ERN GENTURIS PLAIN LANGUAGE SUMMARY OF THE TUMOUR SURVEILLANCE GUIDELINES FOR INDIVIDUALS WITH NEUROFIBROMATOSIS TYPE 1

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This plain language summary of the clinical guideline for tumour management in NF1 is meant for patients with NF1 and caregivers. The full document for health care professionals is available here - Neurofibromatosis 1 guideline (https://www.genturis.eu/l=eng/Guidelines-and-pathways/Clinical-practice-guidelines/Neurofibromatosis-1-guideline.html). Please provide your treating physician with the full document.

This summary is an easy way to understand the breakdown of the recommendations. It aims to increase the patients and caregivers' knowledge of NF1. It should empower them to manage their health and those they care for as well as possible. Health professionals and patients / patients' representatives have taken the initiative to compile this document. It provides information about the different types of tumours associated with NF1. Next, it summarises how patients with NF1 should be assessed for potential tumours, and how to monitor or treat those tumours if being detected. This piece allows you to be aware of warning signs and to understand what the necessary actions of health professionals should be.

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Disclaimer: The content of this plain language summary is based on the "ERN GENTURIS TUMOUR MANAGEMENT IN NEUROFIBROMATOSIS TYPE 1 GUIDELINE (version 1.16)"

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ABOUT NEUROFIBROMATOSIS TYPE 1

NF1 is a genetic disorder. It affects about 1 out of 2,200-2.500 people. The *NF1* gene is located on chromosome 17. NF1 is one of the most common autosomal dominant genetic diseases. Autosomal dominant means that if a parent has NF1, there is a 50% chance that the child will inherit NF1. Half of all cases will be a new gene change in that family, meaning neither parent has NF1. This is called a spontaneous genetic variation. NF1 is a tumour risk syndrome. This means that people with NF1 have an increased risk of certain tumours and cancers. NF1 can cause very different manifestations in every individual patient and at a variable time. Some will develop more tumours than others. People with NF1 may also develop other clinical symptoms as well as psychosocial issues. Although the tumours are usually benign, they can still affect the quality of life or become life threatening if not treated.

DIAGNOSIS

There are diagnostic criteria for NF1 that allow a clinical diagnosis (see below). Please discuss the diagnostic criteria with your treating physician if you require more details.

The revised NF1 diagnostic criteria (https://www.nature.com/articles/s41436-021-01170-5/tables/1) include the presence of two or more of the following symptoms in an individual who does not have a parent diagnosed with NF1:

- 6 or more café-au-lait-macules (CALM) - these are coffee coloured skin marks (onset normally between birth and infancy)
- freckling in the axillary or inguinal region (onset normally between early childhood and adolescence)
- two or more neurofibromas of any type (onset normally between early childhood and adolescence) or one plexiform neurofibroma (onset normally between birth and infancy)
- optic pathway glioma (onset normally between infancy and early childhood)
- two or more Lish nodules (onset normally between early childhood and adolescence) or choroid abnormalities
- bone abnormalities - especially bowing of the lower leg (onset normally between birth and infancy)
- the presence of a heterozygous pathogenic NF1 mutation

A child of a parent who meets the diagnostic criteria specified above merits a diagnosis of NF1 if only one or more of the above criteria are present.

Genetic testing can play an important role to diagnose NF1 patients early, especially in the cases where a clinical diagnosis is not conclusive or needs to be confirmed.

ONSET OF THE SYMPTOMS

NF1 is a chronic disease. In some patients, problems can be mild. However, careful monitoring and management of NF1 related symptoms throughout life is very important.

A patient with NF1 may experience different symptoms. It is highly unlikely for one person to develop all or many of the manifestations of the condition.

The table below (adjusted from Gutman and Ferner 2017, nature reviews disease primers) shows the onset of several NF1 manifestations:

Onset	NF1 manifestation	Description / Location in the body
Birth - infancy	CALMS	Light brown pigmented skin lesions
	Orbital or tibial dysplasia Pseudoarthoris	Orbits and tibia
	Plexiform neurofibroma	Every potential body site
Infancy – early childhood	Learning deficits Attention-Deficit/Hyperactivity Disorder (ADHD) or Autism Spectrum Disorder (ASD) Motor and or speech delays	
	Optic pathway glioma	Brain
Early childhood - adolescence	Skinfold freckling Lisch nodules	Axilla or inguinal region
	Scoliosis	Spine
	Dermal or paraspinal neurofibroma	Skin
	Brainstem glioma	Brain
Adulthood	MPNST	Every potential body site
	Breast cancer	Breast
	High grade glioma	Brain

