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Guidelines for the Multidisciplinary Diagnosis and Treatment of Neurofibromatosis Type 1 (2023 Version)

Multidisciplinary Diagnosis and Treatment Collaboration Group for Neurofibromatosis Type 1 of China Alliance for Rare Diseases

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Abstract: Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary neoplastic disease caused by mutations in the NF1 gene. Features of the disorder typically appear in early childhood. The clinical phenotypes of the patients are diverse but neurofibroma is the main feature. Patients with NF1 also suffer from multi-system involvement and have high risk of malignant tumor. NF1 poses significant challenges for diagnosis, treatment, follow-up and patients management. Therefore, it is imperative to develop a multidisciplinary collaborative diagnosis and treatment protocol. Under the leadership of the China Alliance for Rare Diseases, a multidisciplinary diagnosis and treatment collaborative team for NF1 has been formed and has developed the guideline. This guideline intends to lift the diagnosis and treatment level for NF1 and to provide a standardized treatment protocol for NF1 patients in China.

Keywords: Neurofibromatosis type 1; Multidiscipline; Guideline.

Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary neoplastic disease caused by mutations in the NF1 gene, with an estimated prevalence from 1/4000 to 1/2000 (Kallionpää *et al.*, 2018). It often onsets in early childhood and has diverse clinical features, mainly characterized by café-au-lait macules (CALMs) and multiple neurofibromas. Neurofibromas are benign Schwann cell tumors and can be divided into cutaneous, nodular and plexiform neurofibroma (pNF) (Legius *et al.*, 2021). Cutaneous neurofibroma (cNF) is the most common type, manifesting as a soft, sessile, or pedunculated tumor on the skin surface, with good mobility and no tenderness on examination. Most cNFs are purple and the number ranges from a few to thousands. Nodular neurofibroma is a discrete, firm, rubbery mass that grows under the skin or deep inside the body, which generally does not invade surrounding tissues. It may cause pain or dysfunction due to compression. pNF grows along the nerve plexus and can involve multiple nerve bundles and branches. It's usually congenital and gradually increases in size with age. It can involve the head, neck, orbit, limbs, thoracoabdominal and pelvic cavity, spinal canal, nerve roots, and peripheral nerves. The latter two types, nodular and plexiform neurofibromas, have the risk of transforming into malignant nerve sheath tumors. In addition to neurofibromas, NF1 patients often

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have multi-system involvement, including multiple benign and malignant tumors, bone dysplasia, cardiovascular and cerebrovascular diseases, and cognitive and psychological abnormalities. As a rare disease, there are great challenges in the diagnosis, treatment, follow-up, management, and other aspects of NF1 patients. Guidelines and procedures for multidisciplinary collaborative diagnosis and treatment have not yet been established. Therefore, under the leadership of the China Alliance for Rare Diseases, a multidisciplinary diagnosis and treatment collaborative team for NF1 has been formed and has developed the guideline. This guideline aims to enhance the level of diagnosis and treatment for NF1 and establish a standardized care protocol for NF1 patients.

This guideline was started by the China Alliance for Rare Diseases on July 20, 2022, and finalized on February 26, 2023. A multidisciplinary collaborative diagnosis and treatment group has been established, with members recommended by experts in 12 fields, including dermatology, plastic surgery, oncology, neurosurgery, radiology, ophthalmology, orthopedics, neurology, cardiology, pediatrics, endocrinology, and genetics. The launch meeting identified key clinical problems to be addressed, which were then allocated to each group for evidence search and recommendation formation. The final draft was completed on January 30, 2023, and was sent to all members for review. It was revised following the advice of a seminar on February 6, 2023. Eighteen recommendations in the guideline were voted on February 22, 2023, and a total of 70 questionnaires were returned, with the approval rate of the recommendations ranging from 98.57% to 100.00%.

1. DIAGNOSIS OF NF1

1.1. The clinical diagnostic criteria for NF1

The clinical diagnostic criteria for NF1 are mainly based on the National Institutes of Health (NIH) Consensus Conference in 1987("National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987," 1988). If the patient meets two or more of the following clinical characteristics, he or she can be diagnosed with NF1: ① Six or more CALMs (>0.5 cm in children or >1.5 cm in adults); ② Two or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma; ③ Axillary or groin freckling; ④ Optic pathway glioma (OPG); ⑤ Two or more Lisch nodules (iris hamartomas); ⑥ Distinctive osseous lesions (sphenoid wing dysplasia, bowing of long bone with or without pseudarthrosis); ⑦ First degree relative with NF1 according to the above diagnostic criteria.

An international steering committee in 2021 published revised diagnostic criteria for NF1 based on the 1987 version (Legius *et al.,* 2021). The revision retained the first to fourth criteria and modified the fifth to "Two or more Lisch nodules on slit lamp examination or two or more choroidal abnormalities (CAs) on optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging", the sixth to "A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone". A new seventh criterion was added: "A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells". Patients whose parents do not have NF1, can be diagnosed with NF1 if they meet two or more of the above clinical criteria. For those whose parents have NF1, a diagnosis can be made if one or more of the clinical criteria are met.

NF1 needs to be differentiated from other similar syndromes, including Legius syndrome, McCune-Albright syndrome, neurofibromatosis type II, Noonan syndrome and constitutional mismatch repair deficiency syndrome. (Table 1) (National Multi-Center Treatment Collaboration Group For Neurofibromatosis *et al.,* 2021). Genetic testing can help confirm the diagnosis.

Segmental NF1, also known as mosaic NF1, results from the mosaicism of normal somatic cells and neural crest-derived somatic cells which contain a postzygotic mutant NF1 gene (Messiaen *et al.,* 2011). The clinical features of patients with segmental NF1 are localized to a specific area of the body. Distinctive skin manifestations include segmentally distributed CALMs, freckling or neurofibromas. The severity of symptoms depends on the type of involved tissue and the time of mutation, which is usually milder than the typical form of NF1.

1.2. Genetic diagnosis

1.2.1. Value of genetic testing

Genetic testing can be used to diagnose NF1. The clinical diagnostic criteria are less sensitive in children for their signs usually appear with age

Diagnosis	Clinical manifestations	Pathogenesis
Legius syndrome	CALMs and bilateral axillary/groin freckling; no other NF1-related features such as neurofibromas or OPG.	Biallelic inactivation of SPERED1 on chromosome 15, leading to upregulation of the Ras-MAPK signaling pathway.("National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987," 1988)
McCune-Albright syndrome	CALMs with serrated margins, polyostotic fibrous dysplasia, precocious puberty; no neurofibroma.	Somatic mutations in GNAS genes, especially in Gs protein (Boyce & Collins, 2020)
Neurofibromatosis type II	CALMs occasionally, no Lish nodules; bilateral vestibular schwannoma, meningioma, ependymoma.	Biallelic inactivation of NF2 on chromosome 22 (Asthagiri *et al.,* 2009)
Noonan syndrome	Typical CALMs in small numbers; congenital heart disease; coagulation disorder; short stature, delayed sexual development; characteristic facial features; cognitive impairment.	Germline mutations of several genes in Ras signaling pathway, especially PTPN11 (Roberts *et al.,* 2013)
Constitutional mismatch repair-deficiency syndrome	Typical or atypical CALMs; high risk of malignancies.	A rare pediatric cancer predisposition syndromes, caused by biallelic deletion mutations in one of the four mismatch repair genes (MLH1, MSH2, MSH6, PMS2) (Gallon *et al.,* 2023)

Table 1. Differential diagnosis of neurofibromatosis type 1 (NF1).

(Gutmann *et al.,* 2017). Therefore, for children under age 7 years and those who have CALMs and skin-fold freckling as their only clinical features, genetic testing can be performed to confirm the diagnosis ("National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987," 1988; Zhao *et al.,* 2021).

Identifying genetic variants can provide guidance for disease management. For example, patients with the p.Met1149 variant tend to have a milder phenotype while patients with the p.Arg1276 and p.Lys1423 missense variants are more susceptible to cardiovascular abnormalities. NF1 whole gene deletion results in a higher tumor burden with an increased growth rate, and should be closely monitored to assess tumor risk and the potential for malignant transformation (Koczkowska *et al.,* 2020; Well *et al.,* 2021).

1.2.2. Choice of genetic testing

The mainstream sequencing methods are gene chip detection of NF1 and whole exome sequencing (WES). Trio-whole-exome sequencing (Trio-WES) is recommended for the probands and their parents if conditions permit. With the advancement of whole genome sequencing (WGS) technology and the reduction in costs, WGS becomes feasible when conditions allow. If results are negative and NF1 is still suspected, it can be further confirmed by RNA sequencing or by identifying copy number variants (CNVs) in the NF1 gene region.

Genetic testing can be conducted using blood or saliva samples from patients with generalized NF1. If the results from blood or saliva samples are negative, or if tissue from the lesion is available, the lesion can be prioritized for genetic testing. Neural crest-derived cells at the lesion site are required in genetic testing for segmental (or mosaic) NF1 patients, such as melanocytes from CALMs or surgically removed neurofibromas.

1.2.3. Interpretation of Genetic Testing

In the gene report, the detection of pathogenic (P) and likely pathogenic (LP) variants of the NF1 gene can confirm the diagnosis. For variants of uncertain significance (VUS), interpretation should combine with the genotype-phenotype correlation, RNA

sequencing, and other omics data. If the detection is negative, periodic reanalysis should be performed, focusing on splicing variants, non-coding region variants, and synonymous variants.

Recommendations: Proper genetic testing should be chosen for suspected NF1 patients who do not have a confirmed clinical diagnosis but are in need of further treatment or genetic counseling This aims to clarify the molecular diagnosis and assist in disease management. WES is preferred with sample types varying according to different NF1 types. If the detection is negative, WGS can be considered. The reanalysis of original data should be done every two years to include newly discovered NF1-related genes or new mutations.

1.3. Genetic counseling

1.3.1. Risk for relatives of NF1 patients (parents, siblings, and offspring)

For patients with germline variants, the transmission risk to offspring is 50%. If the proband's pathogenic variant is a de novo variant, his parents and siblings may not be affected. However, due to the possibility of gonadal mosaicism, the siblings of proband are still at higher risk of having NF1 even if their parents have no obvious clinical manifestations. For patients with somatic mosaicism, the risk of disease in offspring is less than 50%. Nevertheless, if the mutation is passed on to offspring, the clinical manifestations are usually more severe ("National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987," 1988).

