocular pressure (Chaudhry et al. 2012, Oystreck et al. 2014). The developmental disorder of the orbit with direct contact between the orbital content and the brain can vary in size and contributes significantly to the facial phenotype, especially as a pulsating exophthalmos (Naran et al. 2018). Other skeletal regions are often also affected, giving the impression of a macro-orbit (Jacquemin et al. 2002, Jacquemin et al. 2003) and, quite rare, a micro-orbit (Friedrich et al. 2010). Given the location of the orbital and periorbital plexiform neurofibroma (in the orbita) autonomous growth has a significant influence on tissue and organs, such as skeletal remodelling, increased cranial pressure, and buphthalmos.

Recommendations		Strength
Rec. 1	The clinical assessment of NF1 patients suspected of having an orbital and periorbital plexiform neurofibroma, should be physical examination looking for blepharoptosis, proptosis, eyelid oedema, orbital dysplasia and/or dystopia, distortion of the (peri)orbital skeleton, pulsation of the eye, and strabismus. Clinical testing of vision and refractive error, visual field, ocular motility and alignment, and evaluation of the optic disc to exclude glaucoma or optic	strong

	neuropathy should be basic steps in the examination of NF1 patients who are suspected of having an orbital and periorbital plexiform neurofibroma.	
Rec. 2	MRI of the brain and orbits should be performed in all children with a suspected orbital and periorbital plexiform neurofibroma. High-resolution MRI sequences with and without contrast should be acquired through the orbit, face, and cavernous sinus. Whenever possible the radiation exposure from CT scans should be avoided in all children with NF1.	strong
Rec. 3	Symptomatic clinical progression, of known orbital and periorbital plexiform neurofibromas, and new findings should be the primary indication for imaging assessment and follow-up, and this should be by MRI.	strong
Rec. 4	Given the burden of visible manifestation in NF1 patients with orbital and periorbital plexiform neurofibroma, people with orbital and periorbital plexiform neurofibroma should be offered psychological support in decisions of management (please see recommendations in the psychosocial needs section 7.14 & 9.14).	weak

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **orbital and periorbital plexiform neurofibromas**?	In the clinical surveillance of NF1 patients suspected of having an orbital and periorbital plexiform neurofibroma, physical examination comes first. Orbital and periorbital plexiform neurofibroma is a congenital and often disfiguring manifestation. In the vast majority of cases, small children are to be examined, whose relatives have become aware of facial asymmetries in the orbital-periorbital region. Therefore, self-assessment is rarely available for the examination of the young patient.
What methods of clinical surveillance?	It is uncommon that a child's symptom will lead to the initial discovery of an orbital and periorbital plexiform neurofibroma. Clinical examination of the eye and periorbital region looking for blepharoptosis, proptosis, eyelid oedema, orbital dysplasia and/or dystopia, distortion of the (peri-)orbital skeleton, pulsations of the eye, and strabismus are mandatory measures in NF1 affected individuals. Clinical testing of vision, visual field, ocular motility, and optic disk evaluation (exclude glaucoma and optic neuropathy) are basic steps in the examination of NF1 patients who are suspected of having an orbital and periorbital plexiform neurofibroma (Avery et al. 2017).
When should surveillance start?	Most orbital and periorbital plexiform neurofibromas are congenital, but they may not be obvious immediately after birth so clinical surveillance should start immediately after diagnosis.
How often should surveillance be repeated?	A comprehensive ophthalmological examination should be performed at the same frequency as the surveillance for OPG (i.e. every 6 months) throughout the period of visual development (i.e. before the age of 8 years) (Chaudhry et al. 2012, Avery et al. 2017). Orbital and periorbital plexiform neurofibroma and OPG are two different

	diseases that can occur simultaneously in an individual suffering from NF1. However, the association of OPG with the orbital and periorbital plexiform neurofibroma in an individual is rare. There is first evidence that monitoring should be intensified in offspring if NF1-associated orbital and periorbital plexiform neurofibroma is clustered in the family (Chai et al. 2019).
Q2. In people with NF1, what imaging surveillance is beneficial for detecting **orbital and periorbital plexiform neurofibromas**?	An MRI scan of the brain and orbits should be performed in all children with a suspected orbital and periorbital plexiform neurofibroma. High-resolution MRI sequences with and without contrast should be acquired through the orbit, face, and cavernous sinus (Fu et al. 2012, Arrington et al. 2013). However, identification of (associated) cranial bone defects on MRI is significantly inferior to that on CT (Arrington et al. 2013). The radiation exposure from CT scans should be avoided whenever possible in all children with NF1, 'black bone' MRI (a 3D low flip angle gradient-echo MRI sequence) can be use. Additional examinations such as display of orbital contents in ultrasound can be valuable for certain ophthalmological diagnoses, e.g. glaucoma associated with orbital and periorbital plexiform neurofibroma (Morales et al. 2009, Avery et al. 2017).
What modality of imaging for surveillance?	MRI is the diagnostic imaging modality of choice for surveillance of orbital and periorbital plexiform neurofibroma (Avery et al. 2017). However, the comorbidities in patients with orbital and periorbital plexiform neurofibroma are varied and often affect the eye and the adnexa. In these cases, the instrumental diagnosis of eye and orbit follows the ophthalmological findings (Avery et al. 2017). CT of orbit has a diagnostic value for assessing orbital dysplasia when it comes to measure suspected progressive loss of bone (Jacquemin et al. 2002, Jacquemin et al. 2003) and the rare case of malignant orbital tumours associated with orbital and periorbital plexiform neurofibroma in NF1. CT is essential for planning surgical measures to correct the position and volume of the bony orbit, e.g. in order to produce preformed implants to replace the orbital walls (de Vries et al. 1998, Guo et al. 2019). However, the benefits of X-ray diagnosis in surveillance of NF1 patients during early childhood and in the growth period in general must be determined individually.
When should surveillance start?	Since a considerable proportion of NF1 patients have general developmental disorders, MRIs are increasingly being indicated for the assessment of CNS involvement. These MRIs may contribute to detect orbital and periorbital plexiform neurofibroma, but should then include the orbital region. Monitoring of the patient should begin after the initial diagnosis of orbital and periorbital plexiform neurofibroma and be carried out at regular intervals. The growth potential of the plexiform neurofibroma is greatest in the first decade of life in terms of the factor local expansion. Therefore, the control intervals should be closer in this phase.
How often should surveillance be repeated?	No studies have been informative about the frequency of follow-up MRIs; therefore, clinical progression should be the primary indication.

	Orbital and periorbital plexiform neurofibroma involving the orbit or moving toward infiltrating the cavernous sinus should be imaged frequently (i.e. at least every 3 to 6 months) until clinical stability and lack of further growth (Avery et al. 2017). If the child experiences progressive orbital and periorbital plexiform neurofibroma growth or demonstrates continued vision loss not related to amblyopia, repeat imaging at higher frequency may be warranted (Avery et al. 2017).
Q3. If **orbital and periorbital plexiform neurofibromas** is diagnosed is the indication for monitoring different in NF1?	Sporadic or mosaic-type orbital and periorbital plexiform neurofibroma are known and rarely reported (Boltshauser et al. 1989, Bechtold et al. 2012). There are no studies that demonstrate lower morbidity in sporadic/mosaic orbital and periorbital plexiform neurofibroma.
Q4. If **orbital and periorbital plexiform neurofibromas** is diagnosed, is the indication for treatment different in NF1? And if YES on, what is the indication for treatment in NF1?	There are no studies that demonstrate a different morbidity in sporadic/mosaic orbital and periorbital plexiform neurofibroma versus syndromic orbital and periorbital plexiform neurofibroma (Bechtold et al. 2012, Friedrich et al. 2015). 1. **Orbital and periorbital plexiform neurofibroma:** The indication for the treatment of orbital and periorbital plexiform neurofibroma is determined by size, growth tendency and functional consequences related to the expanding tumour (Lee et al. 2004, Oystreck et al. 2012). To date, there have been no systematic examinations that have determined the long-term success of the surgical measures. 2. **Orbital dysplasia and dystopia:** The orbital and periorbital plexiform neurofibroma is typically associated with orbital dysplasia (Lee et al. 2004, Latham et al. 2015, Naran et al. 2018). Displacement in horizontal level, (rather than simple expansion of the orbit) requires more extensive craniofacial reconstruction. This is also true when the periorbital skeleton is involved, including zygomatic dystopia and intraoral disorders, such as tooth displacement. This last condition requires the involvement of orthodontist or specialized dentist. To date, there have been no systematic examinations that have determined the long-term success of the surgical measures. 3. **Orbital and periorbital plexiform neurofibroma and OPG:** The combined occurrence of orbital and periorbital plexiform neurofibroma and OPG does occur in NF1 patients, so additional diagnostic and therapeutic measure for these both neoplasms need to be considered. 4. **Strabismus:** The management of strabismus in these children is complex, and no studies exist to support early versus late surgical treatment of strabismus. Rather, the provider should focus on nonsurgical treatment for strabismic amblyopia, including correcting any induced refractive error, conventional occlusion therapy with patching or atropine penalization, and consideration of prisms for smaller angle eye misalignment (Oystreck et al. 2012). If the severity of strabismus precludes the effectiveness of amblyopia treatment, then surgical correction may be considered at an earlier stage in the disease process. A conservative approach to management would advocate later

	surgery once the growth phase of the orbital and periorbital plexiform neurofibroma has attenuated and the overall disease process is more stable (Avery et al. 2017).
Q5. Is treatment different in NF1? And if YES, what is the NF1 specific treatment?	There is no difference in the treatment of sporadic or syndromic orbital and periorbital plexiform neurofibroma. A generally recognised, standardised treatment concept for adult NF1 patients with orbital and periorbital plexiform neurofibroma has not yet been developed. Numerous surgical centres have critically re-evaluated their treatment outcomes for NF1-associated orbital and periorbital plexiform neurofibroma for both children/adolescents and adults (Lee et al. 2003, Marchac et al. 2005, Erb et al. 2007, X. Q. Fan et al. 2007, Acartürk et al. 2009, Morales et al. 2009, Friedrich et al. 2010, Chaudhry et al. 2012, Oystreck et al. 2012, Avery et al. 2013, D. Singhal et al. 2013, Greenwell et al. 2014, Li et al. 2014, Niddam et al. 2014, Pessis et al. 2015, Denadai et al. 2016, Keren et al. 2017, Davidson et al. 2019, Niu et al. 2019). All studies have in common that the combination of pathological findings in each individual case was decisive for the treatment request, treatment indication and treatment result. In the absence of significant tumour growth, initial intervention should be directed toward management of specific symptoms (Avery et al. 2017). For growing tumours, indications for debulking surgery or consideration for enrolling in a clinical trial include: • visual decline • progressive tumour that may soon invade a critical structure (e.g. cavernous sinus) • progressive tumour that is likely to cause a new or worsening functional deficit • progressive tumour that is likely to cause potentially progressive disfigurement (Avery et al. 2017) • Volume changes in the eye (glaucoma) can be an independent factor for the indication of surgical measures (Morales et al. 2009) In individual cases, a combination of these findings can occur, which have a decisive influence on the respective choice of treatment. Standard chemotherapy has not been shown to be of benefit and is associated with the risk of treatment-induced secondary malignant neoplasms. Because of the mutagenic nature of most chemotherapeutic agents, especially alkylator and topoisomerase inhibitors, chemotherapy is not used (Avery et al. 2017). MEK inhibitors have proved to be effective in the treatment of inoperable, symptomatic and/or disfiguring plexiform neurofibroma and could be considered as a therapeutic option in this setting (Gross et al. 2020).
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **orbital**	So far, there is no study that has systematically recorded the psychosocial problems of patients with orbital and periorbital plexiform neurofibroma. From reports on craniofacial plexiform neurofibroma and its impact on quality of life we may conclude the need for multidisciplinary management for these patients including psychosocial interventions (Ren et al. 2020).

and periorbital plexiform neurofibromas or in the management of a diagnosed **orbital and periorbital plexiform neurofibromas**.	
References used:	(Boltshauser et al. 1989, de Vries et al. 1998, Jacquemin et al. 2002, Jacquemin et al. 2003, Lee et al. 2003, Lee et al. 2004, Marchac et al. 2005, Erb et al. 2007, X. Q. Fan et al. 2007, Acartürk et al. 2009, Morales et al. 2009, Friedrich et al. 2010, Bechtold et al. 2012, Chaudhry et al. 2012, Fu et al. 2012, Oystreck et al. 2012, Arrington et al. 2013, Avery et al. 2013, D. Singhal et al. 2013, Greenwell et al. 2014, Li et al. 2014, Niddam et al. 2014, Friedrich et al. 2015, Latham et al. 2015, Pessis et al. 2015, Denadai et al. 2016, Avery et al. 2017, Keren et al. 2017, Naran et al. 2018, Chai et al. 2019, Davidson et al. 2019, Guo et al. 2019, Niu et al. 2019, Gross et al. 2020, Ren et al. 2020)

9.8. Summary of evidence and guideline Recommendations for Cutaneous neurofibroma

Cutaneous neurofibromas are histologically benign tumours composed of multiple cell types and elements of peripheral nerve, and immune cells such as mast cells (Ortonne et al. 2018). Cutaneous neurofibromas are one of the hallmarks of NF1 but are not life threatening because they do not undergo malignant transformation. However, they have a major negative impact on quality of life due to their prevalence and the disfigurement they cause (Wolkenstein et al. 2001, Kodra et al. 2009, Guiraud et al. 2019). Some cutaneous neurofibromas may be present in childhood but they typically start to develop during puberty. They become more numerous throughout life and their number may increase during pregnancy (Duong et al. 2011a). Cutaneous neurofibromas may be itchy or tender, and their treatment is based on the discomfort or aesthetic aspects. To date, there are no medical treatments available (Slopis et al. 2018).

