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Recommendations for the diagnosis and management of neurofibromatosis type 1 in Singapore: A Delphi consensus

Nikki Fong[1] *MRCPCH*, Ee Shien Tan[1] *MRCPCH*, Joanne Ngeow[2,3] *PhD*, Jeanette Yuen[2] *MGC*, Jianbang Chiang[2,4,5] *PhD*

ABSTRACT

Introduction: Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder with wide phenotypic variability, necessitating coordinated multidisciplinary care and Singapore-relevant guidance. This study aimed to develop Singapore-specific, consensus-based recommendations for NF1 diagnosis, surveillance, and management.

Methods: The study involved 2 rounds of online surveys and a participant meeting with 24 experts from Singapore. Following a literature review, a 151-statement questionnaire was developed (133 Likert-style statements, 13 open-ended questions, 5 single-select questions). Statements were rated on a 9-point Likert scale with a predefined consensus threshold of ≥75%; analyses were performed after each round.

Results: Surveys 1 and 2 involved 19 and 17 participants, respectively, with 14 attending the meeting. Consensus was reached for 113/133 statements in Survey 1 and 9/21 in Survey 2. Experts reached consensus on genetic testing across diagnostic scenarios, including Sprouty-related EVH1 domain-containing protein 1 analysis and ribonucleic acid testing. Agreed surveillance incorporated examinations twice a year until the age of 5 years, at least annually thereafter in childhood, annual symptom checks in adults with triennial specialist review, and targeted MRI-based imaging, including whole-body magnetic resonance imaging around transition. Management recommendations favoured multidisciplinary review and surgical resection when feasible.

Conclusion: This Delphi consensus provides unified recommendations to support consistent NF1 care across paediatric and adult services in Singapore, while highlighting areas without consensus and priorities for implementation and further research.

Keywords: Delphi consensus, MPNST, NF1, plexiform neurofibroma, recommendation

CLINICAL IMPACT

What is New

- To the authors' knowledge, this is the first Singapore-specific Delphi consensus providing comprehensive, multidisciplinary recommendations for the diagnosis, surveillance, and management of neurofibromatosis type 1 (NF1).
- The consensus integrates expert practice in Singapore with international evidence and highlights areas where Singapore-specific data remain limited.

Clinical Implications

- Provides unified, practical guidance to support consistent NF1 care across paediatric and adult services in Singapore.
- Identifies implementation priorities, such as surveillance pathways, access to imaging, and use of mitogen-activated protein kinase kinase inhibitors for symptomatic plexiform neurofibromas.

INTRODUCTION

Neurofibromatosis type 1 (NF1), previously referred to as von Recklinghausen's disease, is an autosomal dominant genetic disorder characterised by the presence of tumours affecting the skin and central and peripheral nervous systems.[1] It is estimated that NF1 has an incidence of approximately 1 in every 2500–3000 live births, with a global prevalence of approximately 1 in 3000 individuals.[2,3] Accurately determining the prevalence of NF1 is challenging due to its highly variable clinical presentation, differences among studied populations, and variations in case identification methods.[2,3]

NF1 is characterised by distinct clinical features, including café-au-lait macules, axillary and inguinal freckling, neurofibromas, and Lisch nodules.[4] Cutaneous neurofibromas (CNFs) are the most characteristic feature of NF1. They appear on the skin and develop in more than 90% of patients with NF1. Plexiform neurofibromas (PNs) are another classical feature of NF1. They are slow-growing peripheral nerve sheath tumours arising from deep nerves, with up to

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[1] Genetics Service, KK Women's and Children's Hospital, Singapore
[2] Cancer Genetics Service, National Cancer Centre Singapore, Singapore
[3] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[4] Division of Medical Oncology, National Cancer Centre Singapore, Singapore
[5] Duke-NUS Medical School, Singapore
Correspondence: Dr Jianbang Chiang, Division of Medical Oncology, 30 Hospital Boulevard, National Cancer Centre Singapore 168583.
Email: chiang.jianbang@singhealth.com.sg
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50% of patients developing NF1-PNs.[5,6] NF1-PNs can be symptomatic, depending on their size and location.

In addition to CNFs and NF1-PNs, NF1 is associated with an increased risk of malignant tumours, including malignant peripheral nerve sheath tumours (MPNSTs), gliomas, gastrointestinal stromal tumours (GISTs), breast cancer, and others.[7-9] Patients have a 2.7- to 4-fold higher risk of malignancy and can have a life expectancy 8–20 years shorter than that of the general population.[10] Specifically, NF1-PNs are clinically important because they carry a risk of malignant transformation to MPNSTs, either directly or through premalignant intermediate lesions, such as atypical neurofibromas or atypical neurofibromatous neoplasms of uncertain biological potential. MPNSTs have a poor prognosis despite the availability of aggressive treatments, severely affecting patients' quality of life and imposing substantial psychological and financial burdens.[11] However, the risk of malignant transformation for an individual lesion is not well defined. Individuals with NF1 have an estimated lifetime risk of developing MPNST of approximately 10–15%. NF1 is also associated with neurocognitive complications, such as attention-deficit hyperactivity disorder and learning difficulties.[7,8] In summary, NF1 exhibits highly variable clinical presentations and has lifelong ramifications for patients, making diagnosis, treatment, follow-up, and overall management particularly challenging.