1.3.2. Fertility and prenatal counseling in female patients

Possible pregnancy complications in NF1 patients include gestational hypertension, preeclampsia, intrauterine growth retardation and premature birth. The number and size of cNF and pNF increase during pregnancy (Tadini *et al.*, 2020). Patients with NF1 pathogenic variants should undergo prenatal or preimplantation genetic counseling. Prenatal diagnosis can be performed via chorionic villus or amniotic fluid analysis, as well as ultrasound, MRI or other examinations. Preimplantation genetic testing can detect the presence of specific variants before the embryo is transferred into the uterus, which can also identify chromosome aneuploidy (Tadini *et al.*, 2020).

Recommendation: A multi-system assessment should be conducted for the proband, his parents and siblings referencing the NF1 diagnostic criteria and other common clinical manifestations. The risk assessment of other relatives should be considered on a case-by-case basis. NF1 patients who wish to have children should receive prenatal genetic counseling and pregnant patients should be closely monitored.

2. DISEASE ASSESSMENT AND MULTIDISCIPLINARY TREATMENT

2.1. NF1-related skin manifestations, diagnosis, and treatment

2.1.1. Features and Management of CALMs

CALMs appear as uniformly hyperpigmented light to dark brown macules or patches with oval or irregular shapes, varying sizes and smooth margins. They are usually present at birth and occasionally occur within a few months to one year after birth. Often multiple and scattered anywhere except the palms and planters, they usually increase in size and number with age (Ortonne *et al.*, 2018). Axillary freckling (Crowe sign), which can involve the neck and groin, may aid in diagnosis. Histopathological manifestations include increased pigmentation in keratinocytes and melanocytes in the epidermis. Scattered giant spherical melanin granules can be seen in melanocytes and basal layer keratinocytes. The Dopa reaction shows an increase in the density and activity of melanocytes. CALMs need to be distinguished from freckling, nevi, post-inflammatory pigmentation, and urticaria pigmentosa.

There are no systematic studies on the therapy of CALMs. Symptomatic treatment is mainly adopted. If the skin lesions severely affect appearance, lasers can be used (Chamseddin & Le, 2020) (Beiyao Zhu *et al.*,2022). Q-switched lasers have a selective photothermal effect, including the Q532 nm laser, Q-switched ruby laser (694 nm), alexandrite laser (755 nm) and Q1064 nm laser. Q-switched lasers usually do not cause scars, but the therapeutic response varies greatly among individuals. In addition, intense pulsed light, fractional laser, picosecond and ultra-picosecond lasers can also be adopted.

Recommendation: CALMs generally do not require treatment, but lasers can be considered for lesions that severely affect the appearance.

2.1.2. Other skin manifestations of NF1

In addition to CALMs and groin freckling, nearly 50% of children present with multiple nevus anemicus shortly after birth. Nevus anemicus is a congenital vascular dysfunction which has increased sensitivity to catecholamines and results in persistent vasoconstriction, leading to pale skin especially when the skin is rubbed or chafed (Wang & Lin, 2021). Moreover, nearly 30% of children develop multiple juvenile xanthogranulomas, mostly on the head and neck (Ferrari *et al.*, 2014). Although solitary juvenile xanthogranuloma or occasional multiple juvenile xanthogranulomas can be seen in normal children, the presence of multiple juvenile xanthogranulomas combined with CALMs is uncommon and suggests an early diagnosis of NF1.

Recommendation: In the case of multiple nevus anemicus or multiple juvenile xanthogranulomas in combination with CALMs or cNF, the possibility of NF1 should be alerted.

2.1.3. Clinical manifestations and treatment of cNF

cNF is the most common type of neurofibroma, originating from the proliferation of Schwann cells of the sheaths of peripheral nerves due to the biallelic mutation of the NF1 gene. It is composed of Schwann cells, fibroblasts, mast cells, endothelial cells and a large amount of extracellular matrix.

cNF generally appears in childhood, gradually increasing in size and number, especially during puberty and pregnancy (Gallon *et al.*, 2023). The numbers can vary from a few to thousands. The diameter of cNF ranges from a few millimeters to several centimeters, and large ones cause deformity and compression symptoms.

cNF often appears as rubbery, soft exophytic papules or lumps, which are skin-colored or flesh-colored and can occur in any part of the body (Gallon *et al.*, 2023). For those located in the dermis, the surface skin tends to be violaceous with clear margins and a soft texture. Less commonly, the tumor is a small soft subcutaneous mass that slightly raised compared to the adjacent skin with a dome-like appearance and palpable margin and can be flattened by pressing (buttonhole sign). Some cNFs are pruritic or painful due to massive mast cell infiltration. According to morphological characteristics and the developmental stage, cNF can be classified into five categories including nascent/latent, flat, sessile, globular and pedunculated type (Gallon *et al.*, 2023). With the slow growth of cNF, it brings a heavy psychological burden to patients. For pediatric patients, there are also learning disabilities and maladaptation (Roy *et al.*, 2021; Taylor & Lewis, 2019).

Surgery is the main treatment of cNF. Besides, CO2 laser ablation, laser cauterization, and electrodesiccation can also be used (Chamseddin & Le, 2020) (Beiyao Zhu *et al.*, 2022). Pharmacological treatment requires further investigation. Due to the extensive skin involvement and the large number of tumors, surgical removal of all tumors is not practical. Therefore, only a small number of large, symptomatic cNFs are targeted. Recommended indications for surgery include ① Large tumors, causing significant compression or dysfunction of surrounding tissues; ② Invasion of other systems; ③ Tumors with recent significant growth and suspicious of or having histological evidence of malignant transformation; ④ Tumors rupture accompanied by acute massive bleeding; ⑤ Tumors affecting appearance or causing pain, lowering the patient's quality of life. For patients with extensive skin involvement and many tumors, it is impossible to remove all tumors by surgery. Therefore, destructive treatment can be carried out to remove a large number of tumors at one time with significant aesthetic improvements, such as laser ablation, and electrodesiccation. However, postoperative complications, for example, local infection, scarring and recurrence may occur. The CO2 laser can ablate hundreds of cNFs in a single procedure while sealing off small nerve endings and reducing pain (Gloster & Roenigk, 1995). In a study of 106 patients using CO2 laser ablation, patient satisfaction was 90% for cNF smaller than 1 cm, with good healing and pain reduction, and 94% of patients expressed a desire for further treatment. However, 15% of patients developed a local infection and 22% developed hypertrophic scars (Méni *et al.*, 2015).

Current drugs for cNF include those targeting the Ras-MEK (mitogen-activated protein kinase) pathway (Selumetinib), Ras-mTOR pathway, and receptor tyrosine kinases (Ranibizumab, Imatinib). Topical Ras-MEK pathway inhibitors are also under development.

Recommendation: cNF is a benign tumor and treatment is based on the patient's wishes. Surgery is the main treatment for large tumors or tumors that cause dysfunction. Simultaneously, CO2 laser ablation, electrodesiccation, laser photocoagulation,

and radiofrequency ablation can be used to treat patients with a large number of cNFs that severely affect their appearance.

2.2. Diagnosis, assessment and treatment of nodular and plexiform Neurofibromas

2.2.1. Classification of neurofibromas and their clinical features

2.2.1.1. MRI-based infiltration depth classification

Neurofibromas have no obvious features on T1-weighted images (T1WI), but show high uneven signal intensity on T2-weighted images (T2WI) which can be referred to as the "target sign" characterized by a central low signal and a peripheral high signal. Enhanced scanning shows obvious uneven enhancement. In 2003, Friedrich first proposed the MRI-based classification of neurofibromas, containing superficial, displacing, and invasive types (Friedrich *et al.*, 2003). ① The superficial type is defined as a noninvasive mass limited to the cutaneous and subcutaneous tissues without invading the fascia and muscles; ② The displacing type is usually a multinodular mass located in the deep layers of the skin or within the body, which may compress adjacent structures due to its large size but does not invade adjacent muscles or skin; ③ The invasive type is characterized by a mass with no visible margins and invades muscles, fascia, joints, which cannot be resected without surrounding tissues.

In a retrospective study (Mautner *et al.*, 2006), 82% of displacing and 73% of the invasive type were large tumors more than 10 cm in diameter, while this only occurred in 41% of the superficial type. In addition, 95% of superficial, 51% of displacing and 81% of invasive type caused disfigurement. Dysfunction was found in 17% of superficial, 38% of displacing, and 64% of the invasive type. Moreover, 8% of superficial, 41% of the displacing, and 26% of the invasive type were found to be painful.

2.2.1.2. Location-based classification

Neurofibromas can produce varied clinical symptoms corresponding to their locations. Craniofacial neurofibromas can cause disfigurement and disabilities due to tumor invasion of sensory organs. For example, tumor invasion into the orbit can cause eyeball displacement and vision loss. Paravertebral neurofibromas can compress the spinal cord, leading to paralysis. They can also destroy the vertebrae, resulting in spinal instability and secondary scoliosis. Mediastinal neurofibromas can cause life-threatening cardiopulmonary damage by compressing the trachea or large blood vessels. In addition, neurofibromas in the extremities may cause severe dysfunction due to venous stasis or tumor invasion of surrounding tissues (Needle *et al.*, 1997).

2.2.1.3. Pathology-based classification

As shown in Table 2, neurofibromas can be divided into three pathological types including localized/nodular, diffuse, and plexiform neurofibromas (Magro *et al.*, 2022; Rodriguez *et al.*, 2012). Among them, pNFs are exclusively NF1-related whereas localized/nodular neurofibromas are usually sporadic with a low correlation with NF1. Localized/nodular neurofibromas and diffuse neurofibromas have a very low risk of transformation into malignant peripheral nerve sheath tumors (MPNST) (Schaefer & Fletcher, 2015) (Goldblum, 2014). pNF, almost exclusively appearing in NF1 patients, has the highest risk of transformation into MPNST among all types (Wang & Lin, 2021).

To distinguish neurofibromas of uncertain malignant potential, the concept of atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP) was proposed. ANNUBP is defined as a Schwann cell tumor with at least 2 of the following features: cytological atypia, loss of neurofibroma architecture, hypercellularity, and mitotic activity >1/50 high-power filed (HPF) but <3/10 HPF. ANNUBP has a low risk of recurrence and basically no risk of metastasis (Beert *et al.*, 2011). Therefore, it should be differentiated from low-grade MPNST to avoid overly aggressive treatment. Resection of ANNUBP should be considered to prevent malignant transformation if surgery is feasible and does not lead to major complications. Wide negative margins are not recommended during surgery, as previous studies have shown the efficacy of complete surgical resection without wide negative margins in preventing tumor recurrence and transformation into MPNST, whereas subtotal resection has a higher risk of recurrence (Bernthal *et al.*, 2014; Higham *et al.*, 2018; Nelson *et al.*, 2019). Although multiple or deep lesions may be difficult to remove, surgery is still recommended in such cases. Unresected ANNUBP requires lifelong surveillance, and the development of additional ANNUBP need to be monitored for all patients.