Recommendations		Strength
Rec. 1	Clinical assessment consisting of visual inspection and palpation should begin when NF1 is diagnosed and should be repeated at every clinical visit.	strong
Rec. 2	Discomfort for the patient should be the primary indication for treatment. With regard to aesthetic considerations the impacts are unique to each individual and each health system has its own criteria and thresholds for intervention, so this should be considered on a case-by-case with discussion between the treating team and person with NF1.	weak
Rec. 3	Removal should be by laser, surgery, electrodesiccation or radiofrequency ablation. If multiple tumours are removed, histological assessment of all clinically obvious small cutaneous neurofibroma is not necessary.	moderate
Rec 4	Given the burden of the visible manifestations in NF1 with cutaneous neurofibroma, patients with cutaneous neurofibroma should be offered psychological support (please see recommendations in the psychosocial needs section 7.14 & 9.14).	weak

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **cutaneous neurofibroma**?	Cutaneous neurofibromas are visible and palpable skin in clinical examination.
What methods of clinical surveillance?	Visual inspection and palpation.

When should clinical surveillance start?	When NF1 is diagnosed.
How often should clinical surveillance be repeated?	On every control visit.
Q2. In people with NF1, what imaging surveillance is beneficial for detecting **cutaneous neurofibroma**?	Not applicable. Cutaneous neurofibromas are visible and palpable skin in clinical examination.
Q3. If **cutaneous neurofibroma** is diagnosed is the indication for monitoring different in NF1?	If the patient does not have NF1 diagnosis, finding cutaneous neurofibroma should follow clinical examination to find other signs of NF1 to diagnose or rule out NF1.
And if yes, what is content of monitoring (mode, interval)?	In patient with NF1 the number, size, location and symptoms of cutaneous neurofibromas should be documented in patient records on each follow-up appointment.
Q4. If **cutaneous neurofibroma**, is diagnosed, is the indication for treatment different in NF1?	If the patient does not have NF1, cutaneous neurofibroma should be resected to get the histological diagnosis. In patient with NF1 cutaneous neurofibromas does not need to be operated unless the patient wishes.
And if YES , what is the indication for treatment in NF1?	Discomfort for patient is the primary indication for treatment. Regarding aesthetic considerations the impacts are unique to each individual and each health system has its own criteria and thresholds for intervention, so this requires case-by-case consideration between the treating team and people with NF1 .
Q5. Is treatment different in NF1?	In NF1, removal of multiple cutaneous neurofibromas can be done at the same appointment and histological diagnosis of all clinically obvious cutaneous neurofibromas is not needed (Peltonen et al. 2022).
And if YES, what is the NF1 specific treatment?	Carbon dioxide or erbium-doped yttrium aluminium garnet (Er:YAG) laser, surgery electrodesiccation or radiofrequency ablation using either local or general anaesthesia (Becker 1991, Moreno et al. 2001, Kim et al. 2013, Beverly et al. 2014, Kriechbaumer et al. 2014, Lutterodt et al. 2016).
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **cutaneous neurofibroma** or in the management of a diagnosed **cutaneous neurofibroma**?	Despite the known impact on quality of life of living with cutaneous neurofibroma (Wolkenstein et al. 2001, Kodra et al. 2009, Granström et al. 2012, Guiraud et al. 2019, Varni et al. 2019), there are no studies on psychosocial support for living with cutaneous neurofibromas specifically. Eight-week mind–body programme for NF1 has been reported to result in improvements in perceived coping abilities, social support and mindfulness (Zale et al. 2018).

References used:	(Becker 1991, Moreno et al. 2001, Wolkenstein et al. 2001, Kodra et al. 2009, Granström et al. 2012, Kim et al. 2013, Beverly et al. 2014, Kriechbaumer et al. 2014, Lutterodt et al. 2016, Zale et al. 2018, Guiraud et al. 2019, Varni et al. 2019, Peltonen et al. 2022)

9.9. Summary of evidence and guideline Recommendations for Gastrointestinal stromal tumors (GIST)

GISTs are mesenchymal tumours and originate from the interstitial cells of Cajal. Sporadic GISTs are predominantly observed in the stomach (60-70%) and less frequently in the small intestines (20-30%) (Miettinen et al. 2001, Miettinen et al. 2011). The overwhelming majority of GISTs harbour oncogenic activating mutations in the receptor tyrosine kinase genes *KIT* or *PDGFRA*. In ~10% of GISTs, mutations in the *NF1*, *BRAF*, or *SDH* genes have been found (von Mehren et al. 2018). NF1 patients have been estimated to have at least 200-fold increased risk of developing GIST compared to the general population (Miettinen et al. 2011). GIST without *KIT* or *PDGFRA* mutations are known as wild-type GIST and germline *SDH* or *NF1* mutations may be found in this subgroup.

In contrast to the common sporadic GISTs, the NF1-GISTs often occur in younger patients (mean age 52.8 years), they present as multiple lesions, are more often located in the small intestines and have been often described as clinically indolent and asymptomatic. The mitotic counts for NF1-GISTs are also lower (<5/50 high-power field) than for the sporadic GISTs and the NF1-GISTs do not have mutations in the *KIT* or *PDGFRA* gene (Yamamoto et al. 2009, Miettinen et al. 2011, Salvi et al. 2013, Nishida et al. 2016). Maertens et al. were the first to demonstrate that the biallelic inactivation of *NF1* in neoplastic GIST cells can lead to the GIST formation without *KIT* or *PDGFRA* mutations (Maertens et al. 2006). In the group of sporadic GISTs there is a small percentage with a somatic biallelic inactivation of the *NF1* gene in patients without NF1.

MRI is recommended for diagnosis of GIST and ^{18}FDG PET CT may contribute for staging of GIST. Asymptomatic GIST can show up hot on ^{18}FDG PET CT which may cause diagnostic confusion with MPNST (Yla-Outinen et al. 2019). The diagnosis of GIST is established by histological analysis and immunohistochemical staining (KIT positive, delay of germination 1-positive) (Blay et al. 2005, Landi et al. 2019). Diagnosing NF1-GISTs may be challenging since the traditional diagnostic methods, such as colonic or gastroesophageal endoscopy may fail to detect the tumours in the small intestines (Yamamoto et al. 2009). Regardless of the underlying molecular pathway, the standard procedure for all GISTs is surgical resection with negative margins. After surgery the patients should be closely monitored using MRI, CT, or ^{18}FDG PET (Blay et al. 2005, Landi et al. 2019). Because of the high risk of metastatic relapse after the resection, chemotherapy with a tyrosine kinase inhibitor imatinib is advised for GISTs with *KIT* and *PDGFRA* mutations (Blay et al. 2005). However, GISTs associated with NF1 do not present with these mutations and therefore will not respond to this treatment.

Recommendations		Strength
Rec. 1	Investigation for GIST should only be conducted if there is clinical suspicion.	moderate
Rec. 2	Clinical suspicion should be raised in the presence of gastrointestinal discomfort, weight loss, anaemia, gastrointestinal bleeding, abdominal pain, palpable abdominal mass, or intestinal obstruction.	moderate
Rec. 3	Resection should be considered for at least large (>2cm) or symptomatic tumours as there is a risk for bleeding and rupture and risk for malignancy with metastasis.	strong
Rec. 4	People with an incidentally detected GIST that is asymptomatic AND <2 cm diameter should be monitored at least once a year with abdominal MRI (or CT abdomen if an MRI not possible), for at least 5 years, and thereafter to be performed every 2 years.	moderate

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **GISTs**?	The diagnosis of GIST in NF1 may be challenging because of the typical location of the tumour in the small intestine. Traditional diagnostic tools such as colonic or gastroesophageal endoscopies can fail to detect tumours of the small Intestines (Yla-Outinen et al. 2019). When NF1 patients present with vague abdominal discomfort, close attention must be paid to identifying the coexistence of these and other tumours (Park et al. 2019).
What methods of clinical surveillance?	Patients with NF1 and GIST may be asymptomatic or may suffer from gastrointestinal discomfort, weight loss, anaemia, gastrointestinal bleeding, abdominal pain, palpable abdominal mass, or intestinal obstruction (Scarpa et al. 2008).
When should clinical surveillance start?	In adulthood.
How often should clinical surveillance be repeated?	At every visit.
Q.2 In people with NF1, what imaging surveillance is beneficial for detecting **GISTs**?	Investigation for GIST is only indicated following clinical suspicion. Imaging is used in GISTs for the diagnosis, staging, restaging after commencement of therapy, monitoring response to therapy, and for surveillance after therapy.

What modality of imaging for surveillance?	The utility and frequency of imaging in the management of GISTs is determined by the presentation and extent of the GIST. The mainstay for imaging in GISTs abdominal MRI (or CT abdomen if MRI is not possible) (Yla-Outinen et al. 2019). MRI provides greater anatomical detail in certain anatomical sites such as the anorectal region and is useful in planning sphincter-saving surgery. MRI can also be used as an alternative to CT for monitoring response to treatment. Combined PET CT can be useful for staging of GISTs, but does not offer an additional advantage over contrast-enhanced CT. The traditional diagnostic approach based on colonic or gastroesophageal endoscopies may fail to detect tumours of the small intestine (Yla-Outinen et al. 2019)
When should imaging surveillance start?	When the patient gets symptoms or suffers from gastrointestinal discomfort, weight loss, anaemia, gastrointestinal bleeding, abdominal pain, palpable abdominal mass, or intestinal obstruction.
How often should imaging surveillance be repeated?	For GISTs < 2 cm: once a year for 5 years, after that once every 2 years. GIST that are >5cm (intermediate or high-risk GISTs) are often not cured by surgery alone. The timing of scans for the intermediate and high-risk GISTs recommended by ESMO-EURACAN-GENTURIS includes 3–6 month intervals for the first 3 years, then every 3 months for 2 years and every 6 months for another 3 years. Annual imaging is recommended for another 5 years (Casali et al. 2018, Landi et al. 2019, Casali et al. 2022)
Q3. If **GISTs** is diagnosed is the indication for monitoring different in NF1? And if yes, what is content of monitoring (mode, interval)?	People with known asymptomatic GIST should be screened once a year with either abdominal MRI (or CT abdomen), for at least 5 years, until size exceeds 2 cm or symptoms appear (Casali et al. 2010, Alessandrino et al. 2019).
Q4. If **GISTs**, is diagnosed, is the indication for treatment different in NF1? And if YES on, what is the indication for treatment in NF1?	Surgical resection should always be considered as the primary therapy for all GISTs, independent of the underlying pathway (Nishida et al. 2016, Yla-Outinen et al. 2019). Resection should be considered for large (>2cm) (Blay et al. 2005, Alessandrino et al. 2019) or symptomatic tumours as there is a risk for bleeding and rupture and risk for malignancy with metastasis (Blay et al. 2005, Alessandrino et al. 2019) .