Effective care necessitates a coordinated, multidisciplinary approach integrating diagnosis, surveillance, and treatment. While targeted therapies, such as mitogen-activated protein kinase kinase (MEK) inhibitors, have improved outcomes, many aspects of NF1 management remain inadequately defined, underscoring the need for structured, consensus-driven care.

Existing frameworks, including the Chinese Expert Consensus (2021 and 2025),[12,13] emphasise multidisciplinary care, structured surveillance, and coordinated, patient-centred management, although their applicability varies by healthcare setting.

Compared with China's more heterogeneous healthcare system, Singapore benefits from a more centralised healthcare structure with streamlined referrals and greater access to advanced diagnostics and targeted therapies, enabling earlier integration of precision medicine.

From an epidemiological and genetic perspective, NF1 incidence appears broadly comparable between Chinese and Singaporean populations; however, emerging evidence suggests potential differences in mutation spectra and phenotypic expression across Asian populations. These variations, together with differences in healthcare accessibility and resource allocation, underscore the importance of adapting global and national guidelines to local contexts.

Within Singapore, NF1 represents a rare but clinically significant condition, with an estimated 800–1800 affected individuals based on current prevalence data. The disease imposes a substantial and sustained burden on the healthcare system, requiring lifelong surveillance, repeated imaging studies, multidisciplinary consultations, and, in selected cases, high-cost targeted therapies.[14] Complications such as malignant transformation, complex NF1-PN, and neurocognitive impairment further increase healthcare utilisation and associated costs, as well as indirect socioeconomic burden through reduced productivity and educational challenges. Although international and Chinese guidelines provide important guidance, they do not fully address Singapore's healthcare and resource considerations.

In this context, the present consensus complements existing Chinese and international guidelines by providing a regionally relevant framework for NF1 diagnosis and management. It highlights both shared principles and context-specific adaptations, thereby offering a scalable model that can inform clinical practice not only in Singapore but also across Southeast Asia.

METHODS

Study design

This study employed a modified Delphi technique, comprising 2 rounds of electronic surveys and a virtual expert meeting to develop consensus recommendations for NF1 management in Singapore.

Surveys were conducted between May 2025 and December 2025, with an interim meeting in August 2025. The questionnaire was developed by the research team, administered via an independent vendor using Decipher software version 153 (Decipher Media LLC, San Francisco, US). Responses were analysed with descriptive statistics using Microsoft Excel, with consensus defined as ≥75% agreement after each survey round. Since this was a non-interventional physician survey, no formal ethical approval was required.

Participants

Twenty-four expert clinicians (geneticists, oncologists, neurologists, dermatologists, and surgeons [specialising in neurosurgery and surgical oncology]) from Singapore with recognised expertise in NF1 management were invited to participate. Participants for the study were selected using specific criteria rather than through a random sampling process. Participants meeting the pre-defined eligibility criteria were

invited to participate in the study via individual emails. Participants who completed Survey 1 were invited to join a virtual participant meeting and participate in Survey 2. Participation in Survey 2 was independent of attendance at the meeting. A 2-member steering committee endorsed the questionnaire, moderated the participant meeting, and approved the outcomes of the study. The steering committee was supported by delegated representatives in the conduct of the study.

Informed consent was obtained electronically from all participating experts prior to survey participation. Participants were provided with detailed information regarding the objectives of the study, the voluntary nature of participation, and the intended use and publication of aggregated results. Participants could withdraw consent at any time without consequences.

All data were collected through a secure survey platform and de-identified prior to analysis. Personal information was collected only for descriptive purposes and was not linked to individual responses. Data were reported in an anonymised and aggregated form to ensure confidentiality. Access to data was restricted to the research team, and no personally identifiable information was disclosed in analysis or publication.

Study stages

Development of the survey questionnaire

Survey 1 was developed from key statements drawn from a targeted literature review focused on the objectives of this Delphi study. The objectives included understanding the current practices followed in Singapore and recommending appropriate modifications to optimise outcomes in patients with NF1.

A comprehensive literature search was conducted in the PubMed database using different objective-specific search terms. Additional relevant literature was identified using a grey literature search.

