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Original Article

A National Modified Delphi Consensus on the Referral and Management of NF1 Plexiform Neurofibroma

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ABSTRACT: ***Background and objectives:*** Neurofibromatosis type 1 (NF1) is a genetic disorder. Up to 50% of NF1 patients develop plexiform neurofibromas (PN). Despite revisions in diagnostic standards, there remains a lack of consensus on referral, treatment, monitoring and transition processes for NF1-PN. The study aimed to establish a Canada-wide consensus on the best practice for referral and management of patients with NF1-PN to help generate guidance where evidence on the long-term use of MEK inhibitors is lacking. ***Methods:*** The study used a modified Delphi method. The steering committee (SC) identified 4 topics of focus and developed 44 consensus statements. Following ratification, 43 statements were developed into an online survey sent to 113 healthcare practitioners (HCPs) involved in NF1-PN management across Canada. Respondents used a 4-point Likert scale to indicate agreement with each statement. The threshold for consensus agreement was 75%. ***Results:*** A total of 56 responses were received, predominantly from Ontario. Most respondents were neuro-oncologists (34%) and had over 11 years of experience (57%). Consensus was reached on 41 of 43 statements (95%), enabling the SC to develop recommendations for NF1-PN patient care and a treatment algorithm outlining key timings for treatment and management. ***Conclusions:*** To our knowledge, this is the first national Delphi consensus on NF1-PN. Strong agreement was seen from HCPs on critical timings in NF1-PN treatment and management. The proposed recommendations and treatment algorithm provide a framework to enhance patient care and support ongoing research into optimizing care for NF1-PN patients, not just in Canada but globally.

RÉSUMÉ: Consensus national basé sur la méthode Delphi modifiée portant sur l'orientation et la prise en charge des personnes atteintes de neurofibromatose de type 1 et de neurofibromes plexiformes. ***Contexte et objectifs :*** La neurofibromatose de type 1 (NF1) constitue une maladie génétique. Jusqu'à 50 % des patients atteints de NF1 développent des neurofibromes plexiformes (NP). Malgré la révision des normes diagnostiques, il n'existe toujours pas de consensus au sujet des processus d'orientation, de traitement, de surveillance et de transition pour les NP liés à la NF1. La présente étude vise à établir un consensus à l'échelle du Canada quant aux meilleures pratiques en matière d'orientation et de prise en charge des patients atteints de NP liés à la NF1, et ce, afin de contribuer à l'élaboration de lignes directrices en l'absence de données probantes sur l'utilisation à long terme des inhibiteurs d'enzymes MEK. ***Méthodes :*** L'étude a utilisé la méthode Delphi modifiée. Le comité directeur (CD) a identifié quatre thèmes prioritaires et élaboré 44 déclarations consensuelles. Après ratification, 43 déclarations ont été intégrées à un sondage en ligne envoyé à 113 professionnels de la santé (PS) impliqués dans la prise en charge de la NF1 et des NP partout au Canada. Les répondants ont utilisé une échelle de Likert à quatre points pour indiquer leur accord avec chaque déclaration. Le seuil de consensus était fixé à 75 %. ***Résultats :*** Au total, 56 réponses ont été reçues, principalement de l'Ontario. La plupart des répondants étaient des neuro-oncologues (34 %) et avaient plus de 11 ans d'expérience (57 %). Un consensus a été atteint pour 41 des 43 déclarations (95 %), ce qui a permis au CD d'élaborer des recommandations en ce qui regarde les soins destinés aux patients atteints de NF1 et de NP ainsi qu'un algorithme de traitement décrivant les moments clés d'un traitement et d'une prise en charge. ***Conclusions :*** À notre connaissance, il s'agit du premier consensus national basé sur la méthode Delphi qui porte sur la NF1 et les NP. Les PS se sont montrés largement d'accord sur les moments critiques de traitement et de prise en charge de la NF1 et des NP. Les recommandations et l'algorithme de traitement proposés fournissent ainsi un cadre permettant d'améliorer les soins destinés aux patients et de soutenir la recherche en cours visant à optimiser ces mêmes soins, non seulement au Canada mais aussi dans le monde entier.