DEVELOPMENT OF THE CLINICAL GUIDELINE FOR TUMOUR MANAGEMENT IN NF1 - A DOCUMENT DEDICATED TO HEALTH PROFESSIONALS

An international team of 38 health professionals and patient representatives developed the clinical guideline for tumour management in NF1. It is based on the available scientific evidence, clinical data, as well as expert consensus. The group sent out 3 surveys (feedback loops, a so-called Delphi approach) to a large group of NF1 experts (>100 people), including dermatologists, geneticist, NF1 clinical nurses, neurologists, oncologists, neurosurgeons, ophthalmologists, paediatricians, radiologists, surgeons, neuropsychologists and patient representatives, to finalise the recommendations of the guideline.

This guideline has gathered the most up to date information on NF1. When scientific based evidence was unavailable, NF1 experts composed recommendations based on their best expertise. Depending on the consistency of the evidence and the consensus between the NF1 experts, the recommendations have been graded respectively (weak / moderate / strong). This reflects on whether the NF1 experts' conclusion is quite definitive, or whether the opinions differ to certain extent.

The guideline allows evidence-based tumour monitoring and management. It includes the types of imaging that should be used for surveillance. It states when monitoring should start, and when imaging and other assessments need to be done. It includes recommendations on treatment decisions for each tumour type. Moreover, recommendations on psychosocial care were added at the end of the document. This guideline also highlights the sensitivity of patients with NF1 to radiation, which can cause new (potentially malignant) tumours. Therefore, always discuss with your doctor which assessments (CT scans, x-rays) and treatments (radiotherapy) should be avoided when possible or can be done in an alternative way.

Scope & Purpose of the guideline

The scope of this guideline was set to determine what is currently known about the efficiency, optimal frequency and potential methods for surveillance, monitoring, and treatment for the different tumour types in NF1. It is important to understand that not all tumours related to NF1 will cause symptoms and require intervention.

1. PLAIN LANGUAGE SUMMARY OF THE KEY RECOMMENDATIONS

1.1. General approach

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

1.2. Optic Pathway Glioma (OPG)

OPGs are benign tumours that can form anywhere along the optic pathway. OPGs are the most common brain tumours in NF1. About 1 out of 5 children with NF1 develop these tumours. Only 30-50% of OPGs will ever cause symptoms, because the tumour does damage the optic nerve. Any possible symptoms of the eye need to be regularly assessed by eye doctors with expertise in NF1. Symptoms can be for example issues with sight, the eye is pushed out, eye infection, squint, one eye reacting differently to light stimuli, or endocrinologic disorders (precocious puberty, growth hormone hypersecretion, headache).

Screening	• Clinical assessment needs to start at diagnosis or suspicion of NF1. • Baseline ophthalmological assessment (visual assessment, fundoscopy, visual fields) should be performed when NF1 is diagnosed or suspected. • Baseline ophthalmological assessments need to be performed by paediatric ophthalmologists or neuro-ophthalmologists or equivalent with experience in the assessment of NF1 related visual changes. • Baseline ophthalmological assessment needs to be done at least every year (every 6 months if possible) until the age of 8 years. • From 8 years and above annual visual screening until adulthood is recommended. In case of new visual symptoms diagnostic evaluation by ophthalmologist is recommended. • Optic coherence tomography (OCT) should be done if possible as part of baseline ophthalmological assessment. • Magnetic Resonance Imaging (MRI) should be done if ophthalmologic assessment suggests an OPG, or if the ophthalmological assessment is repetitive unreliable or inconclusive in children 2 years or older.
Monitoring	• Once an OPG is diagnosed, patients need to be urgently referred to a specialised unit with experience in the monitoring and management of OPGs.
Treatment	• 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, • Symptomatic OPGs are usually treated with chemotherapy protocols (according to the standardized SIOP protocols). • Radiation therapy should be avoided in NF1-associated OPGs.