The literature search was conducted in PubMed using combinations of keywords including "neurofibromatosis type 1", "NF1", "plexiform neurofibroma", "MPNST", "guidelines", "consensus", "surveillance", and "management". The search was supplemented by grey literature and existing international guidelines (e.g. ERN GENTURIS, Chinese consensus).

The search was not limited by time, and all applicable literature was screened. All the retrieved articles were screened for population and objectives. A total of approximately 1082 records were retrieved. After screening titles and abstracts, studies were included if they addressed NF1 diagnosis, surveillance, or management in human populations and were published in English. Case reports, non-relevant mechanistic studies, and non-human studies were excluded. Key references were selected based on relevance and used to generate Delphi statements. A detailed search strategy is included in Supplementary Table S1.

A questionnaire with 151 statements consisting of 133 Likert-style statements, 13 open-ended questions, and 5 single-select questions was developed to address the following themes:

- Genetic testing (n=8)
- Adult management (n=50)
- Childhood management (n=31)
- Surveillance (n=62)
    - All ages (n=15)
    - Adults aged >18 years (n=16)
    - Children aged 0–16 years (n=22)
    - Transition age from 16 to 18 years (n=9)

Survey 1 and participant meeting

The first round of the Delphi survey was shared electronically through individual emails to the participants and completed online between May 2025 and July 2025. Participants from the first round of the survey were invited to a virtual meeting to review the survey results and to share their expert views, focusing primarily on statements that did not achieve consensus in Survey 1. The scientific workshop was non-compulsory, and all participants received the follow-up minutes from these discussions before the initiation of Survey 2. This participant meeting was moderated by the steering committee. The sponsor and the members of the steering committee did not participate in the surveys.

Survey 2 and final data analysis

Statements that did not reach consensus in Survey 1 and any additional statements deemed appropriate from the participant meeting were included in Survey 2 (n=21). Survey 2 was shared electronically through individual emails to the participants and was completed between October 2025 and December 2025.

Data analysis

A 9-point Likert scale was used to rate responses to the statements, in line with best practice. Participants rated their level of agreement with each statement anonymously, ranging from 1 (disagreement) to 9 (agreement). These scores were divided into 3 groups: agree (7–9 points), neither agree nor disagree (4–6 points), and disagree (1–3 points). Responses to open-ended and single-/multiple-select questions were quantified. Consensus was deemed to have been reached in either round of the survey when ≥75%

of the respondents allotted either the highest or the lowest range of scores. This threshold was selected based on recommendations from previous Delphi studies and systematic reviews, which commonly report consensus levels between 70% and 80%. A 75% cut-off provides a balance between ensuring strong agreement among experts and maintaining feasibility for achieving consensus without being overly restrictive. Each question also had a "Do not know" option for Survey 1, enabling the respondent to skip questions that were not related to their experience and ensuring that every question was viewed at least once by each respondent.

RESULTS

Participants

Of the 24 invited participants, 19 (response rate: 79.2%) completed Survey 1; these included clinical geneticists (n=4), dermatologists (n=3), neurologists (n=5), neurosurgery specialists (n=3), oncologists (n=2), and surgical oncologists (n=2). These participants were subsequently invited to a virtual participants meeting. In the meeting, 14/19 participants (73.7% attendance) were present. Following the discussion, a revised second survey was circulated to 18/19 participants. One participant withdrew consent to participate further in the study, and Survey 2 was therefore not sent to this participant. Survey 2 was completed by 94.4% (n=17/18) of the expert participants.

Theme-wise consensus

Table 1 summarises the consensus recommendations reached during the study. In Survey 1, participants reached consensus on 113/133 closed-ended statements. The statements that did not reach consensus in Survey 1 were taken forward for further consideration. Following discussion and refinement during the scientific workshop, Survey 2 comprised 21 closed-ended statements, of which 9 reached consensus. All statements rated by the participants are summarised in the Supplementary Materials (consensus in Survey 1 [Table S2]; statements from Survey 2 [Table S3]; open-ended questions [Figs. S1–S6]).

For the genetic testing theme, all the statements achieved consensus during Survey 1 (Survey 1: 8/8; Survey 2: none, as all statements achieved consensus in Survey 1). For the adult management theme, 40/49 statements achieved consensus during the 2 surveys (Survey 1: 34/49; Survey 2: 6/14). For the childhood management theme, all the statements achieved consensus during Survey 1 (Survey 1: 31/31; Survey 2: none, as all statements achieved consensus in Survey 1). For the surveillance theme (including age-specific statements for all ages, adults aged >18 years, children aged 0–16 years, and transition age from 16 to 18 years), 40/47 statements achieved consensus during the 2 surveys (Survey 1: 40/45; Survey 2: 4/7).

DISCUSSION

The expert panel in this Delphi consensus deliberated on various aspects of NF1 management, including genetic testing; disease management in childhood and adulthood; and surveillance protocols for various stages, subtypes, and complications of the disease, such as NF1-PN, breast cancer, and optic pathway glioma.