Q5. Is treatment different in NF1? And if YES, what is the NF1 specific treatment?	Prognosis on average better for same stage as in sporadic GIST. The treatment of NF1 associated GIST is complete surgical resection (Miettinen et al. 2006). In NF1 these tumours do not harbour the mutations in *KIT* and *PDGFRA*, which are typically associated with sporadic GISTs. These tumours are therefore poorly responsive to the tyrosine kinase inhibitor imatinib (Mussi et al. 2008, Izquierdo et al. 2012, Salvi et al. 2013, Landi et al. 2019), although sunitinib, another tyrosine kinase receptor inhibitor, can be useful in metastatic disease (Kalender et al. 2007, Mulet-Margalef et al. 2016). Frequently multiple tumours are detected in the intestine i.e. one large tumour (detected by MRI) and multiple smaller tumours detected only during surgery. Most tumours are localised in the small bowel and few in the stomach. This is opposite in the non-NF1 associated GIST.
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty **GIST** or in the management of a diagnosed **GISTs**?	Some people require psychological support, particularly people who have presented with severe haemorrhage or when diagnosed with multiple GIST.
References used:	(Blay et al. 2005, Miettinen et al. 2006, Kalender et al. 2007, Mussi et al. 2008, Scarpa et al. 2008, Casali et al. 2010, Izquierdo et al. 2012, Salvi et al. 2013, Mulet-Margalef et al. 2016, Nishida et al. 2016, Casali et al. 2018, Alessandrino et al. 2019, Landi et al. 2019, Park et al. 2019, Yla-Outinen et al. 2019, Casali et al. 2022)

9.10. Summary of evidence and guideline Recommendations for Phaeochromocytoma and Paraganglioma

Prevalence of phaeochromocytoma and paraganglioma in NF1 is higher than in the general population. But larger retrospective series show a significantly lower prevalence (0.1% (Uusitalo et al. 2016), 0.72% (Al-Sharefi et al. 2018, Al-Sharefi et al. 2019), and 2.9% (Gruber et al. 2017)) compared to smaller prospective studies with active screening (14.6% (Zinnamosca et al. 2011) and 7.7% (Képénékian et al. 2016)). These differences are probably demonstrating that the real incidence for phaeochromocytoma and paraganglioma in NF1 population is higher than suspected although many of these tumours might never become symptomatic. Further prospective studies are needed to ascertain if applying a surveillance strategy can reduce the rate of complications and improve prognosis.

Most of these tumours are usually diagnosed incidentally (Walther et al. 1999) when imaging for other reasons, and around 50% of phaeochromocytoma and paraganglioma in NF1 do not develop typical symptoms (headache, palpitations, sweating or high blood pressure), reflecting that clinical examination is unreliable for some phaeochromocytoma and paraganglioma in this population.

Metanephrines (blood or urine) have sensitivity higher than 90-95% for detection of phaeochromocytoma and paraganglioma (Lenders et al. 2014), although unexpectedly in the Kénépékian prospective study they found 50% NF1 patients with phaeochromocytoma and paraganglioma had normal urine metanephrines (Képénékian et al. 2016).

The vast majority of phaeochromocytoma and paraganglioma in NF1 are adrenal tumours, (15-20% of them bilateral), although a few extra-adrenal tumours (paragangliomas) are also described (Gruber et al. 2017, Al-Sharefi et al. 2019). Median age when diagnosed is 40-50 years (range 14-82) (Bausch et al. 2006, Al-Sharefi et al. 2018), suggesting that screening could be more efficient if started at age 30 years. Several studies showed that women are more prone to bilateral or more aggressive phaeochromocytoma and paraganglioma, and there is also evidence that women are at increased risk of having maternal and foetal complications during pregnancy if they have undiagnosed phaeochromocytoma and paraganglioma (Mannelli et al. 2002, Gruber et al. 2017, Al-Sharefi et al. 2018). Metastatic tumours (7-12% of phaeochromocytoma and paraganglioma), fatal cases and irreversible sequelae are described (Bausch et al. 2006, Gruber et al. 2017, Al-Sharefi et al. 2018), leading some authors to suggest that an effective active surveillance screening could potentially have avoided morbidity and mortality.

Recommendations		Strength
Rec. 1	Routine biochemical screening for phaeochromocytoma and paraganglioma is not recommended in people with NF1 except for all women with NF1 who are contemplating pregnancy or are already pregnant.	moderate
Rec. 2	Biochemical testing for phaeochromocytoma and paraganglioma should be conducted in any person with NF1 who has raised blood pressure unexplained by other medical reason.	moderate
Rec. 3	Biochemical testing for phaeochromocytoma and paraganglioma might be considered prior to any elective surgical procedures requiring general anaesthesia in adult patients with NF1.	weak
Rec. 4	As in any phaeochromocytoma and paraganglioma predisposition syndrome surgery should be considered for symptomatic or biochemically active lesions.	strong
Rec. 5	A cortical-sparing adrenalectomy should be the preferred approach due to the risk of metachronous contralateral adrenal tumour.	moderate

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **phaeochromocytoma and paraganglioma**?	Further prospective studies are needed to ascertain if applying any systematic surveillance strategy can reduce the rate of complications and improve prognosis. While some authors suggest screening all NF1 patients, others argue that only those symptomatic (hypertension, headache, palpitations or sweating), before an elective surgery or women planning pregnancy should get it (Mannelli et al. 2002). The standard method of clinical screening for any hereditary phaeochromocytoma and paraganglioma is measurement of supine plasma free metanephrines or urinary fractionated metanephrines and, if positive, subsequent appropriate radiological imaging (Al-Sharefi et al. 2019).
What methods of clinical surveillance?	Blood pressure measure and inquiring about clinical symptoms such as headache, palpitation or sweating should be recorded at each visit. phaeochromocytoma and paraganglioma are asymptomatic and normotensive. We recommend restricting biochemical testing to: • any NF1 patient newly diagnosed with arterial hypertension unexplained by other medical reasons • NF1 patient with any of the following symptoms: persistent headache, palpitations or excessive sweating

	• all women with NF1 contemplating pregnancy or already pregnant • prior to any elective surgical procedure under general anaesthesia in any patient older than 14 years old
When should clinical surveillance start?	The incidence of phaeochromocytoma at paediatric age is very low. But since the youngest patient in the literature was 14 years old, and for metastatic disease is 16 years old (Giovannoni et al. 2014), some authors recommend starting surveillance at 10-14 years. The oldest patient described is 82 years, so the screening should be offered lifelong.
How often should clinical surveillance be repeated?	Blood pressure and inquiring about symptoms should be undertaken once a year. In case biochemical surveillance is recommended, it should be repeated every 3 years (Gruber et al. 2017, Al-Sharefi et al. 2018, Al-Sharefi et al. 2019).
Q2. In people with NF1, what imaging surveillance is beneficial for detecting **phaeochromocytoma and paraganglioma**?	Since the benefit of diagnosing small and non-secreting phaeochromocytoma and paraganglioma is unclear and sensitivity of imaging doesn't seem superior to metanephrines analysis, an imaging screening doesn't seem necessary unless it is performed for another reason (plexiform neurofibroma, ANNUBP, GIST).
What modality for imaging phaeochromocytoma and paraganglioma in NF1	Ultrasounds have an estimated sensitivity for detecting phaeochromocytoma and paraganglioma around 80% (lower in obese patients and those small or left sided tumours). CT sensitivity is probably higher (88-100%) and similar to MRI. Hypertensive crisis has been described with high-osmolar contrast media, with those receiving alpha or beta blockers having a higher risk. Low-osmolar contrast seems safer (Képénékian et al. 2016, Itani et al. 2019). In patients with clinical suspicion or laboratory evidence of phaeochromocytoma and paraganglioma, imaging is usually performed to localize the lesion and evaluate for any metastatic disease. 18F-fluoro-l-dihydroxy-phenylalanine PET CT have been described to outperform ^{123}I-meta-iodobenzylguanidine (MIBG) scintigraphy in the detection of phaeochromocytoma, with a sensitivity close to 100% compared to 70% for MIBG scintigraphy, particularly for non-adrenal or metastatic disease. Since the benefit of diagnosing small and non-secreting phaeochromocytoma and paraganglioma is unclear and for most authors, sensitivity of imaging does not seem superior to metanephrines analysis, an imaging screening doesn't seem necessary in all patients unless it is performed for another reason (plexiform neurofibroma, ANNUBP, GIST).
Q3. If **phaeochromocytoma and paraganglioma** is diagnosed is the	There is not enough evidence to suggest that NF1 phaeochromocytoma and paraganglioma behave differently than non-NF1 phaeochromocytoma

indication for monitoring different in NF1? And if yes, what is content of monitoring (mode, interval)?	and paraganglioma and same recommendations as any phaeochromocytoma and paraganglioma predisposition syndrome should be offered. The rate of recurrence seems equally comparable to non-NF1 phaeochromocytoma and paraganglioma (Bausch et al. 2006, Gruber et al. 2017, Al-Sharefi et al. 2018, Al-Sharefi et al. 2019). In patients with a previous diagnosis of solitary phaeochromocytoma and paraganglioma we recommend biochemical testing annually if it was completely resected.
Q4. If **phaeochromocytoma and paraganglioma**, is diagnosed, is the indication for treatment different in NF1? And if YES on, what is the indication for treatment in NF1?	The indications for treatment are the same as in other phaeochromocytoma and paraganglioma predisposing syndrome. Phaeochromocytoma and paraganglioma detected by screening is very rarely malignant and can be resected by laparoscopy if resection is needed. There are few published cases with small asymptomatic tumours that were not initially resected (Képénékian et al. 2016), but for those symptomatic or functioning phaeochromocytoma and paraganglioma surgery after an effective antihypertensive management is warranted (Képénékian et al. 2016).
Q5. Is treatment different in NF1? And if YES, what is the NF1 specific treatment?	Cortical-sparing adrenalectomy in highly specialized centres should be considered when feasible, since the risk of contralateral metachronous phaeochromocytoma. Numerous therapeutic regimens exist for metastatic malignant phaeochromocytoma; however, no regimen has been shown to have a benefit significantly superior to the others (Otoukesh et al. 2014).
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **phaeochromocytoma and paraganglioma** or in the management of a diagnosed **phaeochromocytoma and paraganglioma**?	Same as other chapters. No specific guidelines for phaeochromocytoma and paraganglioma.
References used:	(Mannelli et al. 2002, Bausch et al. 2006, Giovannoni et al. 2014, Otoukesh et al. 2014, Képénékian et al. 2016, Gruber et al. 2017, Al-Sharefi et al. 2018, Al-Sharefi et al. 2019, Itani et al. 2019)

9.11. Summary of evidence and guideline Recommendations for Breast Cancer

The field of breast cancer in patients with NF1 has seen increasing attention in the past few years. Several studies have demonstrated that breast cancer in NF1 patients affects primarily women younger than age 50 years (L. Walker et al. 2006, Sharif et al. 2007, Madanikia et al. 2012, X. Wang et al. 2012b, Seminog et al. 2015, Howell et al. 2017, Uusitalo et al. 2017). These studies from different countries report an overall SIR ranging from 1.9-5.2, with a substantial higher SIR for women < 50 years (ranging from 4.0-8.8) In terms of mortality the proportionate mortality ratio for breast cancer is reported to be was 3.5 (95% CI, 1.3–7.7) (Sharif et al. 2007).

In their follow-up paper Uusitalo et al. (Uusitalo et al. 2017) examined the characteristics of the breast cancer diagnosed in NF1 cases and controls. NF1 associated breast cancer were more often oestrogen receptor (ER) negative (53.8% vs. 20.9%, P=0.001), progesterone receptor negative (65.4% vs. 21.7%, P< 0.001) and Human Epidermal growth factor Receptor 2 (HER2) positive (30.8% vs. 9.6%, P=0.006) all factors associated with adverse prognosis. The NF1 tumours were also larger (P=0.019) and of higher grade (P =0.05). An overall survival analysis was performed against controls matched for age and ER status demonstrating inferior 5-year survival in those with NF1 (68.1% (95% CI 52.0–89.1%) vs. 82.0% (95% CI 75.5–88.9%); p=0.053). The hazard ratio for death was 2.3 (95% CI 0.99–5.6). They demonstrated similar to others (M. D. Wallace et al. 2012, Suarez-Cabrera et al. 2017) *NF1* mutations or deletion in 33% of breast cancers with a significant enrichment in ER negative and HER2 positive subtypes. From these epidemiological studies at least half of the breast cancer of patients with NF1 are diagnosed under 50 years of age (Uusitalo et al. 2017), whereas in the general population <20% occur by this age. The highest incidence in NF1 is in women < 40 years with mortality rates higher than those for women with breast cancer in the general population (Evans et al. 2011, Uusitalo et al. 2017).