Classification	Gross pathological characteristics	Histopathological characteristics	Immunohistochemical characteristics
Localized/nodular neurofibroma	Well-defined cutaneous/subcutaneous nodules; bright tan cut surface; encapsulated fusiform masses when major nerves are involved.	Low to moderate cellularity; spindle cells with wavy or comma-shaped nuclei and ill-defined cytoplasm; disordered cell arrangement; fibromyxoid matrix.	Diffuse expression of S-100 and SOX-10; variable expression levels of epithelial membrane antigen and CD34.
Diffuse neurofibroma	Ill-defined cutaneoues/subcutaneous nodules; tan cut surface.	Low to moderate cellularity; spindle cells with hyperchromatic wavy or comma-shaped nuclei; disordered cell arrangement; fibrous or mucoid interstitial; pseudomeissnerian corpuscles; subcutaneous adipose tissue infiltration with focal honeycomb shape.	Diffuse expression of S-100 and SOX-10; variable expression levels of epithelial membrane antigen and CD34.
Plexiform neurofibroma	A mass with multiple nodules; "bag of worms" appearance.	Low to moderate cellularity; round or spindle cells with hyperchromatic wavy or comma-shaped nuclei; multiple nodules and tortuous nerve-like structures; abundant myxoid or edematous matrix with randomly arranged thick collagen fibers; occasionally extending to surrounding tissue.	Diffuse expression of S-100 and SOX-10; variable expression levels of epithelial membrane antigen and CD34.

Table 2. Histopathological classification and characteristics of benign neurofibroma.

2.2.2. Surgical treatment of neurofibromas

2.2.2.1. Surgical indications and timing

Surgery is recommended for symptomatic neurofibromas, lesions with imaging evidence of malignant transformation, and excessively large masses (>6 cm in diameter) (Garozzo, 2019). The timing remains controversial. Some surgeons advocate early surgery to avoid the occurrence and worsening of complications, such as blindness or meningoencephalocele (Jackson, 2001; Ndiaye *et al.*, 2020; Ransom *et al.*, 2006). Intervention when the lesion is small has a greater chance of complete resection and a lower recurrence rate. Some suggest waiting until after puberty when the disease is stable (Abouchadi *et al.*, 2005). Others advocate delaying intervention as much as possible, because earlier surgery may require more repeated surgeries (Lee *et al.*, 2003; Needle *et al.*, 1997; Wise *et al.*, 2002).

2.2.2.2. Objective and Strategies

The objectives of surgery include the prevention of malignant transformation, improvement of appearance and restoration of function, thus prolonging survival time, and improving the quality of life and the psychological status of patients.

Surgery can be divided into total/near-total resection (>80%/90%,) subtotal resection (50%~80%/90%), and partial resection (<50%) according to the resected proportion of the whole tumor. Total/near-total resection is recommended if feasible (Friedrich *et al.*, 2005). For bulky or invasive tumors, given their benign nature, the operation should aim to relieve symptoms while preserving neurological function. Plastic surgery is recommended to restore a more socially acceptable appearance by shrinking the tumor. The surgical technique depends on the characteristics and location of the tumor and the patient's general condition. The

surgical plan should be developed together with a multidisciplinary team including ophthalmologists and neurosurgeons, which depends on the surgical needs.

2.2.2.3 Surgical techniques

Surgery is the most common treatment for pNFs. However, there is a high surgical risk due to the tumor's origin from nerves and its rich blood supply. Therefore, a comprehensive evaluation is required for individualized treatment, including systematic preoperative preparation, selection of surgical strategies, and post-operative support.

(1) Overview of surgery for nodular and plexiform neurofibromas
Some neurofibromas, especially huge and invasive ones, have the characteristics of extensive involvement and a tendency to bleed during surgery, which may bring great difficulties to the surgery and cause complications like postoperative neurological deficits and intraoperative hemorrhage.

(2) Preoperative preparation
It is recommended to fully evaluate the growth pattern, extent of involvement, malignancy, and system involvement through imaging such as MRI, CT, and PET before surgery. Preoperative angiography or percutaneous angioembolization may reduce the incidence of intraoperative hemorrhage and related complications, especially for tumors with "flow void sign" on MRI (Michimoto *et al.*, 2021). In addition, preoperative nerve conduction study and electromyography can help clarify the function of relevant nerves and provide a basis for the selection of the operation.

(3) Intraoperative techniques
After adequate exposure to the tumor, microsurgical techniques and continuous intraoperative electrical nerve stimulation can better identify and preserve functional nerve fibers while attempting to completely remove the tumor. In addition, fluorescein guidance combined with intraoperative neurophysiological monitoring can increase the safe resection rate and reduce the rate of postoperative neurological deficits (Vetrano *et al.*, 2019). Computer-assisted navigation can help accurately locate tumor margins and standardize surgery for craniofacial tumors (Rana *et al.*, 2012).

(4) Intraoperative hemostatic techniques
Intraoperative hemorrhage should be minimized to prevent blood loss-related complications and death. A tourniquet can help reduce intraoperative bleeding in lesions of the distal extremities. Intraoperative vascular ligation and multi-layered hemostatic sutures should be used. Techniques such as the use of thick nylon sutures at the surgical margins and the use of a Linear Cutting Stapler can help temporarily control intraoperative hemorrhage.

2.2.2.4. Predictors of Postoperative Tumor Recurrence

Postoperative recurrence of pNF is common, with the probability ranging from 25% to 66% (Artico *et al.*, 1997; Donner *et al.*, 1994; Onesti *et al.*, 2009; Wise *et al.*, 2005). Recurrence or progression is associated with several factors (Table 3), including the extent of resection, age, tumor location, and growth pattern (Friedrich *et al.*, 2003; Needle *et al.*, 1997). The smaller the extent of resection and the younger the patient is at the time of surgery, the higher the risk of postoperative recurrence and progression (Manolidis *et al.*, 2006; Needle *et al.*, 1997). Moreover, different locations of pNF exhibit different rates of recurrence and progression, with the highest rates of progression in the head, neck, and face, followed by the trunk, while the extremities have the highest rates of recurrence (Needle *et al.*, 1997; Prada *et al.*, 2012). Among the different growth types, the displacing type has higher recurrence rates than the superficial or invasive types (Vetrano *et al.*, 2019). Furthermore, studies have shown that the postoperative progression of pNF may be the natural course of the disease (Nguyen *et al.*, 2012; Nguyen *et al.*, 2011), suggesting that postoperative growth may be independent of surgery (Nguyen *et al.*, 2013).

Long-term and regular follow-up of pNF patients after surgery is recommended. However, there are no studies about the refined classification of follow-up patients. Some have proposed that patients should be stratified according to age, tumor location and the extent of surgery, which will help guide surgery and risk assessment of recurrence. However, the accuracy and significance of this stratification still need to be verified by further clinical research.

Recommendation: For neurofibromas with obvious symptoms, high risk of malignant transformation, rapid growth, and excessive size (>6 cm in diameter), elective surgery should be performed

Risk factor		Total/near-total resection (≥ 90% resection range)	Subtotal resection (50% ≤ resection range < 90%)	Partial resection (resection range < 50%)
Patient age	Site			
Over 21y	Limbs	Low	Low	Intermediate
10-21y	Limbs	Low	Low	Intermediate
Under 10y	Limbs	Low	Intermediate	Intermediate
Over 21y	Trunk	Intermediate	Intermediate	High
10-21y	Trunk	Intermediate	Intermediate	High
Under 10y	Trunk	Intermediate	High	High
All ages	Face	High	High	High

Table 3. Risk of postoperative recurrence in patients with plexiform neurofibroma (pNF).

after a thorough evaluation. Long-term and regular follow-up are required for pNF patients. Stratification and tumor surveillance should be based on age, tumor location, the extent of surgery to guide operation and risk assessment of recurrence.

2.2.3. Other treatments for nodular and plexiform neurofibromas

2.2.3.1. Targeted therapy

Selumetinib is an oral selective MEK inhibitor that can induce tumor shrinkage. It was approved by the US Food and Drug Administration (FDA) in April 2020 for the treatment of symptomatic or progressive, inoperable NF1-related pNF in patients aged 2-18 at the recommended dose of 25 mg/m^2 twice daily. A phase II multicenter clinical trial showed that partial remission (defined as a ≥20% reduction in tumor volume from baseline, maintaining for at least 4 weeks) was observed in 70% of patients on the drug, of which 80% had a response lasting ≥1 year (Killock, 2020). The most common adverse reactions are increased creatine phosphokinase, acneiform rash, etc. (Hwang *et al.*, 2022). Less common but server toxicities include reduced left ventricular ejection fraction, cardiomyopathy, and ocular toxicity.

In addition to MEK inhibitors, several other types of targeted therapies have been shown to be effective against pNF in clinical trials, such as polytyrosine kinase inhibitors (Fisher *et al.*, 2021). Numerous clinical trials of targeted therapies against pNF are underway. Clinicians can use the ClinicalTrials.gov to search for open clinical trials for patients with NF1.

2.2.3.2. Other treatments

Some potential treatments, including gene therapy, immunotherapy, are still in the research stage and may be useful soon (Champiat *et al.*, 2021; Cui *et al.*, 2020).

Recommendation: Systemic imaging is required for newly diagnosed patients to assess tumor burden, and annual follow-up is recommended for those without malignant signs. Surgical treatment and MEK inhibitors can be selected according to the tumor nature and personal wishes.

2.2.4. Malignant transformation of pNF (MPNST) and treatment

The lifetime risk of MPNST in NF1 patients ranges from 8% to 13% and usually occurs within pre-existing plexiform or nodular neurofibromas. The first sign of malignant transformation can manifest as obvious and persistent pain, a change in tumor texture from soft to hard, or rapid growth of nodules within an existing pNF (Nguyen *et al.*, 2012; Nguyen *et al.*, 2011). On MRI, signs of malignancy include the presence of large tumor size, involvement of deep fascial layer, and necrosis (Nguyen *et al.*, 2013). 18 F-FDG PET may be helpful in distinguishing MPNST from benign plexiform or nodular neurofibromas (Cook *et al.*, 2017; Lovat *et al.*, 2017; Warbey *et al.*, 2009).