Genetic testing

Distinguishing NF1 from other syndromes, such as Legius syndrome, in young children who present only with pigmented skin lesions can be difficult, especially in the absence of a family history or additional clinical features. Genetic testing, when available, is a valuable tool for accurate diagnosis. Experts broadly agreed that genetic testing benefits patients having NF1 who do not meet clinical criteria, those with a confirmed clinical diagnosis, and those with suspected NF1 microdeletions or complex presentations.[15] International consensus guidelines for the diagnosis of NF1 set forth by Legius et al. emphasise the importance of distinguishing NF1 from other genetic disorders, including Legius syndrome, Noonan syndrome, and constitutional mismatch repair deficiency.[4] To distinguish between these disorders, techniques such as multigene panel testing should be considered to establish the exact diagnosis. This aligns with the opinions of the experts participating in this study. Given the complexity of NF1 molecular testing, genotype–phenotype variability, and the potential for mosaic disease, genetic testing should ideally be ordered and interpreted by clinicians with expertise in clinical genetics or in collaboration with genetics services. Appropriate pre- and post-test genetic counselling is important to support informed decision-making and accurate interpretation of test results.

Given the autosomal dominant inheritance of NF1, genetic counselling plays an important role in discussing familial implications, including cascade testing of at-risk relatives and reproductive options. Cascade testing can facilitate the identification of affected family members who may benefit from surveillance and clinical management. Similarly, reproductive counselling may include discussion of prenatal diagnosis and preimplantation genetic testing where available and appropriate. These topics were

Table 1. Recommendations based on consensus reached during the study.

Genetic testing for NF1

• Genetic testing would be valuable for patients suspected of having NF1 in the following scenarios:
  ○ Patients who do not meet the clinical diagnostic criteria;
  ○ When cost is not a limiting factor.
• There is value in genetic testing for patients who have a clinical diagnosis of NF1.

• Genetic testing is considered helpful for patients with suspected NF1 microdeletion or those presenting with complex NF1 presentations, such as malignancy.
• If an *NF1* variant is not detected, sequence analysis and deletion/duplication analysis of *SPRED1* are considered in individuals with only pigmentary features.
• If a variant in *NF1* or *SPRED1* is not detected through DNA analysis, it is advisable to consider RNA analysis.
• If the phenotype cannot be distinguished from those of other disorders, a multigene panel that includes *NF1*, *SPRED1*, mismatch repair, and other genes of interest should be considered.
NF1 surveillance in childhood
• Systematic clinical assessment by NF1 specialists, including skin and neurological examinations, blood pressure measurement, height, weight, and evaluation of pubertal development, should be performed at least annually for children up to 10 years, every 2 years for children over 10 years, yearly for those up to 18 years during transition, and once every 3 years in adults.
• Pain assessment for NF1 symptoms should be conducted during clinic visits.
Children with NF1 are recommended to follow a surveillance protocol that includes: • Physical examinations at least twice a year until the age of 5 years, and at least annually thereafter. • Monitoring growth and overall development. • Annual neurological examinations to detect possible nerve tumours, headaches, or seizures. • Regular measurement of head circumference. • Annual ophthalmological evaluations throughout childhood to screen for optic pathway gliomas. • Screening for learning disorders and attention deficit hyperactivity disorder when the child starts school. • Annual pain score assessment. • Annual cardiac assessment should include blood pressure monitoring, with echocardiography performed based on clinical indication or in patients receiving treatments for which cardiac monitoring is recommended, such as MEK inhibitors.
• Clinical evaluation of children with NF1 who are suspected of having orbital or periorbital PN should include a physical examination for signs such as blepharoptosis, proptosis, eyelid oedema, orbital dysplasia or dystopia, distortion of the (peri)orbital skeleton, eye pulsation, and strabismus; clinical testing of vision, refractive error, visual fields, ocular motility and alignment, and optic disc evaluation to rule out glaucoma or optic neuropathy; and MRI of the brain and orbits for all suspected cases.
Childhood management of NF1
Treatment of NF1 • Treatment for NF1 in children depends on their needs and may include surgical intervention for PNs, pharmacotherapy for headaches or seizures, educational assessment with school support, pharmacological or non-pharmacological approaches for pain management, therapeutic counselling to address low self-esteem and negative body image, and early intervention through speech, physical, or occupational therapy.
Development • Children with NF1 should be monitored for cognitive and behavioural difficulties, including developmental milestones (ideally before school), academic progress, sleep patterns, ability to maintain focus on an activity, distractibility, social interaction, and motor skills. • Management of cognitive and behavioural difficulties in children with NF1 may require early involvement of a special educational needs coordinator, close collaboration among teachers, educational psychologists, occupational therapists, and community paediatricians, cognitive behavioural therapy, and the use of methylphenidate under experienced supervision. • Addressing the effects of NF1 on psychosocial and neuropsychological functioning may involve assessing psychosocial well-being and neuropsychological functioning at every clinic visit, including a psychologist in the multidisciplinary team, providing counselling interventions, and addressing issues such as childhood bullying. • Children diagnosed with NF1 should undergo a speech and language assessment, followed by appropriate intervention if necessary.
Treatment of PNs • Surgical resection is a preferred treatment option for children with NF1-PN when it is feasible. • MEK inhibitors may be considered as a treatment option for children with NF1 who have symptomatic PNs, including cases that are inoperable or remain symptomatic after partial resection.