Keywords: Consensus; MEK; neurofibromatosis; plexiform

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Highlights

- The diagnosis of neurofibromatosis type 1 (NF1) with plexiform neurofibromas (PN) is complex, and treatment options are limited.
- This study presents the first national consensus on the management of NF1-PN.
- A framework for the optimal diagnosis, referral and management of patients with NF1-PN, including a proposed care pathway, is outlined.

Introduction

Neurofibromatosis type 1 (NF1) is a genetic disorder,[1] resulting in tumor growth that can affect any body system.[2] NF1 has a variable global prevalence of between 1 in 3000–6000 and is associated with decreased quality of life and life expectancy.[3,4] Up to 50% of patients will develop plexiform neurofibromas (PN).[3] These tumors cause disfigurement and pain, among other symptoms.[5,6] PN manifest in early childhood and grow most rapidly in children under 5 years of age. In approximately 8%–13% of patients, PN can transform into malignant tumors associated with a high mortality rate.[6,7]

In 2021, the diagnostic criteria for NF1 were revised. Individuals who do not have a parent diagnosed with NF1 must have two or more characteristics of NF1 (café au lait macules [CALMs], freckling in the axillary or inguinal region, ≥2 neurofibromas or one PN, optic pathway glioma, ≥2 Lisch nodules or ≥ choroidal abnormalities, a distinctive osseous lesion or a heterozygous pathogenic NF1 variant).[8] In individuals who have parents with diagnosed NF1, a diagnosis is warranted if one or more of the previous characteristics are present.[8] There are multiple PN classification systems based on histopathologic, clinical and imaging findings;[9] however, there is no universal PN definition.

Treatment options for NF1-PN are limited.[2] Surgery may be considered for superficial PN where the risk of morbidity is low. However, tumors are often ill defined and invasive, leading to partial resection and regrowth.[10,11] Targeted therapies, such as mitogen-activated protein kinase kinase inhibitors (MEKi), have shown promise and are now approved for pediatric patients.[12,13] MEKi are approved for adult and pediatric use.[14,15] They have demonstrated efficacy and safety in pediatric patients, but data on long-term use is limited.[2,16] With the introduction of MEKi into the routine management of NF1-PN, there is now a critical need for guidelines and consensus on managing patients to help bridge the gap in clinical practice until more long-term evidence on their treatment utility is generated.

Monitoring post-diagnosis is required to track disease progression. The use of whole-body MRI to assess tumor load, followed by tailored regional MRI monitoring, has been suggested.[17] Volumetric MRI analysis has been used within clinical trials[18,19] but is not widespread and presents challenges (high costs, long imaging durations and limited accessibility). Efforts to monitor NF1-PN are complicated by pediatric patients transitioning into adult care, often being lost to follow-up.[20] There is a lack of guidance regarding monitoring in adolescents and adults, with few centers having transition of care protocols.[21,22] The duration between follow-up assessments in NF1-PN is based on age and disease-specific factors,[23] and no data or consensus exists on the appropriate monitoring intervals. Research has found considerable variation in practice.[9] Monitoring focuses on the development/progression of clinical features, rather than tumor growth, as these typically influence clinical decision-making.[24,25]

The objective of this study was to establish a Canadian consensus on best practice for referral and management of NF1-PN. There are many nuances to the Canadian healthcare system, so statements were designed to be agnostic of health insurance plans to ensure the resulting recommendations would be applicable nationally. A modified Delphi method was chosen to gain consensus using a recognized process.[26,27] An alternative Delphi method was used previously to revise the international diagnostic criteria for NF1 and Legius syndrome.[8]

Methods

The process followed a modified Delphi methodology (Figure 1), guided by an independent facilitator (Triducive Partners Limited). The study protocol was not registered. All information is reported in line with ACCORD guidelines.

