Neurofibromatosis Type 1
CARE PATHWAY

*The Patient Clinical Pathway is "the whole **care pathway** from identification, diagnostics, and multidisciplinary case discussions to surveillance and preventive surgery", so indeed a pathway in time, focusing on **HOW***

Annual Review Recommended

At time of diagnosis, *or possible diagnosis*, and at the age of transition from adolescent to adult care ALL patients should be seen preferably in a specialist NF1 Centre. Follow-up may vary among different health care settings in Europe, but we advise a systematic assessment by NF1 experts, **as a minimum** annually in children up to 10 years, **as a minimum** once every two years in children >10 years and **with a minimum** of once every 3 years in adults. Individuals with significant complications will be followed up as appropriate through a nationally recognised reference NF1 centre. Annual review should be undertaken preferably by a NF1 expert and should include access to appropriate investigations including imaging.
Patients, paediatricians and GPs should have access to the NF1 expert centre for NF1-related concerns.

AGE	Frequency/interval	NF1 REVIEWS CARRIED OUT BY	CONTENT
All ages	As a minimum once during the diagnostic process	NF1 expert centre	Confirmation of diagnosis & assessment of clinical criteria and (risk for) complications. Genetic counselling for patient and family.
	On indication	NF1 expert centre	Symptoms/findings based diagnostic testing or imaging for potential complications of NF1
Up to and including 10 years	As a minimum annually	Paediatric NF1 specialist	Systematic clinical assessment: symptom check
11-18 years	As a minimum once every two years		
Up to and including 8 years	As a minimum annually, every 6 months if feasible	Paediatric ophthalmologist or neuro-ophthalmologist	Visual acuity, visual fields, pupillary testing, eye movements, optic disc appearance by fundoscopy.
9-18 years	As a minimum annually	Ophthalmologist (preferred) or optician/orthoptist	Visual screening
16-18 years	As a minimum once	NF1 expert centre	Appointment for counselling regarding adult complications and genetics. WB-MRI to detect internal tumour load. CNS-MRI as baseline to screen for brain tumours and spine.
>18 years	As a minimum annually	Primary care physician	Symptom check at NF1 review
	As a minimum once every 3 years	NF1 expert	

Review Checklist—Children (0 - 16/18)

Record **height**, **weight** and **head circumference** and take **blood pressure**.

	WHAT TO LOOK FOR	WHEN REFERRAL and WHERE TO
SKIN	**Café-au-lait macules** may increase in number up to the age of 6 years.	

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	Neurofibromas - can be itchy, and sometimes tender. May be cutaneous or subcutaneous.	Lesions being removed need **REFERRAL** to dermatologist or plastic surgeon.
PLEXIFORM NEUROFIBROMA	**N**ote location, appearance, size and consistency. Monitor large areas of café-au-lait macules &/or excessive hair growth for development of a plexiform neurofibroma.	Rapidly growing, painful, hard or growing plexiform or subcutaneous lesions: **URGENT REFERRAL** to NF1 expert centre or specialist sarcoma team.
NEUROLOGICAL	Neurological symptom review, particularly new onset or change in seizures, unusual or concerning headache, focal neurological deficits, neuropsychological deficits, and visual disturbance.	**REFERRAL** to NF1 expert centre (preferred) or paediatric specialist (neuro-oncologist or paediatric neurologist) if increase in frequency and/or severity of headaches or onset of other symptoms.
EYES	Have regular ophthalmological reviews taken place below age 18 – especially for those aged 0-8 years. Is there any evidence of a **squint**, **proptosis**, or **reduced visual acuity**? Proptosis or asymmetry of the eyes may indicate sphenoid dysplasia or orbital plexiform neurofibroma. Does the child show an abnormal visual behaviour?	**URGENT REFERRAL** to NF1 expert centre or ophthalmologist if there are concerns about the eye or visual symptoms.
DEVELOPMENT AND GROWTH	Monitor growth and puberty. There may be short stature & macrocephaly. Growth retardation, precocious or late puberty should be investigated. Review development - noting in particular milestones, coordination and speech difficulties.	Consider **REFERRAL** to paediatric specialist in case of abnormalities.
BONE	**Scoliosis**– look for signs during entire growth period, and especially at puberty and during adolescent growth spurts. **Pseudarthrosis** - tibia most commonly affected but radius and ulna may be involved. **Decreased bone-density** is more frequent in NF1. **Sphenoid dysplasia:** Facial asymmetry may be present, often associated with periorbital plexiform neurofibroma and / or glaucoma	Optimise vitamin D status. Any curvature or bowing of long bones - **REFERRAL** to NF1 expert centre or orthopaedic surgeon. Referral to craniofacial surgeon
BLOOD PRESSURE	Annual blood pressure measurements. There is an increased risk for vascular renal complications in NF1 as well as idiopathic arterial hypertension. Phaeochromocytoma may occur but is rare in children.	Consider **REFERRAL** to paediatric specialist if increased age-adapted blood pressure.
EDUCATION & BEHAVIOUR	There is an increased incidence of learning disability, specific learning difficulties and behaviour problems (particularly attention difficulties, ADD, ADHD and ASD). Psychosocial wellbeing and neuropsychological functioning and educational or behavioural needs should be addressed at each clinic visit to identify possible special needs and appropriate resources to assess them.	Consider **REFERRAL** for professional assessment of educational needs at regular intervals, e.g. ages related to entering primary school and secondary school, and in case of reported problems.
PSYCHOLOGICAL BURDEN	Impact is underestimated. Disfigurement may lead to feelings of social isolation, and depression. Psychological problems are common but patients, both men and women, may be reluctant to talk about these issues and need encouragement.	Consider **REFERRAL** to an appropriate counselling service or referral for formal psychiatric evaluation.
UNSURE? Do not hesitate to contact the NF1 expert centre if you have any queries		