Table 1. Recommendations based on consensus reached during the study. (Cont'd)

Management of vascular symptoms
- Assessment of hypertension in children with NF1 should include Doppler ultrasonography of the aorta and renal arteries, renal arteriography, and magnetic resonance angiography.

Surveillance of adult NF1

Surveillance in adulthood
- For adults (over 18 years) with NF1, a symptom check should be conducted at least annually by a primary care physician and every 3 years by an NF1 specialist.
- In adults, routine screening for optic pathway gliomas is not recommended. Clinical evaluation should be symptom-driven, including assessment of visual acuity and visual disturbances where clinically indicated.

PNs
- NF1 patients with PNs may undergo WB-MRI, regional MRI, or FDG PET scan by the age of 21 years or prior to transition to adult care.

Pheochromocytoma screening
- In NF1, biochemical or imaging screening for pheochromocytoma in asymptomatic, non-hypertensive individuals is not recommended.
- In NF1, measurement of plasma free metanephrines as a single test is more sensitive and specific in an individual clinically suspected to have pheochromocytoma. Surveillance for pheochromocytoma in patients with NF1 should include an annual blood pressure check starting at the age of 10 years.
- For NF1 patients with hypertension and vasculopathy, management should include MRI as the preferred imaging modality for evaluating renovascular hypertension, spiral CT, and CT angiography for individuals with impaired renal function (GFR <30 mL/min), and selective imaging such as ultrasound for those clinically suspected to have a vascular lesion.

Breast cancer screening

Breast cancer surveillance should consider the following:
- Screening with annual breast MRI should be the primary approach.
- Mammography is the second-best alternative when MRI is not available.
- Annual screening in NF1 should begin at the age of 30 years.
- Breast cancer screening in NF1 should be performed once every 2 years after the age of 50 years.
- Risk-reducing bilateral mastectomy should not be performed in patients with NF1.

Malignancy screening
- WB-MRI may be considered between the ages of 16 and 20 years to assess internal tumour burden, particularly PNs.
- If no internal PNs are detected, routine follow-up with WB-MRI is not recommended.
- Patients with a high internal tumour burden may require ongoing imaging surveillance due to the increased risk of malignant transformation.

Adult management of NF1

General
- Laser treatment for café-au-lait macules and freckles may be considered for patients with NF1.
- Patients with NF1 usually do not exhibit KIT or PDGFRA overexpression in GISTs, limiting the use of imatinib in this population.
- For maintaining the health of patients with NF1, considerations include vitamin D supplementation, monitoring curve progression for scoliosis management, treating osteoporosis as in the general population, and performing annual clinical back evaluations using the Adam's forward bend test.
- Osteoporosis in patients with NF1 is generally managed according to standard clinical guidelines, similar to patients without NF1, provided there are no NF1-specific complications.
- The initial step in pain management is to use age-appropriate pain intensity assessment tools to determine the level of pain.
- Treatment options for adult patients with NF1 may include surgical intervention for PNs, pharmacotherapy for headaches or seizures, therapeutic counselling for pain management and addressing low self-esteem or negative body image, as well as psychosocial counselling.

Benign and malignant tumours
- For patients with CNFs, clinical assessment comprising physical examination and palpation should be repeated at least annually.
- Radiotherapy is not recommended for optic pathway gliomas due to the increased risks of late-onset cerebrovascular complications and secondary malignancy.
- Pheochromocytoma screening is recommended for hypertensive NF1 patients who are over 30 years of age, are pregnant, have paroxysmal hypertension, or experience hypertension-associated symptoms such as headache, palpitations, or sweating.
- Current treatment options for CNFs include surgical excision, laser removal, and electrodesiccation.
- Surgical resection is the preferred treatment for patients with NF1 for specific conditions, including NF1-PN, malignant peripheral nerve sheath tumours, optic pathway glioma with proptosis or hypertensive hydrocephalus, CNFs, and GISTs.
- Risk-reducing bilateral mastectomy is not routinely recommended for NF1 patients without breast cancer; however, it may be considered in individuals with additional significant risk factors (e.g. pathogenic variants in other breast cancer predisposition genes or strong family history), in accordance with established risk thresholds.