Survival in NF1 women without enhanced screening was very poor and worse than predicted for the average population, but some benefit from screening was seen in in an Italian subset who were offered annual screening (Evans et al. 2020a).

Screening for breast cancer has been recommended for patients with heritable risk to be started at the age when the risk exceeds that of general population (Tung et al. 2016). In NF1 this is at the age of 30. From above it can be seen that NF1 risk is equivalent to the risk of the screened general population from this age.

Early screening generates two major concerns. First, the safety of mammography in NF1 patients, especially if started at a very young age, is unknown. Although the radiation exposure is low with mammography, NF1 patients have been shown to develop secondary malignancies in response to therapeutic ionising radiation (Sharif et al. 2006). Second, the lower specificity of MRI may lead to overdiagnosis with the unnecessary core biopsy of lesions that may turn out to be benign neurofibromas rather than breast cancer (Leach et al. 2005). Although digital mammography is the gold standard for screening for early-stage breast cancer, interpreting images of a breast carcinoma in an NF1 patient may be challenging due to the high number of neurofibromas in some women. The structure of the mammary gland tissue in young patients may also compromise the interpretation. The repeated radiation exposure may also increase the risk of other cancers (Pauwels et al. 2016), so screening with breast MRI should be the primary approach if available.

Treatment of NF1-associated breast cancer is similar to that of breast cancer in the general population. Risk-reducing mastectomy is not recommended in NF1 patients as there are no data regarding its benefit; however, it may be suggested based on family history and for the contralateral breast in NF1 women with stage 1 breast cancer at young ages as there is a 1% annual risk of contralateral breast cancer in those with unilateral disease prospectively (Evans et al. 2020a).

Recommendations		Strength
Rec. 1	Despite there being no evidence of outcome benefits from clinical assessment, education about breast self-examination probably should be conducted as it raises awareness and engagement with clinical centres.	weak
Rec. 2	Screening with annual breast MRI should be the primary approach, mammography being second best alternative when MRI is not available. Age at commencement of screening in NF1 should begin as soon after the age of 30 years as feasible in the local health system context.	moderate
Rec. 3	Screening should continue until 50 years after which time, screening should be according to national guidelines for the general population.	moderate
Rec. 4	Risk-reducing bilateral mastectomy for woman without breast cancer should not be performed in NF1 patients unless there are substantial additional risk factors such as a family history of breast cancer that would elevate risk into a high-risk category.	moderate

Q1. What is the evidence that the risk of **breast cancer** is elevated and is it sufficient for interventions?	There is strong consistent evidence from epidemiological and cohort studies of an increased risk of breast cancer especially <50 years which equates to moderate risk which is sufficient for screening in familial breast cancer.
Q2. In people with NF1, what clinical surveillance is beneficial for detecting **breast cancer**?	There is no evidence of outcome benefits from clinical surveillance, however education about breast self-examination can be helpful in raising awareness and engagement with clinical centres.
What methods of clinical surveillance?	Breast self-examination
When should clinical surveillance start?	30 or 35 years
How often should clinical surveillance be repeated?	Annually
Q3. In people with NF1, what imaging surveillance is beneficial for detecting **breast cancer**?	Mammography and/or breast MRI.
What modality of imaging for surveillance?	Screening with breast MRI should be the primary approach if available. If breast MRI is available, mammography might be avoided in patients younger than 40 years (Narayan et al. 2016).
When should Imaging surveillance start?	Based on increased risk of early-onset breast cancer in female patients with NF1, breast screening is recommended, to begin at age 30 years. Screening after 50 years can be as per national guidelines for the general population.
How often should imaging surveillance be repeated?	Annually until 50 and thereafter population screening.
Q4. If **breast cancer** is diagnosed is the indication for monitoring different in NF1?	No.
Q5. If **breast cancer** is diagnosed, is the indication for treatment different in NF1?	No.
Q6. Is **breast cancer** treatment different in NF1?	Treatment of NF1-associated breast cancer is similar to that of breast cancer in the general population. Risk-reducing mastectomy is not recommended in NF1 patients.
References used:	(Narayan et al. 2016)

9.12. Summary of evidence and guideline Recommendations for Glomus tumors of the digits

Glomus tumours are small, benign and painful tumours originating from the glomus body, a thermoregulatory shunt in the fingers and toes (Brems et al. 2009, Stewart et al. 2010). The symptoms associated with glomus tumours are the classic triad of localised tenderness, severe paroxysmal pain and sensitivity to cold (De Smet et al. 2002, Brems et al. 2009).

In 1938 the first association between NF1 and glomus tumours was reported (Klaber 1938). In 2009 Brems et al. proved that the biallelic loss of the *NF1* gene in the alpha smooth muscle actin-positive glomus cells was responsible for the development of glomus tumours in patients with NF1 (Brems et al. 2009). Glomus tumours were then recognized as part of the NF1 phenotype (Ferner 2007, Huson 2008).

Sporadic glomus tumours are usually solitary, subungual masses with benign clinical behaviour (Gombos et al. 2008). In sporadic and NF1-associated glomus tumours the presentation is comparable and females are more likely to present with glomus tumours (55.9% in general population, 66.7%-79% in NF1 patients) (Stewart et al. 2010, Harrison et al. 2014, Kumar et al. 2014). Although, NF1 glomus tumours are more likely to present with multifocal tumours (16-45%) than sporadic glomus tumours (7.1%) (De Smet et al. 2002, Stewart et al. 2010, Brems et al. 2013, Harrison et al. 2014, Kumar et al. 2014). Tumour recurrence after surgical resection was also more common in NF1 glomus tumours (33%) compared to sporadic glomus tumours (7.1%) (Kumar et al. 2014). Moreover, NF1-associated tumours did not exhibit neurofibromin activity, while it was retained in sporadic glomus tumours (Brems et al. 2009, Kumar et al. 2014).

In uncomplicated cases, a clinical exam was sufficient to diagnose the glomus tumours, MRI may be useful and traditionally surgical resection is performed (Stewart et al. 2010, Stewart et al. 2018, Bergqvist et al. 2020). In more atypical presentations or for extremely small glomus tumours (<3mm), preoperative colour Doppler ultrasound can be useful to accurately locate the tumour and inform on the sizing of the tumour (Z. Fan et al. 2016). A remaining problem is the under-recognition of the glomus tumours. The diagnosis is often delayed, resulting in chronic pain for the patient (Stewart et al. 2018). Stewart et al. reports the average time of symptoms before the patient was diagnosed amounted to 10 years (Stewart et al. 2010). An increase of awareness of the association between NF1 and glomus tumours may hopefully result in a better quality of life of these patients.

Recommendations		Strength
Rec. 1	Glomus tumours of the digits are easily missed and therefore clinical suspicion is essential to make a diagnosis of glomus tumours of the digits. Clinical diagnosis should be based on patient reported typical symptoms (see recommendation 2) and on visual examination of the nail beds and palpation.	moderate
Rec. 2	The majority of people will have at least two of the following symptoms: localised tenderness, severe paroxysmal (lancinating, similar to being hit on the nailbed) pain and sensitivity to cold. Visual inspection may show purplish discolouring of the nailbed.	moderate
Rec. 3	Glomus tumours of the digits occur mostly in adulthood, but should also be considered in children/adolescents with typical symptoms.	weak
Rec. 4	Surgical excision should be considered for painful glomus tumours of the digits.	moderate

Q1. In people with NF1, what clinical surveillance is beneficial for detecting **glomus tumours of the digits**?	As people frequently do not spontaneously mention the pain in the digits, **c**linical suspicion is essential to make a diagnosis of glomus tumours (Stewart et al. 2018). Clinical diagnosis is based on the clinical history and on clinical examination. Glomus tumours are recognised as part of the NF1 phenotype (Ferner 2007, Huson 2008).
What methods of clinical surveillance?	Clinical surveillance is based on typical symptoms of pain and cold sensitivity and on visual examination of the nail beds and palpation. The majority of people will have at least two of the following symptoms: localised tenderness, severe paroxysmal (lancinating, likened to being hit on the nailbed) pain and sensitivity to cold (Stewart et al. 2018). It is advised to press the fingertips on clinical examination to provoke pain in case of glomus tumours.
When should clinical surveillance start?	In adulthood however, rarely, cases have occurred in adolescents so the diagnosis should not be discounted in younger people (Brems et al. 2009).
How often should clinical surveillance be repeated?	At every visit.

Q2. In people with NF1, what imaging surveillance is beneficial for detecting **glomus tumours of the digits**?	Imaging surveillance for glomus tumours is generally inappropriate but rather focus should be given to diagnosis in the event of clinical suspicion. Clinical examination is sufficient for diagnosis and surveillance. Both MRI and Ultrasound (Z. Fan et al. 2016) can be useful in support of the diagnosis, and management of glomus tumours. MRI can miss these tumours, so a negative scan does not preclude the diagnosis.
Q3. If **glomus tumours of the digits** is diagnosed is the indication for monitoring different in NF1?	No. As the symptoms will trigger to perform imaging, and therefore set the diagnosis, it has a treatment indication, not a monitoring indication (Stewart et al. 2010, Stewart et al. 2018, Bergqvist et al. 2020).
Q4. If **glomus tumours of the digits**, is diagnosed, is the indication for treatment different in NF1?	No, the indication for treatment is pain and a patient willing to have the tumour removed because of the disability it causes. Surgical excision should be considered for painful glomus tumours (Stewart et al. 2010, Stewart et al. 2018, Bergqvist et al. 2020).
And if YES on, what is the indication for treatment in NF1?	Symptoms (which also will be the trigger to set the diagnosis).
Q5. Is treatment different in NF1?	No, but frequently multiple fingers can be affected, and this is very rare outside NF1 (De Smet et al. 2002, Stewart et al. 2010, Brems et al. 2013, Harrison et al. 2014, Kumar et al. 2014, Bergqvist et al. 2020).
Q6. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of **glomus tumours of the digits** or in the management of a diagnosed **glomus tumours of the digits**?	Prolonged symptoms especially pain and the delay in diagnosis is psychologically very difficult for the patient. In some cases, removing the tumour does not cure the problem because of relapse or because of a complex regional pain syndrome. In non-NF1 related glomus tumours usually only one finger is affected (solitary tumour) but in NF1-related glomus tumours multiple digits can be affected synchronous or metachronous (De Smet et al. 2002, Stewart et al. 2010, Brems et al. 2013, Harrison et al. 2014, Kumar et al. 2014, Bergqvist et al. 2020).
References used:	(De Smet et al. 2002, Ferner 2007, Huson 2008, Brems et al. 2009, Stewart et al. 2010, Brems et al. 2013, Harrison et al. 2014, Kumar et al. 2014, Z. Fan et al. 2016, Stewart et al. 2018, Bergqvist et al. 2020)

9.13. Summary of evidence and guideline Recommendations for Juvenile myelomonocytic leukemia (JMML)

JMML is a rare leukaemia characterized by an overproduction of immature monocytic and granulocytic cells that infiltrate various organs, including the spleen, liver, lung, skin, and gastrointestinal tract. Affected children usually have pallor, fever, and skin petechiae and ecchymosis, which results from anaemia, monocytosis, and thrombocytopenia. Morphological evaluation of a peripheral blood smear is the most important step in suspecting and then, after bone marrow evaluation, establishing the diagnosis. Two characteristics to be mentioned are: elevated levels of foetal haemoglobin and in vitro sensitivity of myeloid precursors to granulocyte macrophage colony-stimulating factor (Locatelli et al. 2015). The link of NF1 with leukaemia is long standing (Bader et al. 1977, Emanuel 2008) and the first major epidemiological study was Stiller et al. 1994 (Stiller et al. 1994).

In the vast majority of cases, JMML is an aggressive and fatal disorder if left untreated (Proytcheva 2011, Porter et al. 2017), but there are as yet no specific treatments for NF1 related cases. The median survival of children who do not receive an allograft transplant can be as short as 10 to 12 months. Two fatal cases of JMML were reported in a UK population of 1186 NF1 patients (Evans et al. 2011) while no CMML or JMML cases were observed in the Finnish NF1 cohort (Uusitalo et al. 2016, Peltonen et al. 2019) nor in the large population-based study from Great Britain (Seminog et al. 2013). Based on these findings, JMML is not a frequent complication of NF1 although NF1 patients represent an unusually large percentage of patients with this leukaemia type. Children with JMML and NF1 are more often diagnosed after the age of 5 years than JMML patients of other subtypes, have a higher percentage of blasts in the bone marrow and have a higher platelet count. Although some of the younger children can initially present a relatively unaffected clinical course, NF1-mutated JMML is invariably fatal unless allogenic hematopoietic stem cell transplantation is successful (Niemeyer et al. 2019).