In March 2024, a literature review on NF1-PN was performed. The search was conducted using publicly available resources, such as PubMed. The search encompassed material published within the last 10 years. Search terms included but were not limited to "diagnosis of NF1-PN" and "monitoring of NF1-PN." Information gathered was used to develop the scope of the research and define questions for the initial steering committee (SC) meeting.

An SC of Canadian clinicians (three pediatric neuro-oncologists) convened in May 2024. SC members were selected due to their close involvement with managing pediatric NF1-PN patients, research background and clinical experience. Pediatric neuro-oncologists were selected, as they represent the main specialty involved in managing NF1-PN in Canada. The SC met online to discuss the challenges in diagnosing and treating NF1-PN and agreed upon four domains of focus:

1. NF1-PN diagnosis, monitoring and referral
2. Treatment selection and initiation
3. Continuing management of NF1-PN
4. Transitioning from pediatric to adult care

These were discussed, and 44 draft consensus statements were generated and then collated by the facilitator. Following the meeting, the SC independently rated the statements as either "accept," "remove" or "reword." Feedback during this stage was qualitative, as per standard Delphi methodology.[28] The SC could also suggest new statements. The facilitator actioned the required changes. The final list was independently ratified by the SC.

The finalized 43 statements were developed into a Likert survey and distributed by the SC to a list of 113 potential respondents. To be included, respondents had to be a Canadian healthcare practitioner (HCP) working in a relevant role (e.g., neuro-oncologist, oncologist, pediatrician or geneticist) and must treat/manage ≥1 patient per year with NF1-PN. The survey primarily targeted pediatric NF1 specialists due to the lower number of adult specialists. Stopping criteria were established *a priori* as a 2-month survey window, a target of 50 responses and 90% of statements passing consensus threshold (set at 75%).[29] A minimum of 50 responses was chosen due to the rarity of the disease. The survey was qualitative only, as per standard Delphi surveys.[28]

All responses were captured using Microsoft Forms. A statement of consent was included at the start, and consent was implied by response submission. No incentives were provided. Anonymity was planned in the study design, and the identity of respondents was unknown. No personal information or protected characteristics were recorded. Demographic data (role, years in role, number of patients treated per year and province) were captured for sub-analyses. As this study only collected the

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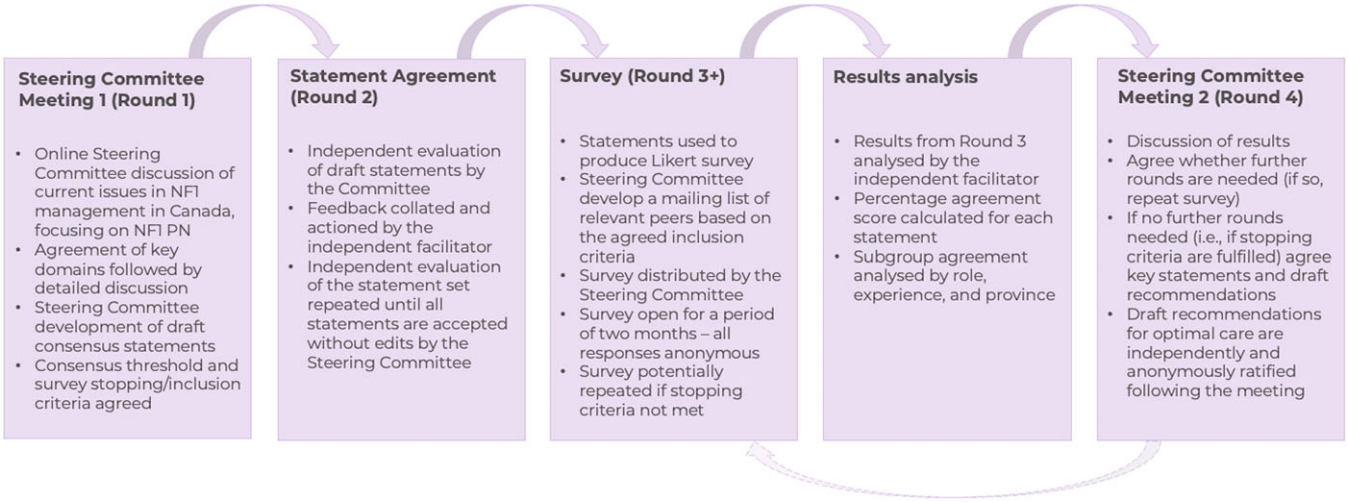

Figure 1. Modified Delphi study design. NF1-PN = neurofibromatosis type 1 plexiform neurofibromas.

anonymous opinions of healthcare professionals and no patient-specific data was captured, ethical approval was not sought.