2.2.4.1. Surgical treatment of MPNST

Appropriate surgical margins should be selected according to the Surgical Staging System (SSS) or Musculoskeletal Tumor Society (MSTS) staging

system (Tables 4-5). For stage I and II tumors without neurovascular involvement, wide local excision or radical local excision is recommended. For stage I and II tumors with major vascular involvement, recommendations include amputation (grade 1), then wide local excision + vascular replacement (grade 2), and local marginal excision + adventitial dissection + radiotherapy or neoadjuvant radiotherapy (grade 3). For stage I and II tumors with major nerve involvement, recommendations include wide local excision or radical local (grade 1), then amputation (grade 2), and local marginal excision + epineurial dissection + radiotherapy or neoadjuvant radiotherapy + local marginal excision (grade 3). Ideally, negative margins should be achieved. However, close margins or microscopically positive margins may be appropriate to preserve key structures like blood vessels, nerves, bones, and joints. For stage III tumors, systemic treatment is mainly adopted after multidisciplinary discussion (von Mehren *et al.*, 2022) (Chinese society of clinical oncology, 2022).

Staging	Histologic grade	Localization	Metastasis
IA	Low-grade (G1)	Intracompartmental (T1)	No metastasis (M0)
IB	Low-grade (G1)	Extracompartmental (T2)	No metastasis (M0)
IIA	High-grade (G2)	Intracompartmental (T1)	No metastasis (M0)
IIB	High-grade (G2)	Extracompartmental (T2)	No metastasis (M0)
III	Any	Any	Regional or distant (M1)

Table 4. Surgical staging system (SSS) or the musculoskeletal tumor society (MSTS).

Type of resection	Dissection plane	Microscopic details
Intracapsular	Piecemeal debulking or curettage	Tumor in the margins
Marginal	Shell out *en bloc* through pseudocapsule or reactive zone	Reaction of neighboring tissues (may contain satellite lesions)
Wide	Intracompartmental *en bloc* with cuff of normal tissue	Normal tissue (may contain skip lesions)
Radical	Extracompartmental *en bloc* entire compartment	Normal tissue

Table 5. Definition of surgical margin.

Ideally, the biopsy site should be excised together with the final surgical specimen. The resection path should pass through normal tissue planes that are not contaminated by tumors. If the tumor is close to or invades major blood vessels or nerves, there is no need to excise the blood vessels or nerves when adventitia or epineurial dissection are performed and the neurovascular structures are not macroscopically involved. Radical resection or en bloc resection of the whole anatomical compartment is not routinely necessary.

Surgical margins should be documented by both the surgeon and the pathologist who receives the surgical specimen. When final pathology indicates positive margins (except for bone, nerves, or important blood vessels), reoperation to obtain negative margins should be strongly considered if there is no major complication. For close margins or microscopic positive margins of bone, important blood vessels, and nerves, adjuvant radiotherapy should be considered.

Multidisciplinary management is required including plastic surgery, reconstructive surgery, and vascular surgery.

2.2.4.2. Other treatment

Other treatments for MPNST contain radiation, chemotherapy and targeted therapy.

Recommendation: Neurofibromas with signs of accelerated growth, pain, and hardened texture should raise high suspicion for the possibility of MPNST, which can be identified through PET or biopsy. At the same time, systemic evaluation should be carried out, and early surgical treatment should be performed as much as possible for patients without distant metastasis. Patients with distant metastasis can opt for radiotherapy, chemotherapy, and targeted therapy.

2.2.5. Treatment Efficacy Evaluation

For the efficacy evaluation after surgery or drug treatment, it is recommended to use the Response Evaluation Criteria in Solid Tumors (RECIST). Lesions ≥10 mm on CT or MRI with a slice thickness of less than 5 mm are considered measurable lesions. Complete response (CR) is defined as the disappearance of all target lesions. Partial response (PR) is defined as at least a 30% reduction in the sum of diameters of target lesions from the baseline. Progressive disease (PD) is defined as at least a 20% increase in the sum of diameters of target lesions from baseline or the appearance of new lesions. Stable disease is defined as neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD. PET/CT can be used to evaluate tumor metabolic activity.

2.3. Surveillance and treatment of other tumor types that complicated by NF1

2.3.1. Common tumor types in NF1 patients

NF1 patients are more prone to develop multiple types of tumors than the general population. The most common type is benign cNFs in NF1 adults. Juvenile xanthogranuloma is non-Langerhans cell histiocytosis involving the skin, commonly seen in NF1 children, especially those under age 2 years or fulfilling fewer than 2 diagnostic criteria for NF1. It should be noted that NF1 patients with xanthogranuloma have a 20-30 times higher risk of developing juvenile myelomonocytic leukemia (JMML) than those without (Ferrari *et al.*, 2014). pNF, a type of neurofibroma that occurs almost exclusively in NF1 patients, has a high risk of malignant transformation. Diffuse pNF in the head and neck often appears before 1 year old. pNF can cause disfigurement or organ dysfunction, and can also transform to malignant nerve sheath tumors. Symptomatic OPG usually develops before the age of 6, and may be accompanied by vision loss or proptosis. It can remain stable or grow very slowly for many years, and some may regress spontaneously (Listernick *et al.*, 2007; Nicolin *et al.*, 2009). The risk of developing pheochromocytoma is increased in young and middle-aged patients. Pheochromocytoma should be considered when signs occur like elevated blood pressure, headache, palpitations and sweating, or when a well-defined, obvious-enhanced mass in the adrenal glands is found unilaterally (>80%) or bilaterally (>10%) on imaging.

MPNST commonly occurs in adults aged 20-50 years and about half of the cases are related to NF1. Patients with pNF have a greater risk of malignant transformation to MPNST. MPNST commonly occurs on large nerve trunks in the neck or limbs, especially peripheral nerve trunks, such as brachial plexus, sacral plexus, sciatic nerve, etc. JMML is a rare, aggressive myelodysplastic disease with an annual incidence of approximately 1.2 per1 million in children aged 0-14 years. The risk of JMML in children with NF1 is approximately 350 times higher than that in children without NF1. Studies have shown that NF1 is a driving factor in the onset of JMML (Mayerhofer *et al.*, 2021). About 11% of JMML children have NF1 at the same time of diagnosis. Some children are diagnosed with JMML before developing typical features of NF1, which may be due to NF1 mosaic or the double-hit of NF1 mutations in hematopoietic cells.

Rhabdomyosarcoma (RMS) is the most common soft-tissue tumor in childhood, with an annual incidence of 4.3 per 1 million in children under 20 years. Between 0.5 and 6.0% of NF1 patients can develop RMS, and the risk is about 20 times that of the general population. NF1-related RMS tends to occur at an earlier age and commonly involves the genitourinary system. The pathological subtype is usually embryonal RMS (de Leeuw & Prayson, 2019). A meta-analysis and systematic review of 3456 articles showed that women with NF1 under 50 years have a five-fold increased risk of breast cancer compared with the general population, which often presents as a more advanced disease and may associated with increased breast cancer-related mortality (Suarez-Kelly *et al.*, 2019).The features, identification, and surveillance of tumors in NF1 patients are shown in Table 6.

Disease	Benign or malignant	Age of onset	Early signs	Monitoring
Cutaneous neurofibroma	Benign	Childhood, can be lifelong.	They are mainly distributed on the trunk and facial skin, also seen on the limbs, mostly pink. The number can be hundreds or even thousands, varying in size. Some tumors can cause pain, tenderness, radiating pain or paresthesia.	Regular physical examination
Juvenile xanthogranuloma	Benign	Infancy and childhood.	They are asymptomatic, well-defined yellow papules of the skin, most commonly on the head, neck, upper trunk and limbs. It can occur singly or in clusters and may involve multiple organs.	Regular abdominal ultrasound is recommended in patients under 3 years old or with more than 10 skin lesions, especially in infants with hepatomegaly or jaundice. For patients with less systemic involvement, it is recommended to follow up once a year. If visceral lesions are found, frequent follow-up at every 1 to 3 months are required and corresponding treatment strategies should be developed based on the involved organs and clinical symptoms.
Plexiform neurofibroma	Benign, but easy to relapse after surgery.	Infancy, with rapid growth during childhood and adolescence, and remain relatively stable in adulthood.	They most occur in the body and are often asymptomatic in the early stage, leading to delayed diagnosis. As the tumor infiltrates into neighboring tissues, it can lead to pain and behavioral abnormalities resulting from neurological dysfunction. Large tumors can cause severe disfigurement.	In addition to CT as a routine monitoring method, MRI can show the size and severity of plexiform neurofibromas and can be used as a routine monitoring method to evaluate the growth of plexiform neurofibromas. Magnetic resonance angiography is valuable in the evaluation of NF1 vasculopathy. CT or three-dimensional CT reconstruction is recommended before undergoing surgery.
Pheochromocytoma	Most benign, 10% malignant.	Between age 20-50 years.	Elevated blood pressure, headache, palpitations, excessive sweating.	Blood and urine catecholamines and their metabolites can be used for diagnosis; Ultrasound, CT, MRI and MIBG scans are used for localization.
Optic pathway glioma	Low grade malignant.	Usually under age 6 years.	It occurs in 15-20% of NF1 children. They may remain asymptomatic for life. Even if symptoms do occur, they are less severe than those of children without NF1, so as NF1 patients with brainstem and cerebellar. Secondary CNS gliomas occur in more than 20% of NF1 patients diagnosed with optic tract gliomas in childhood and treated with radiotherapy (Madden *et al.,* 2014).	MRI can be used for dynamic follow-up

Disease	Benign or malignant	Age of onset	Early signs	Monitoring
Malignant peripheral nerve sheath tumor	The most common NF1-related malignant tumor.	Adolescence or early adulthood.	Risk factors are NF1 patients with a larger number of non-surface plexiform neurofibromas, larger tumor size, younger age, and deletion of the entire NF1 gene. When the mass size or the severity of pain changes significantly, or neurological dysfunction progresses rapidly, malignant transformation should be alerted, with changes in tumor size being the best predictors.	Ultrasound can clearly show the location, size, nature, blood flow, adjacent tissues, and lymph nodes. MRI is of high value for the diagnosis, staging, treatment and prognosis of MPNST, being the preferred imaging examination method. Chest CT is the first choice to screen for lung metastasis while bone scans can help determine bone metastasis. Confirmation of MPNST still requires biopsy, and it is recommended to do open biopsy in multiple tumor sites.
Juvenile myelomonocytic leukemia	Malignant	In infancy and toddlers with the median onset age of 2 years old	Common manifestations include skin lesions, fever, anemia, bleeding, hepatosplenomegaly and pulmonary infiltrates.	Complete blood count, peripheral blood smear, bone marrow cytology, immunophenotype, cytogenetics and genetic testing.
Rhabdomyosarcoma	Malignant	2-5 years old and 15-19 years old.	Lumps appear in head, neck, trunk, limbs, urogenital tract. Other manifestations include bloody nasal discharge with stuffy nose, purulent discharge from the external acoustic meatus, dysphagia, constipation and hematuria.	Ultrasound, CT, MRI can be used for screening. Masses are usually biopsied or surgically removed, with pathology being the gold standard.
Breast cancer	Malignant	Gradually increasing after 25 years old, peaking at 50-54 years old.	Manifestations include painless breast lumps or accompanied by breast pain unrelated to the menstrual cycle, nipple discharge, dimple sign, nipple skin itching, erosion, ulceration, scab, and desquamation.	Ultrasound, mammograms, and MRI-enhanced scans are used for screening, with biopsy being the only definitive way to diagnose breast cancer.