Association of JMML and juvenile xanthogranulomas (JXG) has been described in several case reports (Paulus et al. 2017). JXGs are benign yellowish skin tumours which show accumulation of non-Langerhans cells histiocytes. JXGs are often multiple and even 30 % of under 2-year-old children with NF1 have been reported to have them (Ferrari et al. 2014). A retrospective comparative register study did not find an increased risk for malignancy associated with JXG in children with NF1 (Liy-Wong et al. 2017). Based on the rarity of JMML, and the frequency of JXG we conclude that the presence of JXG does not necessitate special follow-up for JMML.

Recommendations		Strength
Rec. 1	At this time the increased risk for JMML in NF1 is not clear, and is almost certainly <1%. As such specific clinical assessment probably should not be conducted.	moderate
Rec. 2	Observing juvenile xanthogranulomas in children with NF1 may raise awareness to actively search for other alarming signs of JMML (amongst others hepatosplenomegaly, paleness, abnormal lymph nodes), but should not be considered reason enough for extensive investigations for JMML.	weak

Q1. Is the risk of **JMML** sufficient to justify clinical surveillance	At this time the increased risk for JMML in NF1 is not clear, but is almost certainly <1% (Stiller et al. 1994, Niemeyer et al. 1997, Emanuel 2008, Niemeyer et al. 2008, Evans et al. 2011, Seminog et al. 2013, Uusitalo et al. 2016, Evans et al. 2017).
Q2. In people with NF1, what clinical surveillance is beneficial for detecting **JMML**?	As the risk of JMML in NF1 is not clear, but is almost certainly <1% specific surveillance is not indicated especially as this would require repeated venesection.
Q3. Is there a particular concern about risk of **JMML** associated with JXG?	Even in the presence of xanthogranuloma the risks are still not clearly sufficient (Ferrari et al. 2014, Liy-Wong et al. 2017, Paulus et al. 2017).
Q4. In people with NF1, what imaging surveillance is beneficial for detecting **JMML**?	At this time the increased risk for JMML in NF1 is not clear and as such specific surveillance is unnecessary.
Q5. If **JMML** is diagnosed is the indication for monitoring different in NF1?	No
Q6. If **JMML**, is diagnosed, is the indication for treatment different in NF1?	No
Q7. Is treatment different in NF1?	No (Proytcheva 2011, Porter et al. 2017).
References used:	(Stiller et al. 1994, Niemeyer et al. 1997, Emanuel 2008, Niemeyer et al. 2008, Evans et al. 2011, Proytcheva 2011, Seminog et al. 2013, Ferrari et al. 2014, Uusitalo et al. 2016, Evans et al. 2017, Liy-Wong et al. 2017, Paulus et al. 2017, Porter et al. 2017)

9.14. PSYCHOSOCIAL NEEDS

In common with a number of other lifelong long-term conditions, the impact of NF1 on quality of life and mental health is well documented (Ferner et al. 2014, Cohen et al. 2015, Vranceanu et al. 2015, Gutmann et al. 2017, Lai et al. 2017, Hamoy-Jimenez et al. 2020). Chronic pain (often associated with tumours), visible physical appearance (often because of cutaneous neurofibroma), undergoing interventions for tumours and fear of increasing tumour burden or malignancy are all reported to impact negatively on quality of life and mental health (Granström et al. 2012, Smith et al. 2013, Rietman et al. 2018, Bellampalli et al. 2019). Other common difficulties in NF1 such as impaired social skills and poor cognitive processing also have a deleterious effect on mental health. It is important to note that a psychosocial intervention will not be determined by the specific tumour type or diagnosis per se, but by an assessment (derived in consultation with the patient) concerning specific symptoms, illness concerns, psychological and social factors which have the greatest impact on their wellbeing and quality of life.

In the following, we first look at considerations about particular aspects of NF1 that are likely to impact on when an intervention is needed and how it is delivered, and then suggest guidance around the following areas: the importance and timescales of psychosocial and neuropsychological assessment in NF1; psychoeducation; and more tailored psycho-social interventions.

Recommendations		Strength
Rec. 1	NF1 has a significant effect on psychosocial and neuropsychological functioning and impacts on quality of life. It is strongly advised to have a psychologist as a member of the multidisciplinary team, to support patients and families when making decisions about diagnosis, management and treatment.	weak
Rec. 2	Psychosocial wellbeing and neuropsychological functioning should be addressed at each clinic visit. These may include assessing e.g. anxiety and depression, coping mechanisms and patient reported outcomes.	weak
Rec. 3	The information and guidance for NF1 patients and family members should be age-appropriate and tailored to the needs of the individual, potential interventions to reduce the impact of NF1 on psychosocial functioning and quality of life should be included.	weak

Q1. What psychosocial support do people with NF1 benefit from, specifically in living with the uncertainty of at-risk tumours or in the management of a diagnosed tumour?	Despite the impact on psychological and social functioning as well as on quality of life in NF1 and in spite of the advances in medical care for cancer, there is a relative paucity of NF1-specific research into psychosocial interventions to improve quality of life and mental health. Reduced self-esteem seems to be one of the most important factors regarding psychological burden in NF1. Relevant work in related fields, in particular work on chronic pain, visible difference, fatigue, cancer, and other common long-term conditions may support a comparable approach for NF1. For example, cancer survivors and their caregivers report that there is a need for the understanding of psychosocial needs, recognition and treatment of fatigue, pain, depression, and symptoms of stress. Awareness of and referral to available resources, and consideration of psychosocial support should be an integral part of cancer care. Importantly, any clinical assessment in NF1 should incorporate screening or questioning about mental health and quality of life and be able to draw on appropriate interventions to support patients' needs, encompassing a range of allied healthcare professionals including (but not limited to) psychiatrists, psychologists, occupational therapists, physiotherapists, and social workers.
Q2. Considerations when working with people with NF1?	Next to the specific recommendations below, some more general recommendations can be formulated pertaining the monitoring and treatment of psychological and psychosocial needs of patients with NF1. It is to be expected that individuals with a learning disability, specific learning difficulty, emotional problems, or behavioural problems (which are all present in a higher frequency in NF1) need more support during and after tumour management than those without these problems. In particular, those with emotional problems seem to be more at risk for impaired psychological adjustment and lowered quality of life (Graf et al. 2006, D. L. Wang et al. 2012a). Since good family relationships have a positive impact on both Quality of life and psychological adjustment (Graf et al. 2006), guidance of parents, siblings, partners and families should be integrated into care. To ensure that care addresses all aspects of well-being, systematic screening for distress and supportive care needs is recommended (Schouten et al. 2019). A study on the NF1 patients' understanding of their illness, especially the assessment of their risk for benign and malignant tumours (Granstrom et al. 2014) showed that explanations about risks and findings had to be repeated unusually often before the patient became aware of them (Granstrom et al. 2014).
Q3. Which psychosocial and neuro-psychological assessments are used for NF1 patients?	NF1 can cause significant impairments in behaviour and on a cognitive level. Approximately 75% of children with NF1 are at risk of underachieving at school (Krab et al. 2008) , 80% suffer from at least one type of cognitive impairment, and 40% meet the criteria for ADHD (Payne et al. 2019). Typical difficulties include developmental delays in different areas, attention problems, difficulties in visual perception, psychosocial interactions, and a reduced Quality of life (Krab et al. 2008, Lehtonen et al. 2013, Ejerskov et al. 2015, Vranceanu et al. 2015). The stress caused by the condition can also affect the wider family and social environment (Lehtonen et al. 2013, Esposito et al. 2014). Therefore, comprehensive psychosocial monitoring is essential in order to be able to mitigate the effects of these difficulties (Ferner 2007, Bergqvist et al. 2020). Since different challenges arise depending on age and life stage, psychosocial assessments are required at various points in time and are of utmost importance especially during critical developmental phases (e.g. school enrolment). In addition to the standard diagnostics, the examination should always be based on the individual question and it is important to include the burden for the whole

	family. In common with most conditions, it would be appropriate to ask about, and screen for, psychological distress at each clinic appointment, and to consider a neuropsychological assessment where there are particular concerns about cognitive development, which may be most prominent at transition times (e.g. starting school, moving to secondary school, young adult leaving home).
Q4. What is the aim of psycho-education?	The aim of psycho-education is to give a better understanding of a disease, its causes and consequences, as well as possible treatment options, in order to help families develop supportive coping strategies. There is a good evidence base and expert consensus that psycho-educational interventions aimed at enhancing knowledge, understanding, communication and the feeling of control regarding chronic conditions have proved to be effective for children and adolescents and their family members. For example, the "Psychosocial Standards of Care Project for Childhood Cancer" (Wiener et al. 2015) formulated a standard with respect to psycho-education, on the basis of 23 publications analysed, most of which found that psycho-educational interventions were well accepted and regarded as helpful by patients and family members, and that interactive approaches adapted to individual needs were able to increase knowledge of the disease and the feeling of control in particular (A. L. Thompson et al. 2015). In a stepped care approach to psychosocial needs, offering psycho-education (written materials, digital resources, or group or one-to-one sessions) would usually be the first intervention offered prior to thinking about the need for more intensive and tailored interventions as outlined below. A patient organisation can play an important role in answering questions through a regional network or helpline, developing and providing educational materials for people with NF1 and those in their network. Through their website, through regional meetings and patient meetings, a patient organisation can play an important role in psycho-education.
Q5. Which types of psychosocial interventions exist for NF1 patients?	**Chronic Pain** There is some evidence for both CBT approaches and acceptance and commitment therapy for improving quality of life and decreasing disability in people with chronic pain (Williams et al. 2020). Martin et al. have specifically looked at acceptance and commitment therapy in young people with NF1 (Martin et al. 2016). Cross-diagnostic multidisciplinary Pain management programmes may be appropriate for people with pain as a consequence of NF1 (Williams 2019). **Visible Difference** There is a good evidence base for CBT approaches to reduce anxiety and improve confidence in people with visible differences (A. Thompson et al. 2001, Rumsey et al. 2004), with the approach detailed in Clarke et al.'s manual (Clarke et al. 2013) and an English-language online intervention available (Bessell et al. 2012). Other resources in the field are available from the Centre for Appearance Research in the UK. (https://www1.uwe.ac.uk/hls/research/appearanceresearch/research.aspx) **Cancer** There is a large amount of literature on the psychosocial impact of cancer and interventions to support people who are being treated for a malignancy, or who are anxious about potential future

	malignancies. Curran et al. (Curran et al. 2017) reviewed research around anxiety in cancer and proposed a model to explain this and guide interventions, and Grassi et al. (Grassi et al. 2017) reviewed the recent evidence base for psychosocial interventions. **Fatigue** Fatigue is very common in NF1 and it is not yet clear what the association is between fatigue and tumour growth. Since fatigue is so widespread, there are possibly more causes to consider next to tumour growth, such as pain, sleeping problems, motor problems, attentional problems, or emotional problems. There is some support for the effectiveness of psychological interventions for fatigue after cancer treatment (Corbett et al. 2019). **Living with a long-term condition** The reciprocal relationship between mental and physical health, and the evidence base for the usefulness of psychosocial interventions in people with long-term conditions is well-documented (England. 2008, Naylor 2012). Negative beliefs about lack of control and danger are common themes, and there is quite a large literature on how health beliefs, coping skills and intolerance of uncertainty can impact on quality of life in people living with a variety of long-term conditions (Capobianco et al. 2020, Knowles et al. 2020). There are a range of psychosocial interventions that have been shown to help with elements of this, including psycho-education, self-management programmes (Kulinski et al. 2014) increasing coping skills and self-efficacy, and anxiety management and mindfulness-based approaches (Dugas et al. 1998, Graham et al. 2016). Within NF1 there is evidence for the usefulness of mind-body approaches (Vranceanu et al. 2014, Vranceanu et al. 2016). **Voluntary sector and accessing mental health services** When assessing someone with NF1 it is important to consider the above factors and the impact of tumours on quality of life and mental health. Ideally a multidisciplinary team would include professionals with a mental health focus who could help to formulate a patient's difficulties and offer an appropriate intervention, but in many cases there may also be other linked services that would be appropriate (for example, cancer services, chronic pain services, or services specifically aimed at any long-term condition). In addition, there may be voluntary or charitable sector services, such as patient organisations, that could also offer a range of resources and sometimes interventions.