Table 1. Recommendations based on consensus reached during the study. (Cont'd)

NF1-PNs

- Radiotherapy is not recommended for NF1-PNs due to the increased risk of secondary malignancy and moyamoya syndrome.
- The following therapies may be considered for treating patients with NF1-PNs, based on clinical and safety outcomes: surgery, chemotherapy, and MEK inhibitors.
- NF1-PN with rapid growth (>20% increase in volume per year) and impending morbidity is likely a candidate for intervention.
- A slowly growing NF1-PN (<5% increase in volume per year) without actual or impending morbidity may be suitable for observation.
- Surgical resection can be a treatment option, if feasible, for symptomatic NF1-PN.
- MEK inhibitors may be considered as a treatment option for adult NF1 patients with symptomatic PNs, including cases that are inoperable or remain symptomatic after partial resection.
- MRI is preferred over CT to assess NF1-PNs.
- Among different types of neurofibromas, NF1-PNs exhibit the highest tendency to evolve into malignant peripheral nerve sheath tumours.

CT: computed tomography; CNF: cutaneous neurofibroma; DNA: deoxyribose nucleic acid; FDG PET: fluorodeoxyglucose positron emission tomography; GFR: glomerular filtration rate; GISTs: gastrointestinal stromal tumours; KIT: KIT proto-oncogene receptor tyrosine kinase; MEK: mitogen-activated protein kinase; MRI: magnetic resonance imaging; NF1: neurofibromatosis type 1; PDGFRA: platelet-derived growth factor receptor alpha; PNs: plexiform neurofibromas; RNA: ribonucleic acid; *SPRED1*: Sprouty-related EVH1 domain-containing protein 1; WB-MRI: whole-body magnetic resonance imaging

not specifically evaluated as part of the Delphi process and therefore fall outside the scope of the present consensus recommendations.

In addition, mosaic NF1 should be considered in individuals with segmental or atypical presentations, as lower variant allele fractions may reduce the sensitivity of standard genetic testing and complicate clinical diagnosis. Recognition of mosaicism is also important during genetic counselling, as it has implications for the interpretation of genetic test results, recurrence risk assessment, and family counselling.

Surveillance

Experts agreed that systematic clinical assessment for individuals with NF1, including skin and neurological examinations along with monitoring of blood pressure, height, weight, and pubertal development, should be performed annually in children up to 10 years of age, once every 2 years in children older than 10 years, yearly for adolescents up to 18 years during transition, and once every 3 years in adults. Experts also supported the established guideline recommendation of twice-yearly screening until the age of 5 years and yearly surveillance thereafter. These intervals ensure ongoing surveillance tailored to age and developmental stage.

For patients with NF1-PN, whole-body MRI (WB-MRI) and localised MRI are preferred by the participating experts for initial assessment, while localised MRI is preferred for routine surveillance and assessment of treatment response. Factors considered by the study participants included symptoms, change in tumour size, age, timing (prior to transition to adult services), pain, and PN location. The practices recommended by the expert group differ from those set forth by the ERN GENTURIS consensus group, which recommends performing WB-MRI during the transition from childhood to adulthood. If no internal PNs are detected on this scan, routine follow-up with WB-MRI is not advised. However, more frequent WB-MRI assessments may be considered for patients identified as having a high risk of developing MPNST.[7]

In Singapore, breast cancer is the most common malignancy among women and is most frequently diagnosed after the age of 40 years, although it is already the leading cancer in women aged 30–39 years. Singapore data on NF1-associated breast cancer are limited; however, an institutional cohort analysis from Singapore reported a mean age at breast cancer diagnosis of approximately 48 years, with cases occurring as early as 30 years. This observation is consistent with international evidence demonstrating that more than 50% of breast cancers in NF1 occur before the age of 50 years, with a peak incidence between 34 and 44 years. These findings support the recommendation for earlier initiation of screening at the age of 30 years, compared with general population screening programmes in Singapore.[13,16,17] Experts in this study recommended initiating annual breast cancer screening for patients with NF1 at the age of 30 years using breast MRI as the preferred method, with mammography as an alternative. This is consistent with ERN GENTURIS guidelines. In contrast, the transition to biennial screening after the age of 50 years reflects Singapore expert consensus and adaptation to regional clinical practice. Risk-reducing bilateral mastectomy is not advised for NF1 patients without breast cancer, as current evidence does not support its benefit.[7] The Chinese expert consensus similarly supports earlier screening initiation, although exact age thresholds may vary. This alignment suggests a shared recognition across Asian populations of increased early risk, while differences likely reflect variations in Singapore epidemiological data, healthcare system structure, and resource availability.