Neurofibromatosis Type 1 Review Checklist—Adults (16/18+)		
	WHAT TO LOOK FOR	**WHEN TO REFER**
IMAGING	At transition age from adolescence into adulthood (16-18 years):	Patients with high internal tumour load that increase the risk for MPNST should

	WB-MRI to detect internal tumour load from plexiform neurofibromas. CNS-MRI as baseline for brain and spinal tumour screening.	be **REFERRED** to NF expert centre for follow-up. Patients with incidental (asymptomatic) detected gliomas should be **REFERRED** to NF expert centre for follow-up (usually repeated imaging with a first interval of 3 months, and if stable asymptomatic disease, intervals can be prolonged). Any NF1 patient diagnosed with a symptomatic CNS glioma should receive an urgent **REFERRAL** to a NF1 expert centre or neuro-oncology centre.
SKIN	**Cutaneous neurofibromas** - can be itchy, and sometimes tender. Check for cutaneous and subcutanous neurofibromas, any lumps or symptomatic lesions that may require excision.	Lesions being removed need **REFERRAL** to dermatologist or plastic surgeon.
PLEXIFORM NEUROFIBROMA	Note location, appearance, size and consistency. Monitor large areas of café-au-lait macules &/or excessive hair growth for development of a plexiform.	Rapidly growing, painful or hard plexiform neurofibroma or subcutaneous lesions: **URGENT REFERRAL** to NF1 expert centre or specialist sarcoma team.
NEUROLOGICAL	Neurological symptom review, particularly new onset or change in seizures, unusual or concerning headache, focal neurological deficits, novel neuropsychological deficits, and visual disturbance. Consider specific neurophysiological diagnostics (nerve conduction studies) to detect neuropathy, and MRI for CNS tumours.	**REFER** to NF1 Expert Centre (or neurologist) if increase in frequency and/or severity of headaches or onset of other symptoms.
EYES	Optic pathway tumours UNCOMMON in adults but any unusual visual signs/symptoms warrant investigation. Baseline ophthalmological assessment if not previously done.	**URGENT REFERRAL** to ophthalmologist if there are any concerns about the eyes or visual symptoms.
PAIN	Pain should raise the suspicion of NF1 related complications: - localised tenderness, severe paroxysmal (lancinating, similar to being hit on the nailbed) pain and sensitivity to cold in a digit should raise suspicion for glomus tumour. - increased/change in pain in plexiform neurofibroma should raise suspicion of malignant transformation (atypical neurofibromatous neoplasms of uncertain biological potential (ANNUBP)/MPNST) - novel onset of headaches or change in symptomatology may be a sign of a brain tumour - neuropathic pain may be caused by NF1 associated neuropathy	**REFER** to hand surgeon for glomus tumour; **REFER URGENTLY** to sarcoma team or to the NF1 expert centre for assessment of possible malignant change in neurofibroma; **REFER** to NF1 expert or neuro-oncologist for brain tumour and neurologist for neuropathy.
BONE	Review for NF1 related orthopaedic problems (scoliosis) and osteoporosis. Bone related pain may result from NF1-related orthopaedic problems and osteoporosis.	Optimise vitamin D status **REFER** to orthopaedic surgeon or to the NF1 expert centre.
BLOOD PRESSURE	Annual blood pressure measurements. There is an increased risk for phaeochromocytoma or vascular renal complications in NF1.	**REFER** to endocrinologist if phaeochromocytoma is a possibility or **REFER** to nephrologist for renovascular assessment (renal artery stenosis/aneurysm).
BREASTS	Women with NF1 have an increased risk of developing breast cancer between the ages of 30 and 50, classified as ''moderate'' (between 3 and 8%).	**REFERRAL** to local breast screening centre for annual breast-MRI (preferred) from 30 years.

PREGNANCY	Pre-natal and pre-implantation testing is available but relies on pre-pregnancy genetic work up. During pregnancy, internal or skin neurofibromas may increase in size and/or itchiness. Consider phaeochromocytoma/renal artery stenosis in women with particularly high blood pressure, especially if it persists post-delivery.	All women who are planning pregnancy should be **REFERRED** for counselling to clinical geneticist and gynaecologist.
PSYCHOLOGICAL BURDEN	Effects are underestimated. Disfigurement may lead to feelings of social isolation, and depression. Psychological problems are common but patients, both men and women, may be reluctant to talk about these issues and need encouragement. Socioemotional and behaviour problems (particularly attention difficulties, ADD, ADHD and ASD) may influence social life and participation in work and society.	Consider **REFERRAL** to an appropriate counselling service or referral for formal psychiatric evaluation.
ANY OTHER NEW SYMPTOMS	Consider other possible complications and consider the increased risk for any malignancy in NF1. Remember the increased risk of internal neurofibromas and the differential diagnosis to malignant disease. Remember the increased risk of gastro-intestinal stromal tumours (GIST). Clinical suspicion should be raised in the presence of gastrointestinal discomfort, weight loss, anaemia, gastrointestinal bleeding, abdominal pain, palpable abdominal mass or intestinal obstruction.	**REFER** to appropriate specialist preferably with NF1 expertise, and oncology expertise (e.g. sarcoma team, or surgical oncology).

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; ANNUPP, atypical neurofibromatous neoplasms of uncertain biological potential; ASD, autism spectrum disorder; CNS-MRI, MRI (magnetic resonance imaging) of the central nervous system; GIST, gastro-intestinal stromal tumour; GP, general practitioner; MPNST - Malignant peripheral nerve sheath tumour; NF1, neurofibromatosis type 1; WB-MRI, whole-body MRI (magnetic resonance imaging).