Completed surveys were analyzed to produce an arithmetic agreement score for each statement. The results were reviewed by the SC at a second meeting in October 2024. The results were discussed, and it was assessed if the stopping criteria had been fulfilled. Following this, key statements from those with the highest agreement were selected by the SC, and recommendations were drafted. These were then independently ratified by the SC.

Results

Of the draft 44 statements, 2 were removed, 11 were modified, 1 new statement was added and 32 were agreed for inclusion without modification, leading to a finalized set of 43 statements.

Responses were received from a total of 56 HCPs (response rate 48%). Respondents were diverse but predominantly neuro-oncologists ($n = 19$, 34%) (Supplementary Figure 1). Respondents generally had 11+ years of experience in role ($n = 32$, 57%) but were varied in the number of patients managed per year (Supplementary Figures 2–3). Responses were received from seven provinces, primarily Ontario ($n = 27$, 63%) (Supplementary Figure 4).

Survey results showed very strong agreement (≥90%) in 37 (86%) statements, strong agreement (<90% and ≥75%) in 4 (9%) statements and failure to achieve consensus agreement threshold in 2 (5%) statements (Figure 2, Table 1). Distribution of consensus across the 4-point Likert scale is represented in Supplementary Figure 5. As the stopping criteria were satisfied, no additional testing rounds were conducted.

Sub-analyses were conducted to explore the consensus by role, years in role, province and number of NF1 patients managed per year. Results were analyzed for variation in responses greater than ±10% from the mean agreement or with at least one role not achieving the threshold of ≥75%. The results from these analyses are presented in Supplementary Tables 1–4.

Discussion

This work represents the first national cross-specialty consensus on NF1-PN and, to our knowledge, the first consensus to establish guidelines for patient management. A clear consensus was achieved, with high concordance rates. As the statements were designed to be insurance and healthcare system agnostic, there is scope for the recommendations developed to provide the foundation for a global framework for managing patients with NF1-PN.

Topic A. NF1-PN diagnosis, monitoring and referral

Responses showed an understanding of the burden presented by NF1. Clinicians overwhelmingly supported the need for early identification and intervention (Statements (S) 1–3, 100%). Responses showed there is a need to ensure that patients are treated by experienced specialists (S4, 98%; S5, 91%; S8, 96%; S9, 98%). Any treatment for NF1 should involve multidisciplinary collaboration (S14, 100%).

Sub-analyses indicated strong agreement between roles. Pediatricians typically showed lower agreement. However, only five pediatricians responded to the survey, and their opinions may not be representative of the wider pediatrician community. Disagreement centered on referral to specialist care and could relate to a reticence for referring suspected/asymptomatic cases of NF1-PN. Timely referral of patients who may have NF1-PN is imperative to ensure they are diagnosed and that surveillance and/or treatment are initiated promptly.[30] This is crucial in younger patients, in whom PN grow rapidly,[3] and for patients in whom PN may imminently cause symptoms or compression of critical structures.

There was a dichotomy in the responses to S7 and S11. Agreement with S7 (91%; children presenting with CALMs should be referred to a specialist experienced in diagnosing NF1-PN) showed much higher agreement than S11 (77%; referrals of patients with asymptomatic PN should occur within 3 months). Disagreement was driven by low agreement from pediatricians and neurologists; it was unclear whether disagreement was because the stated 3-month timeframe was too long or too short. Disagreement could reflect clinic waiting lists, and if a 5-month timeframe had been suggested, agreement may have been higher. When analyzed by experience, those with <5 years in role were more polarized, showing 73% agreement with S7 and 91% agreement with S11.