Table 6. Surveillance and early identification of tumors in NF1 patients.

2.3.2. Treatment of patients with malignant tumors (non-intracranial, non-malignant schwannoma)

Children with JMML who have NF1 gene mutations should receive allogeneic hematopoietic stem cell transplantation as soon as possible. The median survival time of children with JMML is as short as 10 to 12 months without transplantation. The treatment of RMS is multidisciplinary including surgery, chemotherapy, and local radiotherapy. More than 70% of localized RMS can be cured. The specific treatment plan depends on the patient's risk stratification, which directly contributes to outcomes. Treatment options for breast cancer depend on factors such as pathological type, stage, grade, tumor size, and hormone sensitivity. These options include surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy, and immunotherapy.

Recommendation: NF1 patients are more likely to develop multiple types of tumors than the general population, such as cNF, pNF, OPG, pheochromocytoma, MPNST, JMML, RMS, breast cancer, and colorectal cancer. Early identification and monitoring should be emphasized and treatment principles vary according to tumor types.

2.3.3. Complicated intracranial tumors in NF1 patients and their treatment principles

The most common intracranial tumor in NF1 patients is glioma, which can occur in the optic pathway, cerebellum, brainstem, and basal ganglia, with OPG accounting for nearly 2/3 of glioma. 15% to 20% of pediatric NF1 patients can develop OPG, involving the optic nerve, optic chiasm, optic tract and optic radiation, with only 30-50% being symptomatic and some regressing spontaneously or after first-line chemotherapy. The diagnosis of OPG can be based on MRI or clinical examination since the biopsy carries the risk of vision loss. The complex anatomy of the optic pathway makes surgery difficult and risky. Therefore, patients are usually followed up or treated without pathology evidence. Since OPG most commonly occurs in childhood, newly diagnosed pediatric patients should be screened and monitored for visual acuity until they aged 8 years. Asymptomatic patients can be followed up during childhood. OPG may remain stable for many years, or grow at different rates. When suspicious symptoms occur, such as decreased vision, headache, seizure or endocrine disorders, a cranial MRI should be performed. MRI shows thickening of the optic nerve or optic chiasm, with a slightly high signal intensity in T2WI, a low signal intensity in T1WI and uneven enhancement. The focus of treatment is vision protection, with chemotherapy being the first line, including a combination of carboplatin and vincristine (Evans *et al.*, 2017). Surgical resection of the tumor, primarily of the intraorbital segment, may be considered in cases of severe proptosis that affects appearance, or cases in which large optic nerve tumors result in no light perception or corneal ulcers secondary to exposure. Although radiotherapy is effective, it can cause complications such as long-term endocrine disorders, cognitive impairment, vascular diseases, decreased vision, and secondary malignant tumors. Therefore, radiotherapy is not recommended as the first choice and is considered as the last resort. Other less common intracranial tumors include low-grade gliomas in the posterior fossa, gangliogliomas, the incidence of which is higher than that of the general population (Gutmann *et al.*, 2017; Nix *et al.*, 2020). Multiple clinical trials are using targeted agents to treat OPG and low-grade gliomas, although the efficacy needs to be further determined.

Recommendation: A detailed neurologic physical examination should be performed at the initial diagnosis and during follow-up. Pediatric patients should be monitored for visual acuity until age 8 years, and have brain MRI when suspicious symptoms occur. Once OPG is diagnosed, annual brain MRI is required. The first line of treatment for OPG is chemotherapy. Surgical removal of the tumor may be considered in cases of severe proptosis that affects the appearance of the eye, or in cases where large optic nerve tumors result in no light perception or corneal ulcers secondary to exposure.

2.3.4. Identification and treatment of intraspinal tumors in NF1 patients

In addition to neurofibromas and MPNST, other rare types of NF1-related intraspinal tumors may be present, such as ependymoma, astrocytoma, and ganglioneuroma (Cheng *et al.*, 2014; Giussani *et al.*, 2013; Hayashi *et al.*, 2011; Miyakoshi *et al.*, 2010; Yagi *et al.*, 1997). However, most of the data is from small sample studies or case reports. Multi-center large sample clinical studies are required to testify whether there is a correlation between these intraspinal tumors and NF1 and how their characteristics differ from general population.

NF1-related intraspinal tumors often have no specific clinical manifestations in the early stages and may even be masked by symptoms of neurofibromas involving peripheral nerves. Hence regular spine MRI examination is important. The treatment often refers to that of non-NF1-related intraspinal tumors. Since NF1 patients may need to undergo multiple spinal surgeries throughout their lives, the clinical benefit is relatively low if surgery is performed for a single lesion. Therefore, for NF1 patients with intraspinal tumors, regular follow-up should be considered if there are no related symptoms and slow progression.

Recommendation: Annual spine MRI is required for NF1 patients. The treatment for NF1 patients with intraspinal tumors is the same as those for non-NF1-related intraspinal tumors. Regular follow-up should be considered if there are no related symptoms and slow progression.

2.3.5. Imaging screening for NF1

The long-term management of patients with NF1 is based on early detection and treatment of complications as they arise. Given the long-term risk and the variable location of the tumors, imaging

is not recommended for screening. The use of imaging should be based on the history and physical examination. pNF has the potential to transform into MPNST, with signs of malignant transformation being worsening pain and growth of lesions. Imaging is indicated if patients with pNF develop signs, such as progressive severe pain, rapid tumor growth, or nodular protrusion.

When new symptoms or signs appear, enhanced MRI or PET/CT are recommended. For patients with a heavy tumor burden and a high risk of MPNST, MRI or PET/CT screening can be performed regularly. Follow-up is recommended every 3 months for 3 years, then every 6 months for 2 years, then annually. MRI can observe tumor morphological changes while PET/CT can help differentiate MPNST from benign pNF. The sensitivity of 18 F-FDG PET/CT in detecting malignant transformation is 100%, the specificity is 77 to 95%, which can be used for tumor staging.

2.4. NF1-related ophthalmic manifestations

2.4.1. Ophthalmic manifestations in NF1 patients

2.4.1.1. Optic pathway glioma

OPG is the most common tumor of the central nervous system (CNS) in pediatric NF1 patients, mainly occurring in 15-20% of NF1 children (Listernick *et al.*, 1999). Children diagnosed or suspected of NF1 should be followed up annually until the age of 8 years and then every other year until the age of 18 years (de Blank *et al.*, 2017).

2.4.1.2. Eyelid plexiform neurofibroma

Its manifestations as droopy eyelids with sagging skin, narrow palpebral fissures, an italic S-like course of the eyelid margin, ectropion, and proptosis. Children with amblyopia due to ptosis should undergo surgery as soon as possible whereas surgery to improve appearance should be delayed until after puberty (Ying Cui *et al.*, 2019). pNF is not sensitive to radiotherapy or chemotherapy, hence surgical resection is the first choice with the aim at tumor reduction. Targeted drugs are effective in some patients, of which selumetinib is the only drug approved by the US FDA for pNF (Markham & Keam, 2020).

2.4.1.3. Enlarged corneal nerve and corneal neurofibroma

NF1 keratopathy can manifest as enlarged corneal nerves, myelinated nerve fibers and so on, affecting 6-22% of patients (Gaonker *et al.*, 1992; Sippel, 2001). It also includes shortened corneal nerve length (Barnett *et al.*, 2019), mild reduced corneal sensation, and short tear break-up time. Surgical resection and corneal transplantation are the mainstays of treatment for corneal neurofibromas. Patients with enlarged corneal nerves can be treated with artificial tears as needed.

2.4.1.4. Lisch nodules

Lisch nodules are a type of pigmented iris hamartoma, manifesting as multiple well-defined yellow to dark brown dome-shaped nodules on the iris surface. Multiple Lisch nodules ≥2) are characteristic of NF1(Lewis & Riccardi, 1981), but are also occasionally seen in NF2 (Charles *et al.*, 1989) and segmental NF (Weleber & Zonana, 1983). Lisch nodules are seen in 50% of NF1 patients at age 5 years, 75% of patients at age 15 years, and 95-100% of patients over 30 years (Ragge *et al.*, 1993).

2.4.1.5. Congenital ectropion uvea

Congenital ectropion uvea is a rare manifestation characterized by iris pigment epithelium lining on the anterior surface of the iris stroma and endothelialization of the anterior chamber angle. It often causes refractory glaucoma in infants and children (Edward *et al.*, 2012).

2.4.1.6. Glaucoma

Glaucoma usually begins at an early age, with irregular plaques, marked pigmentation, anteriorly inserted iris, and extensive synechia on the gonioscope (Edward *et al.*, 2012; Quaranta *et al.*, 2004). Ultrasound biomicroscopy reveals angle closure and ciliary body thickness. NF1 patients with glaucoma have a poor visual prognosis and should be treated with medication to lower intraocular pressure. If the disease progresses, surgical options such as glaucoma drainage implant, trabeculectomy, and goniotomy may be considered.

2.4.1.7. Choroidal hamartoma

Choroidal hamartoma can be found in 82-100% NF1 patients (Viola *et al.*, 2012) and choroidal abnormalities under NIR have been incorporated into the new diagnostic criteria for NF1 ("National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987," 1988). Choroidal abnormalities may appear as round, well-defined, bright patches or irregular, ill-defined sheets. Frequency domain optical coherence tomography (FDOCT) scans show hyperreflective placcoid or dome-shaped choroidal nodules (Abdolrahimzadeh *et al.*, 2015). The early sign manifests as hypofluorescent patches on indocyanine green angiography. No treatment is required for choroidal hamartoma.