10. WHAT DO OTHER GUIDELINES STATE?

In this paragraph we compare our recommendations to other existing guidelines on tumour management in NF1. Therefore, a search was performed using the following terms in Pubmed: (neurofibromatosis type 1 [MeSH Terms]) AND (Neurofibromatosis type 1) AND ((guidelines) OR (recommendations) OR (care)) NOT clinical trial. A total of 167 articles, published in the last 5 years, were found. We excluded 10 articles that were not written in English or without full text availability. Manifestation specific guidelines or recommendations were reported in 99 articles, while 47 articles included specific information regarding the clinical features of NF1 patients, diagnostic criteria and characteristics of NF1, MEK inhibitor tumour treatment, molecular screening and genetic counselling, pain, prevalence of NF1, challenges of NF1-specific multidisciplinary team and psychosocial functioning of NF1 patients, family and the surrounding people. Overall, this left us with 10 articles reporting on the management of all possible NF1-related manifestations. From these 10 we chose one European guideline from France (Bergqvist et al. 2020) and one from the UK (Ferner 2007), one from the US (Stewart et al. 2018), and one with international collaborations (Gutmann et al. 2017). Moreover, we also added the paediatric NF1 management guidelines to compare to the adult guidelines (Evans et al. 2017, Miller et al. 2019). Gaps in the current guidelines for NF1 tumour manifestations and lack of consensus on certain guidelines highlight the need for a uniform European guideline for NF1 tumour management.

The guidelines mostly agree on modes of surveillance and monitoring for NF1 associated tumour manifestations, but differ amongst others on thresholds for age and intervals. Bergqvist et al. (Bergqvist et al. 2020) was more explicit on recommendations for the role of radiotherapy in non-OPGs in adults, drug treatment for plexiform neurofibromas, and incorporated some prognostic factors for MPNST. In contrast to previous guidelines, the ERN GENTURIS guideline specifically addresses NF1 associated tumour manifestations such as orbital and periorbital plexiform neurofibromas and phaeochromocytoma and paraganglioma. In addition, we provide more clear and detailed recommendations on the management/treatment of GIST, glomus tumours of the digits, JMML and phaeochromocytoma in NF1, which in other guidelines were either omitted or mentioned briefly. We aimed to raise more awareness of possible development of these rare NF1 tumour complications in the NF1 patients. Moreover, there is a lack of attention to psychosocial needs and support in the context of cancer care. The addition of a psychologist to the multidisciplinary team and consulting the multidisciplinary team when recommended, will greatly improve the management of NF1 tumour manifestations.

	French guidelines (PNDS) (Bergqvist et al. 2020)	Guidelines UK (NHS) and US (Ferner 2007)	US guidelines (Gutmann et al. 2017)	US guidelines (Stewart et al. 2018)	Paediatric NF1 care (Evans et al. 2017, Miller et al. 2019)	ERN GENTURIS -guidelines (EU) The guideline mostly agrees on modes of surveillance and monitoring, but differs amongst others on thresholds for age and intervals. These differences are depicted in blue.
General approach						
Clinical surveillance	High-risk adults and children: annual evaluation by NF1 specialist. NF1 patients without the high-risk or complications should visit the NF1 specialist every 2 to 3 years, with the rest of the visits taking place annually with a primary care physician, dermatologist, or paediatrician.	Children with uncomplicated disease annually. Young adults aged 16–25 years counselling and education. Adults offered the opportunity of annual assessment. Monitoring after the mid-twenties depends on patient preference and disease severity.	Children evaluated yearly in a multidisciplinary clinic. Adults annual assessment by multidisciplinary team.	Strongly encourage evaluation by and care coordination with a specialized NF1 clinic.	Only manifestation specific mentioned.	Based on the risk of occurrence of tumour complications in NF1, systematic clinical assessment by NF1 experts at regular intervals is advised: Minimum of annually in children up to 10 years Minimum of once every two years in children older than 10 years Minimum of once every 3 years in adults During transition (adolescence to adulthood) more frequent systematic clinical assessment may be warranted (rec 1)
OPG						
Clinical surveillance	Annual paediatric ophthalmological follow-up, at least up until the age of 13 years.	Children < 7 years should have annual visual acuity and fundoscopy looking for optic disc pallor and elevation. Annual screening by an orthoptist (optometrist) until 16 years of age and every 2 years thereafter.	Children ≤10 years of age should have complete annual ophthalmological examinations to assess for signs of an OPG. Periodic ophthalmological evaluations at increasing intervals after 10 years of age.	Not mentioned.	Annual paediatric ophthalmological follow-up. More frequent surveillance or the use of diagnostic imaging best made by the ophthalmologist and clinicians of patient.	For children until the age of 8 years without known OPG, ophthalmologic assessment (see rec 1-3) should be repeated annually (every six months if feasible). (rec 5) In children > 8 years without known OPG formal annual visual screening is advised until adulthood. Diagnostic evaluation by an ophthalmologist is also indicated in those with new visual symptoms. (rec 6) Abnormal, inconclusive or unreliable ophthalmological exam should be repeated within a short timeframe. (rec 7)
Content of assessment	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Clinical assessment for OPG should begin immediately after diagnosis or suspicion of NF1 in childhood. Baseline ophthalmology assessment should be done at presentation whatever the age. (rec 1)

						Clinical assessment for OPG should take the form of examination by trained paediatric (neuro-) ophthalmologist or equivalent with experience in assessment of NF1 related visual changes. (rec 2) Clinical assessment for OPG should include age-appropriate assessment of visual acuity, visual fields, pupillary testing, eye movements, and optic disc appearance. (rec 3) Assessment of retinal nerve fibre layer and retinal ganglion cell layer by optic coherence tomography is helpful and should be conducted whenever. (rec 4)
Imaging	MRI screening not recommended.	MRI screening not recommended.	OPGs should be followed by serial MRI and ophthalmological examinations, typically every 3 months for the first year.	Not mentioned.	Not mentioned.	Imaging for OPG with MRI should be performed in people where ophthalmologic examination is suggestive for OPG and in children >2 years with repeated inconclusive or unreliable ophthalmological exam. (rec 7)
Treatment	Symptomatic tumours with clinically significant growth and progressive visual loss.	Symptomatic OPG	Treatment initiated when clear radiographic progression of disease	Not mentioned.	Symptomatic tumours with clinically significant growth and progressive visual loss.	Any patient with NF1 diagnosed with an asymptomatic OPG should receive a referral to a unit with expertise in the monitoring and management of NF1-OPG. (rec 8) Any patient with NF1 diagnosed with a symptomatic OPG should receive an **urgent** referral to a unit with expertise in the management of NF1-OPG. (rec 9)
	Chemotherapy (vincristine and carboplatin)	Chemotherapy (vincristine and carboplatin)	Chemotherapy (vincristine and carboplatin)	Not mentioned.	Chemotherapy (vincristine and carboplatin)	Referral to a unit with expertise in the management of NF1-OPG.(rec 9) A multidisciplinary team guide on appropriate therapeutic agents. (currently the standard chemotherapy is vincristine and carboplatin.)
	Radiotherapy not recommended.	Surgery for severe proptosis or debulk extensive chiasmal gliomas. Radiotherapy not recommended.	Radiotherapy not recommended.	Not mentioned.	Radiotherapy and surgery are usually contraindicated.	Referral to a unit with expertise in the management of NF1-OPG. (rec 9) Radiotherapy not recommended / usually contraindicated.
Non-OPG (low or high grade brain of spine glioma) in children						

Clinical surveillance and assessment	Neurological evaluation early in life. Observation recommended for asymptomatic glioma.	Neurological examination during annual assessment.	Not mentioned.	Not mentioned.	Children with NF1 and a known lesion are monitored for development of clinical symptoms.	Families with children with NF1 should be educated about possible symptoms and signs of brain tumours. (rec 1) Clinical assessment should take the form of patient history taking and examination for signs of brain tumours and should be repeated at every clinical visit from diagnosis. (rec 2) Routine diagnostic imaging screening for non-OPG, in children who are well, is not indicated. Investigative imaging should be recommended in a child with clinical concern for a brain tumour. (rec 3)
Treatment	Not mentioned.	Not mentioned.	Children with tumours that cause neurological signs or symptoms might require shunting, surgical resection or chemotherapy.	Not mentioned.	Not mentioned.	Symptomatic non-OPG in children with NF1 should be treated by the same care pathway as sporadic non-OPG in children without NF1. A multidisciplinary team should guide on appropriate therapeutic agents in the setting of NF1. Radiotherapy should be avoided, if at all possible, and is not indicated in low grade glioma, whilst recognising that it may be required as an important treatment option in the setting of high-grade glioma. (rec 4)
Non-OPG (low or high grade brain or spine glioma) in adults						
Clinical surveillance	Regular neurological examination.	Neurological examination during annual assessment.	Not mentioned.	Not mentioned.	Brain MRI indicated depending on the acuity of symptoms but not necessary if the headaches are easily controlled and if neurologic examination is normal. Brain MRI recommended at presentation new onset of seizure.	Patients with NF1, their carers and primary care physicians should be educated about possible symptoms and signs of brain tumours in a manner appropriate to the individual patient. (rec 1) Clinical assessment should take the form of examination for signs of brain tumours at every clinical visit. (rec 2) Imaging screening for gliomas should be considered at the age of transition from childhood to adulthood for all patients with NF1 and should take the form of brain MRI with contrast. Imaging investigation should also be undertaken after new associated symptoms or positive physical examination findings. (rec 3)
Treatment and follow-up	Surgery Chemotherapy (carboplatin & vincristine) for	Surgery Chemotherapy Radiotherapy not recommended.	Many gliomas do not require treatment and are followed by annual MRI surveillance in most centres. When	Not mentioned.	Not mentioned.	Incidental detected gliomas should be followed up with imaging like sporadic incidental detected gliomas, with a first interval of 3 months, and if stable asymptomatic disease, intervals can be prolonged. (rec 4)

	progressive and symptomatic gliomas Radiotherapy not recommended.		symptomatic, surgery or chemotherapy.			Non-OPG in adults with NF1 should be managed and treated through the same care pathways as sporadic non-OPG. A multidisciplinary team should guide on appropriate therapeutic agents in the setting of NF1. Radiotherapy should be avoided if at all possible, and is not indicated in low-grade glioma, whilst recognising that it may be required as an important treatment option in the setting of high-grade glioma. (rec 5)
Plexiform neurofibromas						
Clinical surveillance	Volumetric whole body MRI	Volumetric whole body MRI	Volumetric whole body MRI	Volumetric whole body MRI	Whole body MRI for location and sizing, PET-CT for malignant transformation.	Clinical assessment should be by observation, palpation and neurological examination and should be performed by clinicians with NF1 expertise at every visit. (rec 1 and 2) Imaging by WB-MRI to monitor for plexiform neurofibromas should be performed at least at transition from childhood to adulthood to evaluate internal tumour burden as a predictor for the development of MPNST risk. WB-MRI assessment at higher frequency may be considered for patients at high risk for MPNST. (rec 3) The frequency of repeat imaging should be determined on an individual basis guided by the multidisciplinary team assessment of the level of risk for the individual. Increased assessment may be considered for patients with high risk for MPNST. In absence of internal neurofibromas at WB-MRI at transition age to adulthood clinical assessment only is required. (rec 4) Symptomatic plexiform neurofibromas require increased monitoring at shorter intervals for ANNUBP/MPNST. With careful judgement, it is appropriate to use ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT combined with clinical assessment and MRI in the diagnostic process, prior to discussing the need for biopsy. (rec 6)
Treatment						Management for plexiform neurofibroma should be decided upon and performed by a multidisciplinary team with expertise in NF1. (rec 9) People with plexiform neurofibromas should be offered psychological support in decisions of management (rec 10)