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Table 1. Defined consensus statements and corresponding levels of agreement. Paired statements are outlined in bold; these are statements designed with standardized wording to compare agreement rates with alternative timeframes for treatment and monitoring

No.	Statement	Agreement
Topic A. PN diagnosis, monitoring and referral		
1.	Patients with NF1 have unique healthcare needs that require specialized management, irrespective of age	**100%**
2.	Prompt referral to healthcare providers with expertise in NF1 ensures thorough evaluation, accurate diagnosis and optimal management of NF1-PN	**100%**
3.	Any suspected NF1 cases should be evaluated by a specialist before the age of 2 to facilitate early intervention and comprehensive care planning	**100%**
4.	Patients referred with suspected NF1 should be seen by a specialist within 6 months	**98%**
5.	Patients with NF1 should be assessed and followed by a specialist with knowledge of NF1 at least annually	**91%**
6.	Patients with NF1 should see an ophthalmologist at least annually up until the age of 7	**96%**
7.	Children presenting with café au lait spots should be referred to a specialist experienced in diagnosing NF1-PN	**91%**
8.	All NF1 patients with suspected PN should be referred to a specialist knowledgeable about NF1 patient management (e.g., a neuro-oncologist)	**96%**
9.	All NF1 patients with diagnosed PN that may warrant future intervention should be referred as soon as possible to a specialist with a knowledge of available treatment options (e.g., neuro-oncologist)	**98%**
10.	Timely diagnosis of NF1-PN enables early intervention strategies aimed at minimizing symptom progression, improving quality of life and preventing potential complications such as functional impairment or neuropathic pain	**98%**
11.	Referrals of patients with asymptomatic PN should occur within 3 months	**77%**
12.	Referrals of patients with symptomatic PN should occur within 1 month	**96%**
13.	There should be an NF1 clinic in every major treatment center	**91%**
14.	Collaboration between members of a multidisciplinary team (including neuro-oncologists, neurologists, geneticists, dermatologists and other specialists) is essential for accurate diagnosis and management	**100%**
Topic B. Treatment selection and initiation		
15.	Treatment should aim for disease stabilization and clinical improvement (e.g., pain alleviation)	**100%**
16.	Asymptomatic patients with potential/impending clinical consequences should be considered for treatment	**93%**
17.	Patients who are symptomatic (e.g., functional deficit, pain, cosmetic issues) should be offered MEK inhibitors	**100%**
18.	Every child who needs treatment for PN should have access to MEK inhibitors as a first-line intervention	**98%**
19.	MEK inhibitors should be initiated by a physician experienced in the diagnosis and treatment of patients with NF1-related tumors	**100%**
20.	Early intervention is crucial for young children with PN lesions in critical areas that have a high likelihood of causing issues like optic, pharyngeal or spinal regions	**100%**
21.	Treatment with MEK inhibitors should be for at least 12 months and then reassessed for benefit	84%
22.	Treatment with MEK inhibitors should be for at least 18 months and then reassessed for benefit	**70%**
23.	Treatment should be continued until after puberty when tumor growth has slowed and then reassessed for benefit	**77%**
24.	Surgery could be considered for PN that can be completely removed without significant morbidity	**95%**
Topic C. Continuing management of PN		
25.	Regular monitoring of PN every 6 months is essential to track disease progression and evaluate treatment effectiveness	**91%**
26.	Regular monitoring of PN every 12 months is essential to track disease progression and evaluate treatment effectiveness	**73%**
27.	Patients receiving MEK inhibitors should undergo regular monitoring for potential toxicity	**100%**
28.	As a minimum, patients on MEK inhibitors should be seen monthly for the first 3 months of treatment and then every 3 months thereafter	**91%**
29.	As a minimum, patients on MEK inhibitors should have bloodwork undertaken monthly for the first 6 months of treatment and then every 3 months thereafter	**93%**
30.	After 18 months on treatment, clinicians could consider a treatment break/drug holiday if no significant morbidity is expected	88%
31.	Ideally, the evolution of PN should be monitored using volumetric MRI	**95%**
32.	Volumetric MRI assessments are more accurate than single-plane measurements for tracking PN progress	**96%**
33.	Patient and parental education regarding NF1 and treatment options empowers informed decision-making and promotes treatment adherence	**100%**
34.	Patients and their parents should be educated about their disease and treatment options so they can identify signs and symptoms of adverse events	**100%**