Osteoporosis represents a clinically relevant condition in the ageing population in Singapore, with studies

reporting a prevalence of approximately 9.3–19.4% among postmenopausal women and around 0.7% among men aged over 50 years.[18]

Available international data suggest that NF1 is associated with impaired bone health, with osteopenia reported in up to 50% of patients and osteoporosis in approximately 20–50%, indicating a higher burden of reduced bone mineral density compared with the general population.[19,20] Nevertheless, these findings are derived from heterogeneous cohorts and may not be directly generalisable to the Singapore population due to differences in genetic background, environmental factors, and healthcare systems.

In the absence of robust Singapore-specific epidemiological data and NF1-specific clinical management guidelines for osteoporosis, the expert panel recommended managing osteoporosis in patients with NF1 according to general population guidelines. This approach represents a pragmatic and evidence-consistent strategy, ensuring that patients receive standard-of-care management while acknowledging the need for future regional studies to better define disease burden and optimise NF1-specific management strategies.

Childhood management

Experts agreed on a structured approach to the management of NF1 in children. Key components include early speech and language assessment, prompt evaluation of persistent headaches, and supportive interventions such as counselling for self-esteem and body image, alongside speech, physical, and occupational therapy.

Management should be individualised, incorporating surgical resection for PNs when feasible, pharmacological treatment for neurological symptoms, and educational support. Additionally, MEK inhibitors were recognised as an option for symptomatic, inoperable, or partially resected PNs.

Experts agreed that the assessment of hypertension in children with NF1 should include Doppler ultrasonography of both the aorta and renal arteries, with additional imaging as clinically indicated.

Experts also agreed that children with NF1 should be monitored for cognitive and behavioural issues, including developmental progress before school, academic performance, sleep patterns, ability to concentrate, distractibility, social interaction, and motor skills. Strong consensus across these areas highlights the importance of comprehensive and ongoing developmental assessment in childhood NF1 management.

Moreover, experts agreed that managing cognitive and behavioural difficulties in children with NF1 may require early involvement of a special educational needs coordinator, close collaboration among teachers, educational psychologists, occupational therapists, and community paediatricians, as well as cognitive behavioural therapy. Additionally, methylphenidate under experienced supervision was considered an appropriate option when necessary. Strong consensus across these strategies highlights the importance of a multidisciplinary approach to support affected children.

Experts recommended routine assessment of psychosocial well-being and involvement of psychological services, highlighting the need for a holistic, multidisciplinary approach to paediatric NF1 care.

Adult management

Management of NF1-PN across paediatric and adult populations reflects a continuum of care consistent with a coordinated, patient-centred approach.

CNFs are histologically benign, multicellular tumours that occur in the majority of individuals with NF1. Despite their high prevalence and significant impact on patients, CNF management remains challenging.[21] For patients with CNFs, clinical assessment including physical examination and palpation should be performed at least annually. Surgical resection is considered the treatment of choice, with current options including surgical excision, laser removal, and electrodesiccation. The participating experts in this study reached consensus on the recommended approach to CNF management.

According to the ERN GENTURIS guidelines, surgery is considered when feasible, although complete resection is often challenging and associated with morbidity.[7] Participating experts in this study did not endorse surgery as the sole primary treatment for NF1-PN, but agreed it should be a treatment option, considered within a multidisciplinary framework, alongside pharmacological options. Additionally, for unresectable or inoperable NF1-PN, radiotherapy is generally avoided, primarily because of the increased baseline risk of radiation-induced neoplasms in patients with NF1 and the potential for NF1-PNs to undergo malignant transformation into MPNSTs.[5] Aligned with the evidence, the experts in this study did not reach consensus on using these treatment methods during Survey 1.

Management of tumours in NF1

Upon deliberation, the panel of experts agreed that surgery and chemotherapy may be used in patients with NF1-MPNST, based on their clinical and safety outcomes. The majority of the experts in the study opined that the decision on whether NF1-PN should be treated surgically or pharmacologically should be made by a multidisciplinary board on a regular basis.

Patients with NF1-associated GISTs typically lack KIT proto-oncogene receptor tyrosine kinase and platelet-derived growth factor receptor alpha mutations, limiting the therapeutic utility of imatinib in this population. NF1-associated GISTs are often characterised by multiple small tumours arising predominantly in the small intestine and differ biologically from sporadic GISTs.[22] In this study, only 50% of the experts agreed with this statement during Survey 1; however, unanimous consensus was reached in Survey 2. The initial lack of consensus likely reflects the specialised nature of this topic and variations in familiarity with the molecular characteristics of NF1-associated GISTs. The absence of consensus may result from either insufficient knowledge among respondents or genuine differences in interpretation, which is understandable given the complexity of the subject matter.