2.4.2. Ophthalmic Surveillance for NF1

Patients with decreased vision, visual field defects or altered color vision need to be further evaluated by a neuro-ophthalmologist as soon as possible (Miller *et al.*, 2019). Follow-up examinations should include visual acuity, visual field, pupillary light reflex, color vision, and eye movement, with an emphasis on emphasizing on iris and fundus changes on slit lamp. High alert is required for the following changes: decreased vision, visual field defects, afferent pupillary defect, Lisch nodules, choroidal abnormalities, pallor optic disc, papilledema, color vision changes, strabismus, and nystagmus. The most vital examination is age-adjusted best-corrected visual acuity (Listernick *et al.*, 2007). OCT and visual evoked potentials (VEP) should be ordered as soon as possible if NF1-related ophthalmic manifestations are present. OCT can assess the thickness of the retinal nerve fiber layer (Danesh-Meyer *et al.*, 2006) and the ganglion cell and inner plexiform layer (GCIPL). Abnormalities in the VEP are often indicative of visual pathway damage. If OPG is considered, an MRI of the optic nerve and optic chiasm should be ordered as soon as possible.

Recommendation: When signs of decreased loss, visual field defects, or color vision changes occur, patients should consult a neuro-ophthalmologist promptly. Confirmed or suspected children under the age of 8 years should have an eye examination at least once a year or every other year for children aged 8-18 years. Patients after puberty should see an ophthalmologist promptly when suspicious symptoms like decreased vision occur. The main items of annual follow-up include visual acuity, visual field, pupillary reflex, color vision, and eye movement, with slit lamp focusing on the changes in the iris and fundus. If NF1-related ophthalmic manifestations occur, OCT, VEP, MRI for optic nerve and chiasm need to be arranged as soon as possible.

2.5. Manifestations, evaluation, and management of NF1-related bone abnormalities

Bone abnormalities in NF1 patients usually involve the axial bones, skull, and limb bones. More than half of NF1 patients may develop bone abnormalities (Patel & Stacy, 2012), including scoliosis, cranial developmental defects, tibial pseudarthrosis, short stature, pectus excavatum and pectus carinatum.

2.5.1. Scoliosis

Scoliosis is a common bone abnormality in NF1, with a prevalence of 2-69% (Toro *et al.*, 2021). It is a spinal deformity characterized by the curvature of one or several spine segments to the side, usually accompanied by vertebral body rotation. There are two types of scoliosis: dystrophic and non-dystrophic, with the latter being more common (Vitale *et al.*, 2002). Some patients may also have kyphosis. The focal decrease in bone density of the vertebral body and the presence of paraspinal neurofibroma is related to the onset of scoliosis (Alwan *et al.*, 2005). An annual Adam forward bend test is required to screen for scoliosis. Full spine anteroposterior and lateral X-rays are necessary to determine the severity of scoliosis for patients with uneven backs or severe razorback deformity. Exercise treatment can be used for patients with a Cobb angle of 10° ~ 25°, bracing and exercise for Cobb angle of 25° ~ 40°, and surgical intervention for a Cobb angle exceeds 40°. Surgical approaches include spinal fusion and non-fusion, sometimes requiring osteotomies to correct severe spinal deformities. The surgical treatment of scoliosis in NF1 patients is very complex (Elefteriou *et al.*, 2009). A preoperative evaluation by a multidisciplinary team on multiple systems of the patient is required. It is crucial to select an experienced spinal orthopedic surgery team for treatment and long-term follow-up.

2.5.2. Skull developmental abnormalities

Skull developmental abnormalities often manifest as a sphenoid wing or orbital dysplasia, calvarial defects, increased head circumference or macrocephaly. These conditions can cause craniofacial deformity and impaired vision, often accompanied by infiltration and decalcification of the skull near the tumor (Jacquemin *et al.*, 2002). Some skull abnormalities have a close anatomical relationship with adjacent space-occupying lesions like neurofibromas, OPG, dural ectasia, etc. (Arrington *et al.*, 2013; Jacquemin *et al.*, 2003). The most common skull defect is sphenoid wing dysplasia, which is also a unique skeletal abnormality of NF1(Friedman & Birch, 1997). Patients with cranial developmental defects need to undergo head CT and MRI before surgery. CT scans can show skull abnormalities while MRI can rule out the presence of adjacent structural lesions. For patients with meningoencephalocele caused by skull abnormalities, early surgery is recommended to restore the normal structure of the brain. Surgical repair of cranial anomalies can utilize bone grafts, titanium mesh, high-density porous polyethylene implants and other materials to remodel the normal skull contour. Normal tissues should be protected during operation. The resection of adjacent space-occupying lesions should be considered individually to alleviate the progression of skull abnormality.

2.5.3. Long bone dysplasia

Long bone dysplasia is usually unilateral and localized, with tibia being the most affected. Pseudoarthrosis is a unique skeletal abnormality in NF1, characterized by progressive anterolateral bowing of the tibia and fibula, pathologic fracture, and then the development of tibial or fibular pseudoarthrosis. The treatment of tibial pseudoarthrosis is challenging, as the fracture is difficult to heal and is prone to re-fracture after healing. Surgery remains the mainstay of treatment for tibial pseudoarthrosis. However, it has many challenges like poor long-term effects, and often requires repeated surgeries.

2.5.4. Chest wall deformities

Chest wall deformities are common in NF1 patients, such as chest wall asymmetry, pectus excavatum, and pectus carinatum (Riccardi, 1993). Surgical intervention is rarely required for NF1 patients with pectus excavatum and pectus carinatum if cardiopulmonary function is compensated and asymptomatic. It is performed only to meet the patient's aesthetic needs.

2.5.5. Osteopenia / Osteoporosis

NF1 patients can have decreased bone density (Poyrazoğlu *et al.*, 2017), associated with an increased risk of fracture and scoliosis. It has been suggested that increased osteoclast activity leads to decreased bone density, with vitamin D deficiency and decreased physical activity being potential environmental factors. If NF1 patients develop osteopenia or osteoporosis, it is recommended to take calcium supplements, and vitamin D and engage in moderate exercise. Preventing fractures are crucial due to the high risk of re-fracture after healing. Reduction and fixation can be performed when a fracture occurs.

Recommendations: An annual evaluation of the skeleton is recommended, including physical examination and imaging when needed, to determine the progression of the abnormalities. Surgery aimed at relieving symptoms of deformity and pain caused by skeletal anomalies. Resection of adjacent space-occupying lesions should be considered individually to alleviate the progression of skull abnormalities.

2.6. Manifestations, evaluation, and management of NF1-related neurologic involvement

2.6.1. Assessment of peripheral nervous system involvement

pNFs can grow diffusely along the long axis of the nerve, often involving nerve roots, trunks and plexuses. In a few cases they may also involve the peripheral nerves, manifesting as a length-dependent symmetrical sensorimotor peripheral neuropathy (Thomas *et al.*, 1990). A detailed neurological physical examination, CT, MRI, neurological ultrasound, electrophysiology and other auxiliary examinations should be performed to assist in localization if relevant symptoms occur.

2.6.2. Other CNS complications other than tumors

Apart from tumors, NF1 patients may also suffer from other CNS abnormalities, including epilepsy, cerebrovascular malformations, headache, cognitive dysfunction, and sleep disorders (Madubata *et al.*,

2015; Stewart *et al.*, 2018). The prevalence of epilepsy in NF1 patients is 4-14% (Bernardo *et al.*, 2020; Pecoraro *et al.*, 2017; Sorrentino *et al.*, 2021), with half considered to be caused by structural abnormalities such as tumors, medial temporal lobe sclerosis, and cortical developmental abnormalities (Bernardo *et al.*, 2020). Most seizures in NF1 are easy to control, and those caused by structural abnormalities like tumor usually respond well to surgery. The incidence of cerebrovascular disease is higher in NF1 patients and the pathogenic mechanism remains unclear. NF1-related cerebrovascular abnormalities include moyamoya disease, aneurysm, vascular stenosis-occlusion, arteriovenous malformation, and artery dolichoectasia. These mainly involves the circle of Willis and can lead to cerebral ischemic and hemorrhagic events. About half of the patients have no clinical symptoms when cerebrovascular abnormalities are discovered (Barreto-Duarte *et al.*, 2021). It is recommended that patients undergo a routine neurological physical examination every year. If conditions permit, routine cerebrovascular assessment should be performed using transcranial Doppler ultrasound, magnetic resonance angiography or CT angiography. Consultation with a neurologist should be sought if new symptoms develop. Patients with NF1 are more likely to have headaches at an earlier age (Madubata *et al.*, 2015).

2.6.3. Treatment of chronic pain in neurofibromatosis

NF1-related chronic pain can involve different parts of the body and is mainly caused by tumor compression and orthopedic complications such as scoliosis and pseudoarthrosis. These conditions can cause musculoskeletal pain (Bellampalli & Khanna, 2019). There are no specific treatments for NF1-related pain (Créange *et al.*, 1999; Jeong *et al.*, 2013). Non-steroid anti-inflammatory drugs (NSAIDs) can be given for mild pain, while opioid analgesics such as morphine and Oxycontin can be prescribed for moderate to severe pain. When the tumor compresses and invades the nerves, it can cause symptoms of nerve irritation, manifesting as transient paroxysmal and recurrent radiating tingling or burning pain along the nerve distribution. This often occurs at night and can be triggered or aggravated by changes in body position and forced defecation. Medications for neuralgia like pregabalin or gabapentin can be added, and tumor resection can also be performed to achieve the long-term pain control. In addition, NF1 patients usually have psychological problems and should be given anxiolytics, antidepressant and bio-psycho-social treatment under the guidance of professional doctors (Bellampalli & Khanna, 2019).

Recommendation: A detailed neurological physical examination should be performed at the initial diagnosis and follow-up. If deep lesions involving paraspinal nerve roots, trunks and plexuses are suspected, MRI and CT should be used to identify the scope of the lesions. If peripheral nerve involvement is suspected, nerve ultrasound and electrophysiological examinations should be performed. Patients should undergo prophylactic cerebrovascular imaging screening. Cerebrovascular malformation, epilepsy and headache in NF1 patients should be treated in the same way as in non-NF1 patients.

2.7. NF1-related cardiovascular abnormalities

2.7.1. Screening and monitoring of cardiovascular comorbidities

Prevalence of congenital heart disease in NF1 patients is higher than that in the general population, with pulmonary stenosis being the most common type followed by mitral valve abnormalities, atrioventricular septal defects, tetralogy of Fallot, and ventricular wall thickening (Pinna *et al.*, 2019). Congenital heart disease is closely related to the patient's growth, development, and surgical risks. Hence, heart auscultation is required during follow-up. If a heart murmur can be heard, further echocardiographic evaluation should be performed. If no heart murmur is heard, echocardiography is usually not necessary (Dunning-Davies & Parker, 2016).