(*Continued*)

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Table 1. Defined consensus statements and corresponding levels of agreement. Paired statements are outlined in bold; these are statements designed with standardized wording to compare agreement rates with alternative timeframes for treatment and monitoring (*Continued*)

No.	Statement	Agreement
35.	New or rapidly growing PN and the onset of new pain should prompt evaluation for potential malignant transformation	**100%**
Topic D. Transitioning from pediatric to adult care		
36.	Pediatric patients with NF1-PN should have access to dedicated adult care from the age of 18 onward	**100%**
37.	Transition planning for adult care should commence during adolescence or earlier to ensure smooth transition	**98%**
38.	Transition planning should facilitate connection with relevant adult NF1 specialists to maintain continuity of care	**100%**
39.	Efforts should be made to ensure continuity of care during the transition period	**100%**
40.	Seamless continuation of comprehensive and coordinated multidisciplinary care is essential for patients transitioning to adult care	**98%**
41.	Patients who need ongoing treatment with MEK inhibitors should have continued access going into adulthood	**100%**
42.	There is a need to better understand plexiform evolution into adulthood	**100%**
43.	Transition programs should incorporate patient and family education on the unique challenges and considerations associated with NF1-PN in adulthood	**100%**

PN = plexiform neurofibromas; NF1 = neurofibromatosis type 1.