1.3. NON-OPTIC PATHWAY GLIOMA (NON-OPG: LOW- OR HIGH-GRADE BRAIN OR SPINE GLIOMA) IN CHILDREN

Benign and rarely malignant brain tumours are also possible in other areas of the brain beside the optic pathway. These tumours are called non-optic gliomas. Less than 10% of patients with NF1 develop tumours on their brain stem. Other areas of the brain can be affected as well. While benign tumours can be asymptomatic, close monitoring is important. Symptoms that non-optic gliomas can cause are for example unusual or concerning headache, nausea/vomiting, neurological deficits, neuropsychological deficits, focal neurological deficits, seizures and problems with balance.

Screening	• Families with children with NF1 should be educated about possible symptoms and signs of brain tumours. • The clinical assessment of non-optic gliomas should be repeated at every visit. • If a child is asymptomatic no routine imaging is needed. • If a child shows symptoms that raise suspicion of a brain tumour, then investigative imaging should be performed.
Monitoring	• If a symptomatic non-optic glioma is diagnosed, a multi-disciplinary team should decide on the management and treatment.
Treatment	• A multidisciplinary team should guide on the treatment, which can include surgery and chemotherapy. • Radiation therapy should be avoided in low-grade non-optic gliomas. • Radiation therapy might be a treatment option in case of highly malignant non-optic gliomas.

1.4. NON-OPTIC PATHWAY GLIOMA (NON-OPG: LOW- OR HIGH-GRADE BRAIN OR SPINE GLIOMA) IN ADULTS

See chapter above: 1.3. NON-OPTIC PATHWAY GLIOMA (NON-OPG: LOW- OR HIGH-GRADE BRAIN OR SPINE GLIOMA) IN CHILDREN	
Screening	• Patients with NF1, their carers and primary care physicians should be educated about possible symptoms and signs of brain tumours. • Clinical assessment should be repeated at every visit. • Any symptom suggestive for a brain tumour should prompt a consultation by the NF1 expert team to decide about the further procedure, i.e. MRI. • An MRI with contrast should be considered in asymptomatic patients at the age transitioning from childhood to adulthood.
Monitoring	• If a symptomatic non-optic glioma is diagnosed, a multi-disciplinary team should decide on the management and treatment. • If an asymptomatic non-optic glioma is detected it should be followed up with brain MRIs after 3 months. If the non-optic glioma is stable and remains asymptomatic the imaging intervals can be extended.
Treatment	• A multidisciplinary team should guide on the treatment, which can include surgery and chemotherapy.

	• Radiation therapy should be avoided in low-grade non-optic gliomas. • Radiation therapy might be a treatment option in case of highly malignant non-optic gliomas.

1.5. PLEXIFORM NEUROFIBROMA

A plexiform neurofibroma is a tumour that forms in the tissue that covers and protects the nerves. Plexiform neurofibromas can occur anywhere in the body outside of the brain and spinal cord. They can occur on the face (including around the eye), neck, arms, legs, back, chest, abdomen, and internal organs. Plexiform neurofibromas can also affect the appearance of the skin (darker skin colour, unusual hair growth in the affected area, thicker skin). Large tumours can affect the structure of a nearby bone, skin, and muscle. Plexiform neurofibromas can cause severe pain, mobility problems, vision and hearing loss, or obstruction. Plexiform neurofibromas are usually not malignant (or, in simpler words, cancerous), but some may turn into malignant peripheral nerve sheath tumour (MPNST). Some patients with NF1 are at higher risk of developing MPNSTs. That is why genetic testing for NF1 and counselling is useful, even if a clinical diagnosis NF1 can be made without a genetic test.	
Screening	• A clinician with expertise in NF1 should check for a plexiform neurofibroma at every visit, starting at diagnosis or birth. • At transitioning from childhood to adulthood an MRI of the whole body should be performed to check for internal plexiform neurofibromas. This allows doctors to estimate the individual risk of a patient to develop a malignant tumour called MPNST. • Some patients have a higher risk for MPNST due to their specific genetic variation. In that case an MRI of the whole body might be needed at a higher frequency. A geneticist can counsel a patient/ caregiver on the individual risk for MPNST.
Monitoring	• Clinical monitoring needs to start when a plexiform neurofibroma is first detected and repeated at each visit. • A multidisciplinary team with expertise in NF1 will decide on the monitoring and management of a plexiform neurofibroma, like imaging methods, and intervals, or if a biopsy is needed.
Treatment	• For symptomatic plexiform neurofibroma, surgery is the first line of treatment in operable neurofibromas. Disfigurement, pain and the threat of functional impairment are the major reasons for surgical intervention. • Surgery can be a treatment option which needs to be assessed and decided by an expert surgeon for each case.