Besides, NF1 is associated with vascular disease, although the prevalence is not well documented. Both large and small vessels can be involved, manifesting as stenosis, occlusion, rupture, aneurysm, arteriovenous fistula, thrombosis, etc. (Friedman *et al.*, 2002). Different sites and types of vascular involvement may present with corresponding manifestations. Vascular disease is an important cause of disability and death, so the recognition of related symptoms is vital during follow-up and vascular imaging should be performed when necessary to further clarify.

2.7.2. Management of hypertension in NF1 patients

Hypertension is the most common cardiovascular manifestation in NF1 patients and is more common

in adults. Hypertension is usually primary, but can also be secondary to a renal artery or abdominal aortic stenosis (Fossali *et al.*, 2000) or pheochromocytoma (Al-Sharefi *et al.*, 2019). Blood pressure should be measured during annual follow-up visits. If elevated blood pressure is found, the abdominal blood vessels should be auscultated for murmurs. For patients with hypertension, renal artery imaging should be completed (Fossali *et al.*, 2000). Pheochromocytoma-related manifestations should be inquired such as episodic headaches, sweating, and palpitation. Plasma and urine catecholamines and their metabolite levels should be measured, and CT or 131 I-metaiodobenzylguanidine ((131)I-MIBG) should be performed if necessary (Al-Sharefi *et al.*, 2019). Screening for pheochromocytoma is recommended in patients planning surgery or pregnancy to reduce the risk of cardiovascular crisis. Individualized antihypertensive treatment should be carried out according to the cause of hypertension, including drug treatment, percutaneous transluminal angioplasty (PTRA) or stent implantation for renal artery stenosis, drug preparation and surgical resection for pheochromocytoma.

Recommendation: A detailed cardiac physical examination should be performed for NF1 patients at initial diagnosis and follow-up. If a heart murmur is heard, an echocardiogram should be performed to screen for congenital heart disease. Blood pressure should be measured at least once a year during follow-up visits, paying attention to the symmetry of blood pressure and pulse in the extremities, and to abdominal bruits. Doppler ultrasound of the renal artery and aorta should be performed in children with hypertension, while adults under 30 years only require a Doppler ultrasound of the renal artery. For those who have uncontrolled hypertension and symptoms related to pheochromocytoma, screening for pheochromocytoma should be performed.

2.8. Assessment and management of cognition, psychology, growth, and development in Children with NF1

2.8.1. Monitoring and Intervention of the impact of NF1 on children's cognition

Approximately 80% of children with NF1 exhibit multiple cognitive impairments, which involve various cognitive domains and the ability to interact with each other. Visuospatial dysfunction, a characteristic phenotype of children with NF1, includesimpaired perception and interpretation of spatial features of visual information, impaired memory for visual information, and impaired visual motor integration. Children with NF1 have significantly lower intelligence than their peers, displaying poor advanced cognitive processing abilities. They are 5-6 times more likely to develop phonological disorders than normal children. These children often experience executive dysfunction, an advanced ability based on goal-directed behavior. Such dysfunction can lead to learning difficulties, impacting daily life. Additionally, other research suggests that children with NF1 have difficulties to recognize facial expressions in others, potentially affecting their social skills and reducing their ability to empathize. Furthermore, approximately 52% of children with NF1 experience learning disabilities, 21-40% have autism spectrum disorder, and 40-50% have attention deficit hyperactivity disorder (ADHD) (Glad *et al.*, 2021). All three disorders have varying degrees of cognitive impairment.

Cognitive impairment in NF1 can usually be assessed through several examinations, including Visual Comprehensive Analysis, Visual Cognitive Motor System Examination, Academic Achievement Test, Intelligence Test, Neuropsychological Testing, The Pupil Rating Scale, Wisconsin Card Sorting Test, Test of Attention Performance, Stroop Test.

Medication is the main treatment of cognitive impairment in NF1. Methylphenidate hydrochloride has been proven effective, mainly targeting NF1 children with ADHD. Further clinical trials are needed to broaden its indications (Pobric *et al.*, 2022; Torres Nupan *et al.*, 2017). Drugs such as p21-activated kinase (PAK) inhibitors are still in the animal experimental stage, and clinical trials are required to verify their efficacy. A variety of treatments based on patients' conditions is gaining increasing attention, like cognitive behavioral therapy (CBT). Efforts should focus on the assessment of NF1 cognitive function and early recognition of abnormalities to select proper medication, behavioral and psychological treatments. Individualized treatment should be based on patients' manifestations to improve patients' cognition and quality of life (Miller & Halloran, 2022).

Recommendation: Growth and development should be monitored at the initial diagnosis and follow-up. Speech therapy, functional training and

physiotherapy should be provided for children with speech and language disorders and motor disorders causing balance and gait abnormalities.

2.8.2. Impact, Monitoring and intervention of NF1 on psychology

NF1 is also associated with a range of psychological problems. Research has found that 55% of children with NF1 are prone to depression and 15% prone to anxiety. These conditions lead to higher levels of stress perception, greater psychological pressure, and lower self-esteem. The common psychiatric disorders include anxiety disorders, depressive disorders, sleep disorders, language disorders, ADHD, learning disorders, autism spectrum disorder, social impairment, and enuresis.

Recommendation: When psychological problems or mental disorders are suspected, referring children to a pediatric psychologist or psychiatrist, or requesting a consultation is recommended. Treatment should be tailored to the specific situation and common treatment options include psychotherapy, medication, and physical therapy.

2.9. Impact and monitoring of NF1 on growth and development

Short stature is one of the unique features of NF1 patients (Alshahrani *et al.*, 2022; Ferner & Gutmann, 2013; Miller *et al.*, 2019), with about one-third having a height lower than the target height (Gui *et al.*, 2021). Children may experience reduced pubertal spurt growth, which is more pronounced in males than in females (Clementi *et al.*, 1999; Zessis *et al.*, 2018). The short stature may be related to the following factors: 1. CNS tumors such as OPG, leading to central precocious puberty and premature closure of the epiphysis; 2. Primary or acquired growth hormone deficiency (GHD) (Sani & Albanese, 2017; Vassilopoulou-Sellin *et al.*, 2000) (Xiaodan Long *et al.*, 2018); 3. Scoliosis and other skeletal deformities; 4. The use of Methylphenidate hydrochloride in patients with ADHD. GHD is one of the important causes of short stature in patients with NF1, but the exact prevalence is unknown (Mei Zhang *et al.*, 2014). The 5′ end of the NF1 gene to the GRD domain may be a hot spot mutation region for short stature in NF1 patients (Ben-Shachar *et al.*, 2013; Yao *et al.*, 2016). Children carrying severe truncating mutations in this region should be monitored for height growth as early as possible. When the growth rate deviates from the normal curve, endocrine evaluation is required, including tests for thyroid hormone, growth hormone, and sex hormones. NF1 has a potential risk of malignancy. Current studies on the treatment of NF1 patients with recombinant human growth hormone (rhGH) are mostly case reports and retrospective studies of small samples (Tornese *et al.*, 2015; Vurallı *et al.*, 2016). Prospective, multi-center, randomized controlled trials are needed to further evaluate the effectiveness, safety and optimal dosage of rhGH treatment in NF1 patients. rhGH should be given carefully based on fully informed consent, weighing factors such as efficacy, safety, cost, and patient willingness.

Central precocious puberty is another endocrine abnormality in patients with NF1 (Bizzarri & Bottaro, 2015), with the prevalence being 3%, higher than that of the general population (0.6%) (Cnossen *et al.*, 1997; Habiby *et al.*, 1995). Involvement of the hypothalamus by OPG can prematurely activate the hypothalamic-pituitary-gonadal axis and lead to precocious puberty (Bizzarri & Bottaro, 2015; Cnossen *et al.*, 1997). It is important to detect precocious puberty promptly in children with NF1, as it indicates the possible presence of OPG. Furthermore, treatments that inhibit growth can minimize height impairment and adolescent psychological problems caused by precocious puberty.

Recommendation: Growth and development should be accessed annually, including height, weight, and head circumference. Secondary sexual characteristics and linear growth also need to be assessed annually for older children to assess short stature, precocious puberty, and delayed puberty. In patients with accelerated growth or precocious puberty, brain MRI should be performed to evaluate hypothalamic-pituitary lesions, especially OPG. For NF1 patients with GHD, rhGH treatment based on fully informed consent can be considered after comprehensive assessment of benefits, risks, patient willingness and cost. Adverse reactions, especially the risk of tumor occurrence, should be closely monitored during treatment.

3. LIFE-CYCLE HEALTH MONITORING OF NF1 PATIENTS

Since NF1 patients have varying ages of onset, diverse manifestations involving multiple systems,

they should receive regular health monitoring at all stages to assess disease progression and intervene early.

Proper genetic testing can be chosen on demand at the initial diagnosis and reanalysis can be performed at intervals of 2 to 3 years during follow-up when necessary. Patients with NF1 who wish to have children should undergo prenatal genetic counseling at least once before childbirth.

Head circumference should be evaluated annually in prepubertal children, and precocious puberty should be monitored annually from age 5 until the onset of puberty. All patients with childhood or adolescent-onset NF1 should receive a developmental and psychological evaluations during childhood and adolescence.

For NF1 patients of all ages, full life-cycle health monitoring is required including the following items

Skin examination: Annual skin examinations should be conducted to assess CALMs, cNF and pNF. Imaging or histopathological examinations are decided based on the patient's symptoms.

Eye examination: Confirmed or suspected children under the age of 8 should have an eye examination at least once a year or every other year for children aged 8-18 years. The main items include visual acuity, visual field, pupillary reflex, color vision, eye movement and slit lamp focusing on changes in iris and fundus. Patients after puberty should see an ophthalmologist promptly when they develop suspicious symptoms like decreased vision.

Orthopedic Examination: Patients with NF1 should have an annual physical examination of the skeletal system and routine spinal MRI.

Nervous system: All patients with NF1 should undergo an annual neurological physical examination. Imaging or electrophysiological examination will be chosen based on the patient's symptoms or new positive signs.

Cardiovascular system: All patients with NF1 should undergo at least one cardiac physical examination at initial diagnosis. If a heart murmur is heard, echocardiography should be performed. Besides, patients should undergo annual blood pressure and pulse examinations of their limbs.

Breast: Mammography should be performed annually at the age of 30, and breast magnetic resonance scanning is recommended between the ages of 30 and 50 (Miller *et al.*, 2019).