	Radiotherapy is contraindicated.	Radiotherapy is contraindicated.	Radiotherapy is contraindicated.	Radiotherapy is contraindicated.	Not mentioned.	Radiotherapy is contraindicated.
	Surgical excision as first line treatment; however, expert advice should be sought from experienced surgeons.	Expert advice from experienced soft tissue tumour or plastic surgeons is essential before removal. Pain management	Pain management and the excision of surgically amenable tumours for associated morbidity or tumour progression.	Patients who undergo surgery to remove a plexiform neurofibroma may have a significant intra-operative transfusion requirement, given the challenges of maintaining adequate haemostasis in these tumours.	Surgery	For symptomatic plexiform neurofibroma, surgery is the only treatment that can potentially cure the tumour. Plexiform neurofibroma surgery should be considered. (rec 7)
	Selumetinib	Not mentioned.	Biologically targeted therapies (such as mTOR inhibitors, imatinib and selective MEK inhibitors); Selumetinib	Not mentioned.	Not mentioned.	If part of standard national care, MEK inhibitors may be considered as treatment option for symptomatic plexiform neurofibroma, and inoperable symptomatic plexiform neurofibromas. (rec 8)
MPNST and ANNUBP						
Symptoms suggestive for MPNST	- persistent, substantial or difficult to control pain - new neurological deficit - rapid increase in the size - alteration in its consistency from soft to hard	- persistent pain - pain that disturbs sleep - new or unexplained neurological deficit - sphincter disturbance - alteration in the texture (from soft to hard) - rapid increase in the size	- hard - rapidly growing neurofibromas - persistent or nocturnal pain - neurological deficit	- pain - rapid growth - neurologic symptoms - deep, truncal location of plexiform neurofibroma	- persistent pain - rapid growth - change in consistency (e.g., from soft and pliable to firm and hard)	Clinical assessment for MPNST should consist of assessing the following: - Tumour growth: a rapid increase in the size or a change in growth rate or of an existing plexiform neurofibroma. - Pain: new and persistent, nocturnal, substantial pain / pain that is difficult to control. - New motor deficit, sensory deficit associated with any neurofibroma or peripheral nerve. This includes bladder function, bowel disturbance, swallowing problems and breathing difficulty. - Tumour consistency: development of hard nodule in a previously soft plexiform neurofibroma. People with NF1 and any of the above should be investigated for MPNST. (rec 2)
Risk factors for MPNST development	- large internal neurofibroma burden - numerous	- Individuals treated with radiotherapy - personal or family	- large internal neurofibroma burden -numerous subdermal	Germline microdeletion of the NF1 locus, previous radiation.	Not mentioned.	The following groups of people with NF1 should be considered at high risk of MPNST:

	subcutaneous neurofibromas - atypical neurofibromas -neurofibromatous neuropathy	history of cancer - whole gene deletion - multiple subcutaneous neurofibromas - neuro-fibromatous neuropathy	neurofibromas - atypical neurofibromas - neuro-fibromatous neuropathy - previous treatment with radiotherapy - personal or family history of MPNSTs - microdeletions of the NF1 locus			- *NF1* microdeletion affecting SUZ12 - missense variants affecting codons 844-848 - previous ANNUBP - high internal tumour load on whole body MRI (WB-MRI) or large or multiple plexiform neurofibroma in absence of WB-MRI - neurofibromatous neuropathy - previous radiotherapy - a relative with NF1 and MPNST (rec 1)
Factors poor prognosis MPNSTs	- Site: axial/ trunk - > 1 primary tumour - larger tumour size - High histological grade - Telomerase activity and overexpression TERT - Genomic changes in chromosome 10, 16 and X	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.
Clinical and radiologic assessment	MRI helps define the size and location. ^{18}FDG PET indicator of malignant potential using visual assessment and semiquantitative assessments with a cut-off SUV. MPNST suspected, patients evaluated and managed by a multidisciplinary team.	^{18}FDG PET is a useful diagnostic tool in differentiating benign plexiform neurofibroma from MPNST	MRI-guided or ^{18}FDG PET guided biopsy is advocated. MRI delineates the site and extent of the lesion. PET is the most sensitive and specific non-invasive diagnostic tool for MPNSTs	Detection by targeted MRI. ^{18}FDG PET to identify increased risk of malignancy.	MRI for symptomatic neurofibromas. PET-CT to distinguishing benign NFs from MPNSTs	When clinical signs and symptoms point towards malignancy, investigation should begin with regional MRI. Prior to surgery, MRI should be carried out and ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT is undertaken, using visual assessment and semiquantitative assessments with a cut-off standardised uptake value. (rec 3)
Treatment	Complete surgical resection with tumour-free margins (3 cm if	Surgery, adjuvant radiotherapy and chemotherapy.	ANNUBP: complete excision	Surgery with clear margins.	Wide surgical resection (primary) and adjuvant	In case of a suspected ANNUBP or MPNST, primary resection is recommended if it is safe and feasible. Otherwise, radiologically (preferably ^{18}FDG PET MRI) guided diagnostic biopsy should be

	possible). Adjuvant radiotherapy and chemotherapy.		MPNST: complete excision with tumour-free margins. Neoadjuvant chemotherapy Adjuvant chemotherapy remains controversial. Metastatic MPNST: anthracycline	Adjuvant chemotherapy or radiation in non-metastatic MPNST only benefit.	therapies such as radiotherapy, and chemotherapy.	performed. This biopsy should be taken at the discretion of a (sarcoma) multidisciplinary team, as tumours can be heterogeneous, with the potential for a false negative result by missing malignant parts of the tumour. (rec 4) Treatment decisions, on initial surgery and/or (neo)adjuvant chemo- or radiotherapy should be guided by an experienced multidisciplinary team. (rec 6)
Follow-up	Clinical examination and imaging, frequency determined by tumour site and histological grade. Following patients every 3 months for 3 years, then every 6 months of 2 years then annually.	Clinical surveillance	Not mentioned.	Clinical surveillance	Not mentioned.	If an ANNUBP cannot be resected with acceptable morbidity, initial screening with MRI should be conducted at least every 6 months. In case of tumour growth or increase in symptoms, screening should include ^{18}FDG PET MRI (preferred) or ^{18}FDG PET CT. After an initial clinical assessment, the follow-up interval should be determined by the characteristics of the tumour. (rec 8)
Orbital and periorbital plexiform neurofibroma						
Clinical surveillance	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	The clinical assessment of NF1 patients suspected of having an orbital and periorbital plexiform neurofibroma should be physical examination looking for blepharoptosis, proptosis, eyelid oedema, orbital dysplasia and/or dystopia, distortion of the (peri)orbital skeleton, pulsation of the eye, and strabismus. Clinical testing of vision and refractive error, visual field, ocular motility and alignment, and evaluation of the optic disc to exclude glaucoma or optic neuropathy should be basic steps in the examination of NF1 patients who are suspected of having an orbital and periorbital plexiform neurofibroma. (rec 1) MRI of the brain and orbits should be performed in all children with a suspected orbital and periorbital plexiform neurofibroma. High-resolution MRI sequences with and without contrast should be acquired through the orbit, face, and cavernous sinus.

						Whenever possible the radiation exposure from CT scans should be avoided in all children with NF1. (rec 2) Symptomatic clinical progression of known orbital and periorbital plexiform neurofibromas, and new findings should be the primary indication for imaging assessment and follow-up, and this should be by MRI. (rec 3)
Treatment	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Not mentioned.	Pathological, individual findings may be decisive for treatment and should be done in a multidisciplinary setting. If part of standard national care, MEK inhibitors may be considered as treatment option for symptomatic plexiform neurofibroma, and inoperable symptomatic plexiform neurofibromas. (rec 8: plexiform neurofibroma) People with orbital and periorbital plexiform neurofibroma should be offered psychological support in decisions of management (rec 4)
Cutaneous neurofibroma						
Clinical surveillance	For severe clinical manifestations and/or aesthetic discomfort with secondary psychological repercussions	Detailed skin examination	Not mentioned.	Appear in puberty, increase in number with age, and display periods of rapid growth during puberty and pregnancy. May be symptomatic (tenderness, bleeding, itching).	Not mentioned.	Clinical assessment consisting of visual inspection and palpation should begin when NF1 is diagnosed and should be repeated at every clinical visit. (rec 1)
Treatment	First line treatments include surgical excision and/ or CO_2 laser ablation. Second line treatments include radiofrequency ablation and electro-desiccation	Surgical excision for painful lesions or cutaneous neurofibroma causing emotional distress. Depending on size and location, laser surgery or an electric current (electro-desiccation) recommended.	Management of cutaneous neurofibroma involves surgical removal, laser ablation for small lesions, electrodesiccation, emollients (moisturizers), camouflage make-up and psychological support.	Surgical excision, laser removal, or electro-desiccation.	Surgical removal by a plastic surgeon or dermatologist Laser surgery and electrodesiccation.	Discomfort for the patient should be the primary indication for treatment. With regard to aesthetic considerations the impacts are unique to each individual and each health system has its own criteria and thresholds for intervention, so this should be considered on a case-by-case with discussion between the treating team and person with NF1. (rec 2) Removal should be by laser, surgery, electrodesiccation or radiofrequency ablation. If multiple tumours are removed, histological assessment of all clinically obvious small cutaneous neurofibroma is not necessary. (rec 3)

						Patients with cutaneous neurofibromas should be offered psychological support (rec 4)
GIST						
Screening and treatment	Poorly responsive to tyrosine kinase inhibitor imatinib. Complete surgical resection.	Management specialist centre.	GIST causes intestinal obstruction, abdominal pain, gastrointestinal bleeding. Complete surgical resection; however, individuals with higher-risk lesions (larger size or higher mitotic index) might be treated with adjuvant imatinib.	Not mentioned.	GIST causes GI bleeding and abdominal pain. GISTs are rare in childhood and do not respond to tyrosinase inhibitors.	Investigation for GIST should only be conducted if there is clinical suspicion. (rec 1) Clinical suspicion should be raised in the presence of gastrointestinal discomfort, weight loss, anaemia, gastrointestinal bleeding, abdominal pain, palpable abdominal mass, or intestinal obstruction. (rec 2) Resection should be considered for at least large (>2cm) or symptomatic tumours, as there is a risk for bleeding and rupture and risk for malignancy with metastasis. (rec 3) People with an incidentally detected GIST that is asymptomatic AND <2 cm diameter should be monitored at least once a year with abdominal MRI (or CT abdomen if an MRI not possible), for at least 5 years, and thereafter to be performed every 2 years. (rec 4)
Phaeochromocytoma and paraganglioma						
Screening	Physicians should explore the presence of phaeochromocytoma and paraganglioma in all NF1 patients with symptoms of catecholamine excess and hypertension. Diagnosis based on the plasma and/or urinary free metanephrine levels and abdominal imaging.	Not mentioned.	When suspected, phaeochromocytoma diagnosed by assessing the levels of plasma free metanephrines and MRI, combined with functional imaging using 123I-tagged metaiodobenzyl-guanidine.	Phaeochromocytoma considered in hypertensive NF1 patients > 30 years, pregnant, and/or paroxysmal hypertension, hypertension-associated headache, palpitations, or sweating. Biochemical or imaging screening in asymptomatic patients not recommended.	Screening for phaeochromocytoma if acute and dramatic increase in heart rate and/or blood pressure.	Routine biochemical screening for phaeochromocytoma and paraganglioma is not recommended in people with NF1 except for all women with NF1 who are contemplating pregnancy or are already pregnant. (rec 1) Biochemical testing for phaeochromocytoma and paraganglioma should be conducted in any person with NF1 who has raised blood pressure unexplained by other medical reason and might be considered prior to any elective surgical procedures requiring general anaesthesia in adult patients with NF1. (rec 2-3)

				Measurement of plasma free metanephrines for clinically suspected phaeochromocytoma.		
Treatment	Alpha and beta blockade before surgery.	Not mentioned.	Surgical resection	Not mentioned.	Not mentioned.	As in any phaeochromocytoma and paraganglioma predisposition syndrome surgery should be considered for symptomatic or biochemically active lesions. (rec 4) A cortical-sparing adrenalectomy should be the preferred approach due to the risk of metachronous contralateral adrenal tumour. (rec 5)
Breast cancer						
Breast screening	Regular/annual mammography-based screening starting the age of 40 years.	Breast screening appointments starting at the age of 40 years.	Regular breast self-examinations, follow-up with mammography or MRI of the breast in women <40 years of age.	Annual mammogram starting at age 30 years, and consideration of contrast-enhanced breast MRI between ages 30 and 50 years for women with a clinical diagnosis of NF1.	Not mentioned.	Education about breast self-examination probably should be conducted as it raises awareness and engagement with clinical centres. (rec 1) Screening with annual breast MRI (preferred) or mammography should begin as soon after the age of 30 years as feasible in the local health system context. (rec 2) Screening should continue until 50 years after which time, screening should be according to national guidelines for the general population. (rec 3)
Mastectomy	Risk-reducing mastectomy is not recommended; however, it may be suggested based on family history.	Not mentioned.	Not mentioned.	Risk-reducing mastectomy should be guided by family history.	Not mentioned.	Risk-reducing bilateral mastectomy for woman without breast cancer should not be performed in NF1 patients unless there are substantial additional risk factors such as a family history of breast cancer that would elevate risk into a high-risk category. (rec 4)
Glomus tumours of the digits						
Screening	No recommendation mentioned.	MRI or ultrasound.	Biopsy.	MRI imaging.	Not mentioned.	Clinical diagnosis should be based on patient reported typical symptoms (see recommendation 2) and on visual examination of the nail beds and palpation. (rec 1-2) Glomus tumours of the digits occur mostly in adulthood, but should also be considered in children/adolescents with typical symptoms. (rec 3)

Treatment	Surgical excision when painful.	Surgical removal.	Not mentioned.	Surgical removal.	Not mentioned.	Surgical excision should be considered for painful glomus tumours of the digits. (rec 4)
JMML						
Clinical surveillance and treatment	Physicians should be aware of presenting signs and symptoms of JMML and clinical examination must be thorough and directed.	Risk is too low to warrant surveillance for leukaemia.	Management is similar to that for leukaemia arising in the general population, including bone marrow transplantation and chemotherapy.	Not mentioned.	Not mentioned.	The increased risk for JMML in NF1 is not clear, and is almost certainly <1%. As such specific clinical assessment probably should not be conducted. (rec 1) Observing juvenile xanthogranulomas in children with NF1 may raise awareness to actively search for other alarming signs of JMML, but should not be considered reason enough for extensive investigations for JMML. (rec 2)

11. SUGGESTIONS FOR FUTURE RESEARCH

Further research into the following areas is recommended:

General approach: Evidence is lacking concerning the timing and intervals of routine surveillance for tumours in NF1. The NF1 Tumour Management Guideline Group agreed with some age dependent intervals, but felt in particular the need for increased monitoring of NF1 during transition age. This is also supported by a study among parents and adolescents with NF1 (Rietman et al. 2018). However, future studies exploring the need and showing effects of increased controls on outcomes are needed.