	• A class of drugs called MEK inhibitors may be considered to treat symptomatic plexiform neurofibromas, or where plexiform neurofibromas are inoperable and pending on whether available in your country. • Psychological support should be offered to all patients with plexiform neurofibromas in decisions of treatment and monitoring.

1.6. Malignant Peripheral nerve sheath tumour (MPNST) and atypical neurofibromatous neoplasm with uncertain biologic potential (ANNUBP)

A plexiform neurofibroma might transform into a MPNST (malignant peripheral nerve sheath tumour). About 10 % of NF1 patients with plexiform neurofibroma develop this malignant tumour usually during young adulthood. (There are certain genetic risk factors that might cause MPNSTs in children. Please discuss with your treating physician/ geneticist if your child is at increased risk. A MPNST is a type of aggressive, soft tissue sarcoma. It is challenging to diagnose and to treat.

Atypical neurofibromatosis neoplasm (ANNUBP) describes plexiform neurofibromas that may currently be transforming into MPNSTs.

Screening	• Some people are more at risk of developing MPNST's. Your treating doctor/ geneticist can explain to you if you/ your child is at high risk of developing an MPNST. In general, it concerns:
	  ○ those having some specific mutations in the *NF1* gene, associated with a higher risk of malignancy,
	  ○ those with ANNUBP,
	  ○ those who present with many plexiforms and tumours in their body after having a full body MRI,
	  ○ those who have had radiotherapy ,
	  ○ those who have a relative with NF1 who had a malignant tumour.

Monitoring	• If there are any changes with a plexiform neurofibroma a clinical assessment is needed urgently to check for a MPNST. Examples are:
	  ○ rapid growth,
	  ○ new or increased pain,
	  ○ a hardening of a PN,
	  ○ any new motor deficits or weakness, sensory deficit associated with any neurofibroma or peripheral nerve (problems with the bowel or the bladder or swallowing and breathing.
	• If a plexiform is thought to be malignant, the tumour needs to be investigated. Assessments should be guided by a multidisciplinary team.

	Using PET-MRI is preferred over PET- CT as there is no radiation involved in PET-MRI.
Treatment	• A MPNST or ANNUBP should be surgically removed if it can be done safely. • In case of a MPNST, surgery needs to be done as soon as possible and the patient should be regularly monitored for further malignancy. • It is important that all the treatment decisions about a malignant tumour (surgery, radiotherapy or chemotherapy) are taken by a group of expert clinicians. • If after a biopsy a tumour is proven to be an ANNUBP the primary treatment option is to remove the tumour, if this does not harm the patient significantly.

1.7. Orbital and Periorbital plexiform neurofibromas

Orbital or periorbital plexiform neurofibromas are eye and eyelid abnormalities that may result in significant visual loss or significant alteration in physical appearance.	
Screening	• Clinical assessment should be physical examination looking for eye or eyelid abnormalities (such as dropping of the upper lid, proptosis (the eye is pushed out), and swelling of the eyelid). • The first steps to examine patients with NF1 who are suspected of having an orbital or periorbital plexiform neurofibroma should be: clinical testing of vision, visual field, eye movement and alignment, and evaluation of the optic disc to exclude glaucoma or optic neuropathy. • An MRI scan of the brain and orbits should be performed in all children with a suspected orbital or periorbital plexiform neurofibroma. • Whenever possible, the radiation exposure from CT scans should be avoided in all children with NF1.
Monitoring	• Symptomatic clinical progression of known orbital or periorbital plexiform neurofibromas and new findings should be the primary indication for imaging assessment and follow-up. Such imaging should be performed using MRI.
Treatment	• Surgery can be a treatment option. It needs to be decided by a multidisciplinary team. • A class of drugs called MEK inhibitors may be considered (if available in your country) to treat symptomatic plexiform neurofibromas, where surgery is not an option.

	• Psychological support should be offered to patients with NF1 with orbital and periorbital plexiform neurofibromas to support them and reduce the burden of visible manifestation (for example, where there is a significant alteration in physical appearance causing a negative impact on the overall wellbeing).