4. SUMMARY OF THE MULTIDISCIPLINARY APPROACH

As a rare disease involving multiple systems and exhibiting diverse manifestations, patients with NF1 are often misdiagnosed in general outpatient clinics. NF1 patients often encounter difficulties in management and follow-up as they enter adulthood. Therefore, it is recommended to establish a dedicated NF1 multidisciplinary platform within qualified centers to provide patients and their families with a long-term, individualized, and comprehensive approach to disease management and consultation (Figure 1). All recommendations are summarized in Table 7.

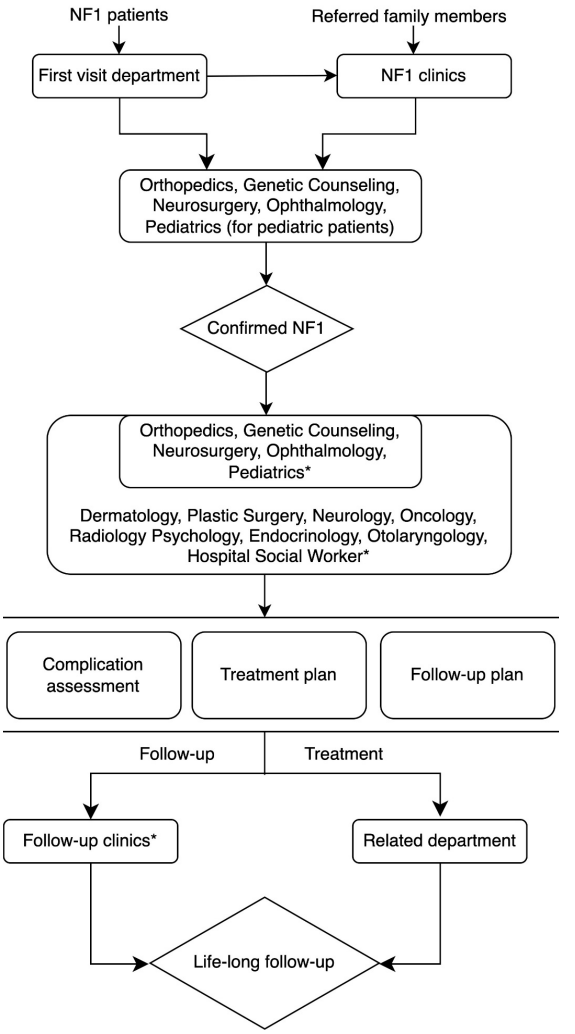

Figure 1. Multidisciplinary approach to care for NF1 patients.
* Pediatric patiens should visit corresponding pediatric clinics.

Genetic diagnosis	For suspected NF1 patients who do not have a confirmed clinical diagnosis but are in need of further treatment or genetic counseling, proper genetic testing should be chosen. This aims to clarify the molecular diagnosis and assist in disease management. WES is preferred with samples types varying according to different NF1 types. If the detection is negative, WGS can be considered. The reanalysis of original data should be done every two years to include newly discovered NF1-related genes or new mutations.
Genetic counseling	A multi-system assessment should be conducted for the proband, his parents and siblings referencing to the NF1 diagnostic criteria and other common clinical manifestations. The risk assessment of other relatives should be considered on a case-by-case basis. NF1 patients who wish to have children should receive prenatal genetic counseling and pregnant patients should be closely monitored.
CALMs	CALMs generally do not require treatment, but laser can be considered for lesions that severely affect the appearance.
Other skin manifestations	In the case of multiple nevus anemicus or multiple juvenile xanthogranulomas in combination with CALMs or cNF, the possibility of NF1 should be alerted.
cNF	cNF is a benign tumor and treatment is based on the patient's wishes. Surgery is the main treatment for large tumors or tumors that cause dysfunction. Simultaneously, CO2 laser ablation, electrodesiccation, laser photocoagulation, and radiofrequency ablation can be used to treat patients with a large number of cNFs that severely affect their appearance.
Nodular and plexiform Neurofibromas	1. Systemic imaging is required for newly diagnosed patients to assess tumor burden, and annual follow-up is recommended for those without malignant signs. Surgical treatment and MEK inhibitors can be selected according to the tumor nature and personal wishes. 2. For neurofibromas with obvious symptoms, high risk of malignant transformation, rapid growth, and excessive size (>6 cm in diameter), elective surgery should be performed after thorough evaluation. Long-term and regular follow-up are required for pNF patients. Stratification and tumor surveillance should be based on age, tumor location, the extent of surgery so as to guide operation and risk assessment of recurrence.
MPNST	Neurofibromas with signs of accelerated growth, pain, and harden texture should raise high suspicion for the possibility of MPNST, which can be identified through PET or biopsy. At the same time, systemic evaluation should be carried out, and early surgical treatment should be performed as much as possible for patients without distant metastasis. Patients with distant metastasis can opt for radiotherapy, chemotherapy and targeted therapy.
Complicated tumors (non-intracranial)	NF1 patients are more likely to develop multiple types of tumors than the general population, such as cNF, pNF, OPG, pheochromocytoma, MPNST, JMML, RMS, breast cancer, and colorectal cancer. Early identification and monitoring should be emphasized and treatment principles vary according to tumor types.
Complicated intracranial tumors	A detailed neurologic physical examination should be performed at the initial diagnosis and during follow-up. Pediatric patients should be monitored for visual acuity until age 8 years, and have brain MRI when suspicious symptoms occur. Once OPG is diagnosed, annual brain MRI is required. The first line of treatment for OPG is chemotherapy. Surgical removal of the tumor may be considered in cases of severe proptosis that affects the appearance of the eye, or in cases where large optic nerve tumors result in no light perception or corneal ulcers secondary to exposure.
Complicated intraspinal tumors	Annual spine MRI is required for NF1 patients. The treatment for NF1 patients with intraspinal tumors is the same as those for non-NF1 related intraspinal tumors. Regular follow-up should be considered if there are no related symptoms and slow progression.

Eye examination	When signs of decreased loss, visual field defects, or color vision changes occur, patients should consult a neuro-ophthalmologist promptly. Confirmed or suspected children under the age of 8 years should have an eye examination at least once a year or every other year for children aged 8-18 years. Patients after puberty should see an ophthalmologist promptly when suspicious symptoms like decreased vision occur. The main items of annual follow-up include visual acuity, visual field, pupillary reflex, color vision, eye movement, with slit lamp focusing on the changes in iris and fundus. If NF1-related ophthalmic manifestations occur, OCT, VEP, MRI for optic nerve and chiasm need to be arranged as soon as possible.
Orthopedic examination	An annual evaluation of the skeleton is recommended, including physical examination and imaging when needed, to determine the progression of the abnormalities. Surgery is aimed at relieving symptoms of deformity and pain caused by skeletal anomalies. Resection of adjacent space-occupying lesions should be considered individually to alleviate the progression of skull abnormalities.
Nervous system	A detailed neurological physical examination should be performed at the initial diagnosis and follow-up. If deep lesions involving paraspinal nerve roots, trunks and plexuses are suspected, MRI and CT should be used to identify the scope of the lesions. If peripheral nerve involvement is suspected, nerve ultrasound and electrophysiological examinations should be performed. Patients should undergo prophylactic cerebrovascular imaging screening. Cerebrovascular malformation, epilepsy and headache in NF1 patients should be treated in the same way as in non-NF1 patients.
Cardiovascular system	A detailed cardiac physical examination should be performed for NF1 patients at initial diagnosis and follow-up. If a heart murmur is heard, an echocardiogram should be performed to screen for congenital heart disease. Blood pressure should be measured at least once a year during follow-up visits, paying attention to the symmetry of blood pressure and pulse in the extremities, and to abdominal bruits. Doppler ultrasound of the renal artery and aorta should be performed in children with hypertension, while adults under 30 years only require a Doppler ultrasound of the renal artery. For those who have uncontrolled hypertension and symptoms related to pheochromocytoma, screening for pheochromocytoma should be performed.
Growth and development	1. Growth and development should be accessed annually, including height, weight, and head circumference. Secondary sexual characteristics and linear growth also need to be assessed annually for older children to assess short stature, precocious puberty, and delayed puberty. In patients with accelerated growth or precocious puberty, brain MRI should be performed to evaluate hypothalamic-pituitary lesions, especially OPG. For NF1 patients with GHD, rhGH treatment based on fully informed consent can be considered after comprehensive assessment of benefits, risks, patient willingness and cost. Adverse reactions, especially the risk of tumor occurrence, should be closely monitored during treatment. 2. Speech therapy, functional training and physiotherapy should be provided for children with speech and language disorders and motor disorders causing balance and gait abnormalities.
Psychology	When psychological problem or mental disorders are suspected, referring children to a pediatric psychologist or psychiatrist, or requesting a consultation is recommended. Treatment should be tailored to the specific situation and common treatment options include psychotherapy, medication, and physical therapy.

Table 7. All recommendations.

Authors contribution

All members were involved in the guideline and were listed according to their last name strokes.

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List of abbreviations

NF1, neurofibromatosis type 1; CALMs, café au lait macules; pNF, plexiform neurofibroma; cNF, cutaneous neurofibroma; NIH, National Institutes of Health; OPG, Optic pathway glioma; CAs, choroidal abnormalities; OCT, optical coherence tomography; NIR, near-infrared reflectance; WES, whole exome sequencing; Trio-WES, Trio-whole-exome sequencing; WGS, whole genome sequencing; CNVs, copy number variants; P, pathogenic; LP, likely pathogenic; VUS, variants of uncertain significance; T1-WI, T1 weighted images; MPNST, malignant peripheral nerve sheath tumors; ANNUBP, atypical neurofibromatous neoplasms of uncertain biologic potential; HPF, high-power filed; MEK, mitogen-activated protein kinase; FDA, Food and Drug Administration; SSS, Surgical Staging System; MSTS, Musculoskeletal Tumor Society; RECIST, Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; PD, progressive disease; JMML, juvenile myelomonocytic leukemia; RMS, rhabdomyosarcoma; CNS, central nervous system; FDOCT, frequency domain optical coherence tomography; VEP, visual evoked potentials; GCIPL, ganglion cell and inner plexiform layer; NSAIDS, non-steroid anti-inflammatory drugs; (131)I-MIBG, 131 I-metaiodobenzylguanidine; PTRA, percutaneous transluminal angioplasty; ADHD, attention deficit hyperactivity disorder; GHD, growth hormone deficiency; PAK, p21-activated kinase; CBT, cognitive behavioral therapy; rhGH, recombinant human growth hormone.

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Conflict of interest

All members declare no conflict of interest. ♦

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