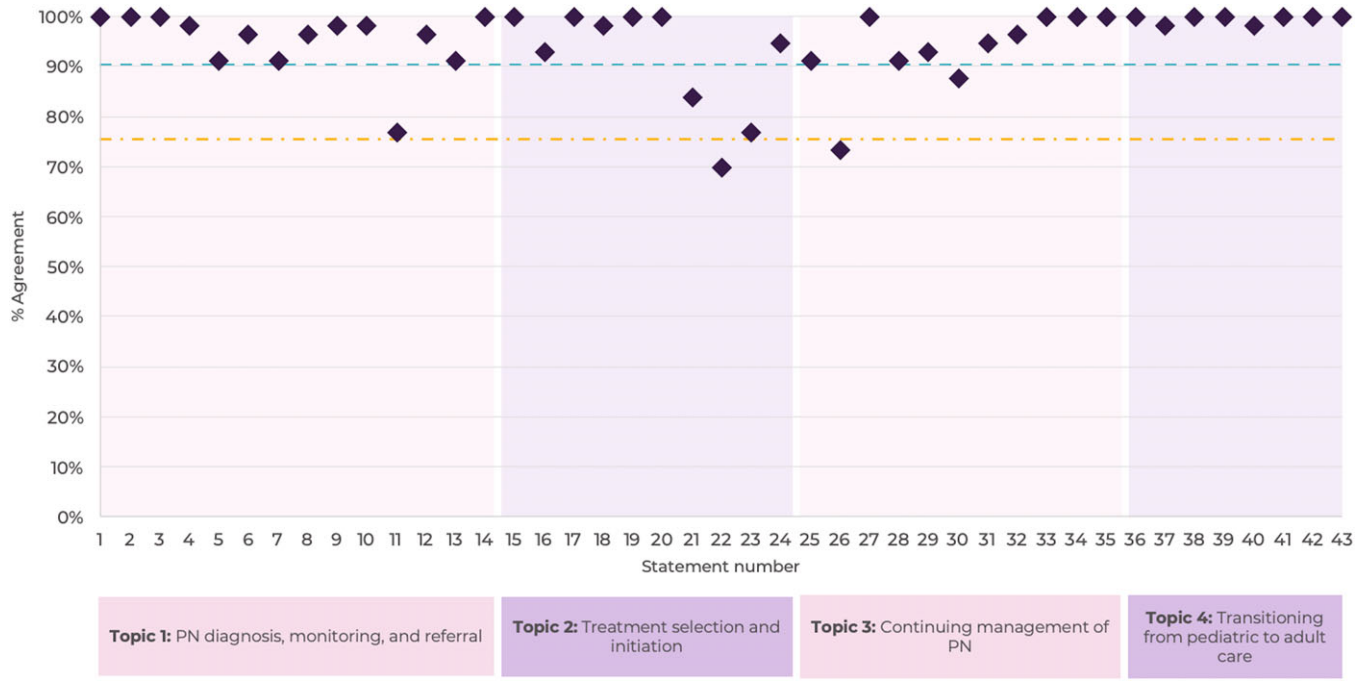

Figure 2. Consensus agreement levels by statement. The threshold for consensus is depicted by the orange line (75%). The blue line signifies the threshold for very strong agreement (90%). PN = plexiform neurofibromas.

Discrepancies in agreement with S7 and S11 could have been due to the inclusion of PN within the statements. This could highlight the need for clinicians to pay greater attention to skin examination when considering referral. The presence of CALMs should indicate that NF1 may be present and warrants specialist investigation.[8,25,31] It is hoped that raising awareness of NF1 and PN, the importance of close monitoring and intervention before functional deficit and the contradiction in these results will increase the impetus to refer patients who have suspected NF1 or asymptomatic PN.

Topic B. Treatment selection and initiation

MEK inhibitors are the primary treatment for NF1-PN if the PN cannot be removed through surgery (S17, 100%; S24, 95%). There was clear agreement that care must be delivered by experienced practitioners (S19, 100%). Having a multidisciplinary team of practitioners experienced in managing NF1, using MEKi and monitoring PN growth is essential.[4,32,33] Experienced practitioners can provide tailored care for patients and greater levels of assistance in managing symptoms and adverse events. These results further emphasize the need for timely referral.

Discrepancies were observed regarding the reassessment of treatment with MEK inhibitors. Survey respondents agreed that all patients with symptomatic PN or with potential/impending clinical consequences should be offered MEKi as a first-line treatment (S18, 98%). However, 84% felt that treatment should be continued for at least 12 months and then reassessed for clinical benefit and whether to continue MEKi treatment (S21), compared to 70% agreeing that treatment should be continued for at least

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18 months and then reassessed (S22). Non-neurologists showed higher agreement with S21, while neurologists favored the 18-month timeframe. These statements highlight the point at which patients need to be reassessed for clinical benefit, rather than the total treatment duration. Therefore, S21 was preferred as many respondents wish to reassess their patients earlier. Reassessment should be done carefully. Research shows a wide range of initial response to MEKi, with a gradual response to treatment in which the bar of >20% volume reduction to achieve partial response may only be achieved after 12 months.[34] Furthermore, many patients will likely need to be treated for much longer periods to maintain treatment benefits.[34,35]

Regarding the overall treatment duration, 77% felt it should continue until after puberty when tumor growth has slowed (S23). Nurses showed the lowest agreement (40%), followed by oncologists (67%), while other roles showed ≥80% agreement. It could be that as nurses are more patient-facing, they are more aware of potential side effects, leading them to perceive the treatment timeframe as too long, depending on when treatment is started (in childhood or during puberty). However, the statement did not provide a clear overall timeframe for when treatment would begin, stating only that it would continue "until after puberty."

Overall, while it is generally believed that treatment should continue until the patient has finished growing, it is acknowledged that the appropriate duration of treatment with MEKi varies by patient. Care is complex, and PN will grow proportionally to the rate of the patient.[9,13,34] Optimal treatment timeframes should be based on age, lesion location, disease burden and patient factors (e.g., preference, comorbidities, etc.).[9,13,23] There is also a need to generate evidence evaluating the efficacy of treatment timeframes extending beyond puberty, considering the total duration of treatment in years.