1.8. CUTANEOUS NEUROFIBROMAS

Cutaneous neurofibromas are soft benign tumours that derive from peripheral nerves and manifest on the skin or near the surface of the skin. Such nodules are commonly brown, pink, or skin coloured. Some cutaneous neurofibromas may be present in childhood but they typically start to develop during puberty.	
Screening	• After NF1 is diagnosed, clinical assessment of cutaneous neurofibromas should be repeated at every clinical visit. Such assessment consists of visual inspection and touching.
Monitoring	• The need to do something about the cutaneous neurofibromas is evaluated by a multidisciplinary team per person and per visit. It depends on how they look and how much they bother a person and where they are located. • When a cutaneous neurofibromas is uncomfortable or painful it should be treated.
Treatment	• If a decision is taken to remove cutaneous neurofibromas, this can be done by different methods (by laser, surgery, electrodessication or radiofrequency ablation). • Psychological support should be offered to patients with NF1 with visible manifestations of cutaneous neurofibromas.

1.9. GASTROINTESTINAL STROMAL TUMOURS

A gastrointestinal stromal tumour (GIST) is a type of tumour that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine. Affected individuals can develop one or more tumours. Individuals with NF1 are more likely to develop gastrointestinal stromal tumours than those without this condition.

Small GISTs may not cause any symptoms, and they may grow so slowly that they have no serious effects. However, they may cause morbidity, and have a potential risk for malignancy with metastasis. Some people with GISTs may experience pain or swelling in the belly area (abdomen), nausea, vomiting, loss of appetite, or weight loss. Sometimes, tumours cause bleeding into the

gastrointestinal tract, which may lead to low red blood cell counts (anaemia) and, consequently, weakness and tiredness. Bleeding into the intestines may cause black and tarry stools, and bleeding into the throat or stomach may cause vomiting of blood.	
Screening	• Clinical suspicion should be raised in the presence of gastrointestinal discomfort, weight loss, anaemia, gastrointestinal bleeding (blood on stool or vomiting blood), abdominal pain, palpable abdominal mass, or intestinal obstruction (faeces mass blocked in the bowel). • Imaging for GIST should only be conducted following clinical suspicion.
Monitoring	• 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 is not possible, for at least 5 years. After that, the screening should be performed once every 2 years.
Treatment	• Resection (surgery) should be considered for at least large (>2cm) or for symptomatic tumours as there is a risk for bleeding and rupture as well as a risk for malignancy with metastasis.

1.10. PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

Phaeochromocytoma and paragangliomas are rare and usually benign neuroendocrine tumours. When they arise in the adrenal gland, they are called phaeochromocytoma and when arise outside the adrenal gland near to blood vessels or nerve (i.e. on the neck, paravertebral) they are called paraganglioma. Vast majority in NF1 are adrenal tumours, but a few extra-adrenal tumours are also described. Being affected by NF1 increases the risk of developing phaeochromocytoma. However, this type of tumour occurs in only 1–5.7% of patients with NF1. Some people with pheochromocytoma have symptoms, but others do not. These symptoms can include high blood pressure, headaches, irregular heartbeat and sweating. Most paragangliomas are asymptomatic, present as a painless mass, or create symptoms such as hypertension, tachycardia, headache, and palpitations.	
Screening	• Routine laboratory tests (blood and urine) are not recommended in people with NF1 except for all women with NF1 who are contemplating pregnancy or are already pregnant. • Laboratory testing for phaeochromocytoma and paraganglioma should be conducted in any person with NF1 who has raised blood pressure, which is unexplained by other medical reasons.

	• Laboratory testing for phaeochromocytoma and paraganglioma probably should be considered prior to any elective surgical procedures requiring general anaesthesia in adult patients with NF1.
Treatment	• Surgery should be considered for symptomatic or biochemically active lesions. • A partial removal of the adrenal gland should be the preferred approach due to the risk of a tumour developing in the opposite adrenal gland.

1.11. BREAST CANCER

Patients with NF1 have an increased risk of developing breast cancer. Patients with NF1 also develop breast cancer earlier than the general population and have significantly poorer outcomes.	
Screening	• Education about breast self-examination should start in the late teens. • Annual breast cancer screening should take place from age 30. MRI or ultrasound being preferable to a mammography. • Screening should continue until 50 years. After that screening should be done according to the national guidelines for the general population.
Treatment	• Treatment of NF1-associated breast cancer is similar to that of breast cancer in the general population. • Risk-reducing mastectomy (surgical removal of both breasts to prevent breast cancer) is not recommended in patients with NF1. It might only be considered in patients with family history with breast cancer.