Interestingly, in Survey 1, the participants agreed on using MEK inhibitors for the treatment of NF1-PN. These inhibitors have been shown to shrink NF1-PNs and improve pain in the paediatric population. Selumetinib is approved in Singapore for the treatment of patients aged 3 years and above with symptomatic and inoperable NF1-PNs.[23] MEK inhibitors have also demonstrated promising efficacy in adult patients, supported by clinical trial data. In the KOMET trial in adults with symptomatic and inoperable NF1-PNs, selumetinib demonstrated an objective response rate of 20% (n=14/71; 95% confidence interval [CI] 11.2–30.9) by cycle 16, compared with 5% (n=4/74; 95% CI 1.5–13.3) with placebo (P=0.011).[24] In addition to tumour response, studies have reported reductions in tumour volume and improvements in patient-reported out-comes, including pain and quality of life, highlighting the broader clinical benefits of treatment.[25-27] Considering the growing evidence for the use of MEK inhibitors in adult patients with NF1, the participants reached consensus on using these agents for the treatment of symptomatic NF1-PNs; inoperable, symptomatic NF1-PNs; and NF1-PNs that remain symptomatic following partial resection.

Although tipifarnib and mechanistic Target of Rapamycin (mTOR) inhibitors, such as sirolimus, are approved for NF1 in Singapore, consensus on their use for NF1-PNs or NF1-MPNSTs was not achieved. Tipifarnib, a farnesyltransferase inhibitor, although well tolerated, did not significantly prolong time to progression in patients with NF1-PN in a phase 2 trial.[28] Another phase 2 study assessed sirolimus in non-progressive NF1-PNs and found that sirolimus did not meaningfully shrink NF1-PNs.[29]

The divergence in expert opinion is likely due to limited and inconsistent efficacy in clinical trials. The observed variability reflects clinical equipoise, differences in expert experience, and ongoing safety concerns. Similar patterns are noted in the Chinese consensus, where these agents are not routinely recommended. Overall, the lack of consensus reflects broader uncer-tainty in the global evidence base, rather than practice variation specific to Singapore.

Strengths and limitations

This study offers several strengths, including a focused design and a multidisciplinary expert panel representing key specialties involved in NF1 management. To the authors' knowledge, this is the first and largest study of its kind in Singapore to examine multiple aspects of NF1 diagnosis and management, achieving a high response rate that reflects strong engagement from the expert community. The use of independent facilitators and anonymous feedback enhanced the rigour and reliability of the process.

However, certain limitations should be acknowledged. First, the purposive, non-random sampling and a relatively small sample size (n=24) may limit generalisability and introduce selection bias. Although experts were selected based on recognised involvement in NF1 management, formal quantitative criteria were not uniformly applied. Second, the absence of patient representatives and primary care physicians may restrict the consideration of patient-centred and real-world perspectives. Third, the analysis was based primarily on agreement proportions without detailed statistical measures, and responses may have been influenced by the interim discussion between survey rounds. In addition, the questionnaire was not formally validated. Finally, the recommendations are based on expert opinion without long-term outcome validation, and their applicability to other settings may require adaptation.

The recommendations were not formally graded by strength (e.g. strong/moderate/weak) as is done in frameworks such as ERN GENTURIS, due to the consensus-based Delphi methodology and lack of systematic evidence synthesis. Future work could incorporate formal evidence grading systems to enhance interpretability and clinical applicability.

CONCLUSION

In this study, consensus was achieved on the key aspects of NF1 diagnosis and management in Singapore. Experts agreed on the role of genetic testing and the importance of multidisciplinary team-guided decision-making for individualised treatment. Surgical resection remains central for NF1-PNs and MPNSTs, with treatment strategies tailored through multidisciplinary team review. Among pharmacological therapies, only MEK inhibitors achieved consensus, supported by evidence demonstrating meaningful tumour reduction and clinical benefit, whereas no consensus was reached for other agents, such as mTOR inhibitors or tipifarnib.

Consensus was also established on age- and risk-adapted surveillance protocols across the lifespan. Overall, these findings align with Chinese and international frameworks in emphasising multidisciplinary team care and lifelong management, while reflecting region-specific adaptations. This consensus provides a pragmatic, context-specific guide for NF1 management in Singapore.

Supplementary materials

Table S1. Search strategy.
Table S2. Statements that achieved consensus in Survey 1.
Table S3. Statements that did not achieve consensus in Survey 1 and achieved/did not achieve consensus in Survey 2.
Fig. S1. Open-ended question 1.
Fig. S2. Open-ended question 2.
Fig. S3. Open-ended question 3.
Fig. S4. Open-ended question 4.
Fig. S5. Open-ended question 5.
Fig. S6. Open-ended question 6.

Ethics statement

This work synthesised expert insights and publicly available literature and did not include patient-level data; therefore, institutional ethics approval was not needed. All experts provided consent to participate in the advisory discussions.

Declaration

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