In the current guideline WB-MRI and cerebral MRI is introduced as a screening modality during transition age. There is evidence that this approach will detect tumours, but there is no evidence yet that standard and interval scanning will prevent neurological deficit, prolong life and/or will give a better patient outcome. Unnecessary (harmful) interventions and uncertainty / stress within NF1 patients may even result in a less perceived patient outcome and Quality of life. There is need to study the effects of implementation of this guideline on patient outcome.

As NF1 has a broad spectrum, it may also be important to define specific outcome measures for NF1 manifestations or for NF1 in general for future therapy studies. Currently we focus on single symptoms in small sub-cohorts (e.g. symptomatic or non-operable plexiform neurofibromas), but including more parameters (e.g. cognition) will inform on effects of treatment on other manifestations in NF1.

Finally, to define aimed response rates for manifestations in future trials, we need knowledge of the current course of NF1 manifestations. A European wide NF1 registry including longitudinal natural history data is essential, but challenging.

OPG: Approximately 40-50% of children develop symptoms due to their OPG, with 20% undergoing oncological treatment. However, risk factors for poor functional outcome in NF1 patients have not been prospectively assessed, nor have any clinical or biological biomarkers for visual deterioration been found. This makes it impossible to predict when or if the OPG will become symptomatic and if treatment will be necessary. The aim is to prevent unnecessary treatment, but to initiate treatment in time to prevent (further) visual deterioration. However, the best timing for treatment of symptomatic OPG in these NF1 patients hasn't been identified yet, therefore the decision on treatment versus observation remains unclear.

Novel MRI sequences like diffusion tensor imaging and volumetric analysis of the optic pathway may predict visual outcome or future vision loss (Schupper et al. 2009, de Blank et al. 2013, Avery et al.

2016a, Avery et al. 2016b, de Blank et al. 2017, de Blank et al. 2018) and might represent a useful biomarker which are being validated in prospective studies In NF1-OPG.

Non-OPG (low or high grade brain or spine glioma) in children: Whilst there are some similarities between sporadic non-OPG and NF1 related non-OPG in children, pre-morbid classification into "likely to progress and require therapy", versus "observation alone", remains difficult. Multi-parametric imaging paradigms will be necessary to better stratify patients on the basis of pre-morbid imaging metrics with cross correlation to molecular analysis when tumour tissue becomes available with regard to outcome prediction modelling. Multi-centre prospective advanced imaging studies which allow for such data acquisition will therefore be necessary and paradigms for modelling that integrates imaging, clinical and mutational analysis data are needed.

Prospective studies should define which patients are at higher risk for malignant brain tumours and define best strategy for early detection and also find new targeted therapies to improve survival.

Non-OPG (low or high grade brain or spine glioma) in adults: Although the impacts on management and outcome of biopsy results in patients with LGG is unclear, mutational analysis of tumour specimen may be a future prognostic marker for risk stratification and differential therapy.

Plexiform neurofibroma: Patient leads felt that it was unclear to them why only patients with *NF1* microdeletions should be screened with a WB-MRI before the age of ten, as all NF1 patients are at risk of developing plexiform neurofibromas. Since the evidence is weak, there should be further research to find out if early detection is necessary or beneficial in patients without *NF1* microdeletions. This may in particular be more relevant for internal plexiform neurofibromas if MEK inhibitors will be part or routine treatment (MEK inhibitors have been available through clinical trials or compassionate use programmes; a first MEK inhibitor has recently been approved by the EMA in 2022). However, evidence is lacking currently on improved outcome in patients treated with MEK inhibitors for asymptomatic internal NFs. Future research should address when a MEK inhibitor treatment should start and the duration of treatment; robust clinical and patient focused outcome measures are also needed. For those patients not responding to MEK inhibitors, new medical options are needed.

Finally, current therapy for plexiform neurofibroma is mainly surgery, although the indication and type of surgery is expert-based, and lacks well defined criteria. As more treatment options become available it is necessary to define indications for potential specific therapies.

MPNST/ANNUPB: There is more research needed to understand the transition of a benign neurofibroma to ANNUBP and eventually to MPNSTs to be able to better predict the timing of resection of a tumour in transition. More importantly, the prognosis of a high grade MPNST is not good, therefore better oncological treatment protocols are highly needed. Specific biomarkers for malignant transformation might be of interest such as those derived from the genetic analysis of circulating cell free DNA. These biomarkers could help in diagnosing MPNSTs or relapses in an earlier stage and therefore improve overall survival. In addition, it could help with the development of new targeted therapies or with identifying personalised treatment options.

Future research might also look at artificial intelligence as a tool to see if any imaging markers on MRI are present predicting a high likelihood for malignant transformation of a nerve sheath tumour. Lastly, there is a need for more robust outcome measures including motor function and patient focused quality of life studies for patients with NF1 and MPNSTs.

Orbital and periorbital plexiform neurofibroma: With the designation orbital and periorbital plexiform neurofibroma, a topographically-histologically based diagnosis has been introduced into the list of NF1-associated diseases, which can have very different manifestations in individual cases (Avery et al. 2017). As much as the term is suitable for bringing a specific - and often disfiguring - manifestation of NF1 to the attention of the medical community, it must be described in detail in each case which disease(s) of individual organs is/are present and which consequences individual changes of organs/tissues in this area have for other organs/tissues of the region (Riccardi 2010). These detailed descriptions of orbital and periorbital plexiform neurofibroma-associated lesions/defects/deformities etc. are equally necessary for the evaluation of the success/failure of surgical measures in this region as well as for any analysis of suspected drug effects on orbital and periorbital plexiform neurofibroma. In view of the relatively rare orbital and periorbital plexiform neurofibroma (Huson et al. 1989) and the plausibly low level of experience in dealing with orbital and periorbital plexiform neurofibroma patients even in NF1 centres, the task here is to establish international co-operations that can record and evaluate diagnostic and therapeutic experience with orbital and periorbital plexiform neurofibroma. In Europe, this is a task for institutions dedicated to rare diseases.

Cutaneous neurofibroma: cutaneous neurofibroma can be removed surgically, through laser treatment (CO_2 or Er:YAG), electrodesiccation or radiofrequency ablation. However, there is not

much data available on the outcomes of these different treatments compared to each other. For patients it is very important to understand which treatment has the best outcome (depending on size and location of the tumour). Therefore, we encourage further research to be carried out in the area of (patient reported) outcome measures. Once they become available there is a great opportunity to investigate the topical application of new targeted drugs such as topical MEK inhibitors designed to degrade rapidly in circulation to avoid systemic side effects. In addition to that we want to emphasize that training programs should be developed to educate plastic surgeons/ dermatologist on the major impact of cutaneous neurofibroma on patients' Quality of life, and how to perform the various techniques for optimal outcomes for the patients.

GIST: Recommendations of surveillance and management are in line of the ones proposed for sporadic GIST. It will be helpful to better know the natural history of GIST in the context of NF1. Additionally, as for other critical manifestations of NF1, the identification of biomarkers of GIST development will be helpful for diagnosis and surveillance.

Phaeochromocytoma: Further prospective studies are needed to ascertain if applying a surveillance strategy can reduce the rate of complications and improve prognosis.

Breast cancer: More information is required on the effectiveness of early detection in NF1 and especially on use of MRI and its impact false positivity rate. Given the high mortality rate in NF1 development of tailored treatments should be investigated.

Current basic research studies indicate alterations in the response of NF1 associated breast cancer to endocrine therapies (e.g. tamoxifen). Therefore, specific therapeutic approaches and guidelines for NF1 should be addressed in near future (Mendes-Pereira et al. 2012, Howell et al. 2017, Philpott et al. 2017, Piombino et al. 2020, Zheng et al. 2020) .

Glomus tumours: Given availability of MEK inhibitors as new treatments for some benign tumours in NF1, studies may focus on its effect on relapsing glomus tumours but are currently lacking.

JMML: Given the almost 100% mortality in JMML without bone marrow transplantation there is an urgent need for investigation of tailored treatments and in particular whether there is a role for MEK inhibitors in patients with NF1 and JMML.

Psychological needs: In the current guideline, recommendations for psychological support are mainly based on general studies, only few exist for NF1-specific populations. Future studies may define content and type of psychological support and evaluate its impact on patients.

It has been demonstrated that body image is an important link between disease visibility and psychological well-being in patients with NF1. Development of adequate patient reported outcome measures will help to evaluate psychotherapeutic interventions to improve body image in NF1.

In both clinical settings and in NF1-research, fatigue is found to have a significant effect on the quality of life of people with NF1. Further research is needed into the causes of fatigue in NF1. As for now, the question is whether an approach to fatigue should be generic or NF1-specific.

General recommendations on psychological support for patients at risk for malignancies have been incorporated in this guideline. Information is lacking on the NF1-specific need, as the condition has both a risk of malignancies and neurocognitive deficits. There is a need to improve the knowledge on how to educate and guide people with cognitive deficits or problems in social skills and symptoms of ADHD and ASD on risks of tumours and their potential management.

12. ABBREVIATIONS

^{18}FDG PET CT	18F-Fluorodeoxyglucose Positron Emission Tomography - Computerized Tomography
^{18}FDG PET MRI	18F-Fluorodeoxyglucose Positron Emission Tomography - Magnetic Resonance Imaging
95% CI	95% confidence interval
ADHD	Attention-deficit hyperactivity disorder
ANNUBP	Atypical neurofibromatous neoplasm with uncertain biologic potential
ASD	Autism spectrum disorder
CBT	Cognitive behaviour therapy
CMML	Chronic Myelomonocytic Leukemia
CNS	Central nervous system
CT	Computerized Tomography
ER	Oestrogen receptor
Er:YAG	Erbium-doped yttrium aluminium garnet
ERN	European Reference Network
EU-PEARL	EU Patient-centric clinical trial platform
GBM	Glioblastoma
GIST	Gastrointestinal stromal tumour
HER2	Human Epidermal growth factor Receptor 2
HGG	High-grade brain gliomas
JMML	Juvenile myelomonocytic leukaemia
JXG	Juvenile xanthogranulomas
LGG	Low-grade gliomas
MAPK	Mitogen-activated protein kinase
MEK	Mitogen-activated protein kinase
MIBG	^{123}I-meta-iodobenzylguanidine
MPNST	Malignant peripheral nerve sheath tumour

MRI	Magnetic resonance imaging
NF1	Neurofibromatosis type 1
Non-OPG	other low-grade and high-grade brain or spine gliomas
OCT	Optic coherence tomography
OPG	Optic pathway glioma
PDGFRA	Platelet-derived growth factor receptor alpha
PET	Positron Emission Tomography
RAS	Rat sarcoma
SIR	Standardized Incidence Ratio
SUV	Standardised uptake value
VA	Visual acuity
WB-MRI	Whole body MRI

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