1.12. GLOMUS TUMOURS OF THE DIGITS

A glomus tumour is a benign tumour in the fingers and toes that usually affects the nail bed. They can be extremely painful. Pain can be induced by temperature change or pressure.	
Screening	• Glomus tumours are more common in adulthood but can also occur in children/adolescents. Any pain under the fingernails, discolouration or elevation of the nail bed needs to be checked by a NF1 expert.
Treatment	• Surgery should be considered to help alleviate pain.

1.13. JUVENILE MYELOMONOCYTIC LEUKAEMIA

Juvenile myelomonocytic leukaemia (JMLL) is a very rare form of blood cancer and is also rare in individuals with NF1. It usually affects young children. Boys are more likely to develop JMML than girls. It is an aggressive and hard to treat disease. Amongst the symptoms are an abnormal paleness of the skin, weakness, fatigue, fever and a dry cough. Almost in all cases the liver and spleen are very enlarged, which can cause a swollen abdomen, resulting in abdominal pain and lack of appetite. Allogeneic hematopoietic stem cell transplantation remains the therapy of choice for most patients with JMML.	
Screening	• It is currently unclear if there is an increased risk for JMML in NF1. The risk of a child with NF1 for JMML is below 1%. Therefore, there is no need for specific clinical assessments. • While it is important to be aware of a risk of JMML there should not be extensive investigations for JMML without specific symptoms.
Treatment	• Treatment of NF1-associated JMML is similar to that of JMML in the general population. Treatment can include different chemotherapy and bone marrow transplantation.

1.14. PSYCHOSOCIAL NEEDS

Chronic pain (often associated with tumours), visible difference (often because of cutaneous neurofibromas), tolerating interventions for tumours, and fear of increasing tumour burden or malignancy are common in NF1. This can have a negative impact on quality of life and mental health in individuals with NF1 and family members. Patients and caregivers should be aware of available resources and referred to a psychologist when needed. Psychosocial support should be an integral part of NF1 care. Any clinical assessment in NF1 should incorporate screening or questioning about mental health and quality of life. Appropriate interventions to support the patients and caregivers' needs should be discussed. A wide range of healthcare professionals can be helpful including (but not limited to) psychiatrists, psychologists, occupational therapists, physiotherapists, and social workers.
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, especially in terms of tumour management. That way patients and families can be supported when making decisions about diagnosis, management and treatment.

Psychosocial wellbeing and neuropsychological functioning should be addressed at each clinical visit. These may include assessing anxiety and depression, coping mechanisms and patient reported outcomes.
The information and guidance for patients with NF1 and family members should be age-appropriate and tailored to the needs of each individual. Potential interventions to reduce the impact of NF1 on psychosocial functioning and quality of life should be included.

GLOSSARY

Disclaimer: this glossary has been compiled at the initiative of, and by patient representatives and is for informational or educational purposes only. Its main objective is to help patients, caregivers and general public understand scientific terminology. Definitions in this glossary may differ from those given in legislation, scientific articles, manuals, or any other sources of information, whether official or not.

None of the definitions is intended to substitute professional medical advice or consultations with healthcare professionals.

ASYMPTOMATIC	Showing no visible or detectable signs or symptoms of a disease.
ATYPICAL NEUROFIBROMATOSIS NEOPLASM WITH UNCERTAIN BIOLOGIC POTENTIAL (ANNUBP)	The term ANNUBP is typically used in medical literature and discussions to describe a subset of tumours or growths associated with neurofibromatosis that pose challenges in terms of diagnosis, management, and predicting their clinical outcome. ANNUBPs differ from typical neurofibromatous neoplasms as they exhibit atypical features and behaviour and the potential for malignancy is unclear.
AUTOSOMAL DOMINANT DISEASE	A disease that can be passed down from parent to child; one copy of a mutated gene from one parent can cause the genetic condition. Each child who has a parent with the mutated gene has a 50% chance of inheriting that mutated gene.
BENIGN	Describes a tumour that is non-cancerous, does not spread to other parts of the body, or invade nearby tissues.
BIOCHEMICAL SCREENING	Screening (or testing) that uses samples of serum, plasma, urine, and other chemicals to have their levels measured and compared with those of a healthy individual. Biochemical testing allows indicating certain abnormalities in a human's body.
BIOPSY	A medical test where a sample of tissue or cells is taken from the body for further examination. For example, it can help determine whether the cells are cancerous or not.
BONE ABNORMALITY	A general description of various bone deformities that are typical for a given disease (for example, osteoporosis, low bone density, bowing of the lower leg, etc.).
CAFE-AU-LAIT-MACULES	Pigmented spots on the skin that can visually resemble birth marks and that vary in colour from light brown to dark brown.
CAREGIVER	A person who takes care and regularly looks after a patient having a medical condition. This includes both paid and unpaid caregivers.
CHOROID ABNORMALITY	Refers to a group of eye diseases or disorders in a given disease (for example, retinal detachment when the tissue at the back of the eye pulls away from a layer of blood vessels that provide necessary oxygen and nourishment).
CLINICAL ASSESSMENT	A way of diagnosing a disease and planning treatment through observation and evaluation by a physician. Such evaluation is provided based on patient's reports, medical documentation, visual assessment and observation that do not require genetic testing or taking samples.
CLINICAL GUIDELINES	An evidence-based written document developed by clinicians that contains recommendations on how to diagnose and treat a specific medical condition.
CLINICAL SYMPTOMS (MANIFESTATIONS)	Visible or detectable signs or symptoms that can be observed and assessed by a physician during the clinical assessment.
CUTANEOUS NEUROFIBROMA	A soft benign tumour that derives from peripheral nerves and manifests on the skin or near the surface of the skin. Such spots are commonly brown, pink, or skin coloured.
DIAGNOSTIC CRITERIA	A set of signs, symptoms, and tests used in clinical care to diagnose, treat, and guide the care of individual patients.

ELECTRODESSICATION	A medical procedure commonly performed by dermatologists, surgeons, and general practitioners to treat cancers of the skin or non-cancer tumours such as neurofibromas.
GASTROINTESTINAL STROMAL TUMOUR (GIST)	A type of tumour that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine.
GENETIC TESTING (also: DNA TESTING)	A test performed on a sample of blood, hair, skin, or fluids and using DNA sequences to identify mutations in genes that can cause or increase the risk of a genetic disorder.
FIRST DEGREE RELATIVE	A category of family members that commonly includes a person's parent (father or mother), full sibling (brother or sister) or child. In NF1, first-degree relatives include parents, siblings, and children. This definition may vary from one country to another or in different areas of law – for certain purposes, e.g. family law, children may include adopted children which is not the case in NF1.
FUNDOSCOPY (also: OPHTHALMOSCOPY)	An eye examination that uses a magnifying lens and a light to check the back of the inside of the eye, including the retina and optic nerve. In NF1, fundoscopy is used to detect a symptomatic optic pathway glioma.
FUNCTIONAL IMPAIRMENT	Limitations of mobility and movement caused by the complete or partial loss of function of a body part. Pain and stiff joints are the example of functional impairment.
GLOMUS TUMOUR	A benign tumour of the fingers and toes that usually affects the nail bed or palm and can be extremely painful.
JUVENILE MYELOMONOCYTIC LEUKAEMIA (JMLL)	A very rare and aggressive form of blood cancer that usually affects young children under the age of 4 years. Boys are more likely to develop JMML than girls. Symptoms include abnormal paleness of the skin, weakness, fatigue, fever, a dry cough, and some others.
HEALTHCARE PROFESSIONAL	A wide category that generally describes providers of healthcare treatment that have formal training and experience. They include nurses, physicians, psychiatrists, radiologists, surgeons, medical assistants, occupational therapists, etc.
HEARING LOSS	Damage to the inner ear that results in total or significant loss of hearing.
HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT) (also: BONE MARROW TRANSPLANTATION)	Transplantation of multipotent hematopoietic stem cells in order to replicate inside of a patient and to produce additional normal blood cells. This is often the therapy of choice for patients with JMML.
HIGH GRADE GLIOMA	A tumour of the cells found in the brain and spinal cord. They are called "high-grade" because these tumours are fast-growing and they spread quickly through brain tissue, which makes them hard to treat.
LIFE EXPECTANCY	Refers to the number of years a person is expected to live based on the year of its birth, its current age, and other factors.
LISCH NODULE	A pigmented eye tumour that grows on the iris of the eye and has a clear, yellow, or brown colour.
LOW-GRADE GLIOMA	A brain tumour that occurs from glial cells within the brain. Symptoms may include headaches, problems with speaking or understanding, personality changes, memory difficulty, numbness, weakness, and vision problems. Low-grade gliomas can progress to high-grade gliomas if left untreated.
MAGNETIC RESONANCE IMAGING (MRI)	A non-invasive imaging technology using radio waves, a powerful magnet, that produces 3D detailed anatomical images of the organs of the body and its physiological processes. This technique can be used to find a tumour in the body.
MALIGNANT	Describes a tumour that is cancerous, that spreads to other parts of the body, or invades nearby tissues.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOUR (MPNST)	A cancer of the cells that form the cover that protects peripheral nerves (i.e. located outside of the central nervous system, i.e. outside brain and spinal cord).
MEK INHIBITORS	A group of drugs that inhibits the mitogen-activated protein kinase enzymes MEK1 and/or MEK2. Simply speaking, this type of drugs prevents further cell proliferation, i.e. further growth of a tumour.
MULTI-DISCIPLINARY TEAM	A team that consists of multiple health professionals from several different disciplines. In NF1, such may include physician, dermatologist, ophthalmologist, psychologist, etc.
NEUROLOGICAL DEFICIT	Refers to an abnormal function of a body area due to injury of the brain, spinal cord, muscles, or nerves. This may include weakness or paralysis of the face, arm, or leg, and other neurological conditions.
NF1 MICRODELETION	Refers to a situation when the entire NF1 gene is missing. It may also affect other nearby genes.
NON-OPTIC GLIOMA	A benign brain tumour that grows in other areas of the brain beside the optic nerve located in the brainstem. Symptoms may include unusual or concerning headache, nausea/vomiting, neurological deficits, neuropsychological deficits, seizures, and others.
OPTIC COHERENCE TOMOGRAPHY (OCT)	A non-invasive imaging technique that uses light waves to capture cross-section images of the retina. In NF1, OCT is used to detect optic pathway gliomas.
OPTIC PATHWAY GLIOMA	A benign tumour that grows in various parts of the brain and can affect one or both optic nerves that carry visual information to the brain from each eye. Symptoms may include difficulties with seeing things, an eye being pushed out, one eye reacting differently to light stimuli, and other.
ORBITAL OR PERIORBITAL PLEXIFORM NEUROFIBROMAS	Eye and eyelid abnormalities that may result in significant visual loss or significant alteration in physical appearance.
PARAGANGLIOMA	A rare type of tumour that forms along nerve pathways in the head and neck, and in other parts of the body. Most paragangliomas are asymptomatic, present as a painless mass, or create symptoms such as hypertension, tachycardia, headache, and palpitations.
PHAEOCHROMOCYTOMA	A rare, usually noncancerous (benign) tumour that develops in an adrenal gland. Some people with pheochromocytoma have symptoms, but others do not. These symptoms can include high blood pressure, headaches, irregular heartbeat and sweating.
PLEXIFORM NEUROFIBROMA	A tumour that forms in the tissue that covers and protects the nerves. Plexiform neurofibromas can occur anywhere in the body outside of the brain and spinal cord. They can occur on the face (including around the eye), neck, arms, legs, back, chest, abdomen, and internal organs.
RADIATION THERAPY (RADIOTHERAPY)	A type of cancer treatment that uses beams of intense energy (ionising radiation) to control or kill cancer cells.
RADIOFREQUENCY ABLATION	A medical procedure in which part of the electrical conduction system of the heart, tumour or other dysfunctional tissue is ablated (deleted) using the heat generated from medium frequency alternating current.
RISK-REDUCING MASTECTOMY	Surgical removal of both breasts to prevent breast cancer.
SEIZURE	A sudden and uncontrolled burst of electrical activity between brain cells that causes temporary abnormalities in muscle tone or movements, sensations, or states of awareness.
SYMPTOMATIC	Showing visible or detectable typical signs or symptoms of a disease.
TUMOUR	A swelling of a part of the body caused by an abnormal growth of tissue; tumours can be benign (non-cancerous) or malignant (cancerous).
TUMOUR SUPPRESSOR GENE	A type of gene that produces a protein called a tumour suppressor protein that helps control cell growth and cell proliferation (also: anti-oncogene).

Disclaimer: The content of this plain language summary is based on the "ERN GENTURIS TUMOUR MANAGEMENT IN NEUROFIBROMATOSIS TYPE 1 GUIDELINE (version 1.16)"

VISUAL FIELD TEST	A test designed to evaluate how much a person can see out of the corners of their eyes and to determine if this person has blind spots in their vision.
QUALITY OF LIFE	Is defined by the World Health Organization as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns". Simply put, it is the degree to which an individual is healthy, comfortable, and able to participate in or enjoy life and social events.