Topic C. Continuing management of NF1-PN

Regular monitoring is critical for patients with NF1-PN to track disease progression and to monitor treatment response and drug toxicity. Regular assessment is especially important in younger patients, who generally see faster PN growth.[9,13,34] HCPs acknowledge patients should be monitored for progression every 6 months after diagnosis (S25, 91%), with more regular monitoring for toxicity (every month for the first 3 months and every 3 months thereafter) (S27, 100%; S28, 91%; S29, 93%). More frequent assessments should be considered when vital structures are at risk. These timings form the core of the treatment recommendations outlined below.

Respondents agree that the use of volumetric MRI provides the most accurate way to measure PN growth (S32, 96%), as supported within the literature.[17–19] However, there are discrepancies in the way that lesions are reported by HCPs and in the availability of volumetric MRI. Volumetric MRI is typically used in clinical trials but is often not available in routine clinical practice, and clinicians often rely on 1D/2D scans to assess tumors.[9,19] In most regions in Canada, there is no access to volumetric MRI, and more holistic evaluation of patients, including clinical analysis of symptoms, is used to track disease evolution. Given the level of support for using volumetric MRI, efforts will need to be undertaken to ensure improved access. This should include research to make the volumetric MRI analysis more practical. Given the time constraints faced by HCPs, it would be useful to explore artificial intelligence to speed up the process for calculating PN volume.

The necessity of treatment breaks was explored. Overall, 88% of respondents thought treatment breaks could be explored after 18 months of therapy (S30). This was supported very strongly by oncologists (100%) and neuro-oncologists (95%) but not by nurses (60%). All other roles achieved 80% agreement. The concept of treatment breaks for patients with NF1-PN on MEKi is a relatively novel concept, largely confined to discussions between specialists, hence higher levels of agreement from neuro-oncologists. It was again believed that as nurses are more patient-facing, they are more cognizant of the side effects, which often re-emerge upon ceasing therapy. The necessity of treatment breaks is something that will need to be assessed on a case-by-case basis.[35–37] If patients do cease treatment, assessments should still be undertaken to track tumor growth and symptoms. It is anticipated that patients who discontinue treatment may eventually need to return for further rounds of therapy.[37,38] Given the historic lack of effective treatments for NF1-PN, and the paucity of long-term research, further studies will need to be conducted to assess the viability of treatment breaks and their impact on patient outcomes.

Topic D. Transitioning from pediatric to adult care

The transition from pediatric to adult care for patients with NF1 is a critical time. Respondents were unanimous in their agreement that patients with NF1-PN should have access to dedicated adult care from the age of 18 onward and that there must be transition planning in place to ensure continuity of care (S36, 100%; S38, 100%; S39, 100%). Unlike pediatric NF1 care, adult NF1 care is lacking in many parts of Canada. There are very few adult NF1 specialists and clinics, and many areas do not have the resources available for clinics. There is currently a pressing unmet need to address this gap in care, not just in Canada but globally.[21,22]

While the development of clinics may be a long-term goal, short-term goals are required to provide immediate care for current patients. There is a requirement for more research to be undertaken in adult NF1 patients to fully understand optimal care for these patients. It is suggested that clinicians develop care networks to help bridge service gaps, with neuro-oncology acting at the center. This will help to build capacity while work is undertaken to better understand NF1 disease progression. Once programs/networks are developed, their success may be assessed, with a view to replicate them and extend patient care.

Recommendations

Based on the consensus achieved, the SC developed a series of recommendations:

1. All patients with suspected NF1 or PN must be referred to an NF1 specialist for a confirmatory diagnosis and evaluation to help facilitate early intervention and comprehensive care planning.
2. All patients with NF1 and PN who are symptomatic should be offered MEKi, the initiation and monitoring of which should be overseen by a physician experienced in treating NF1-related tumors.
3. Treatment with MEKi should be for at least 12 months, overseen by experienced physicians, before reassessing for patient response.
4. More research needs to be undertaken to establish the benefit of continuing treatment with MEKi until after puberty.

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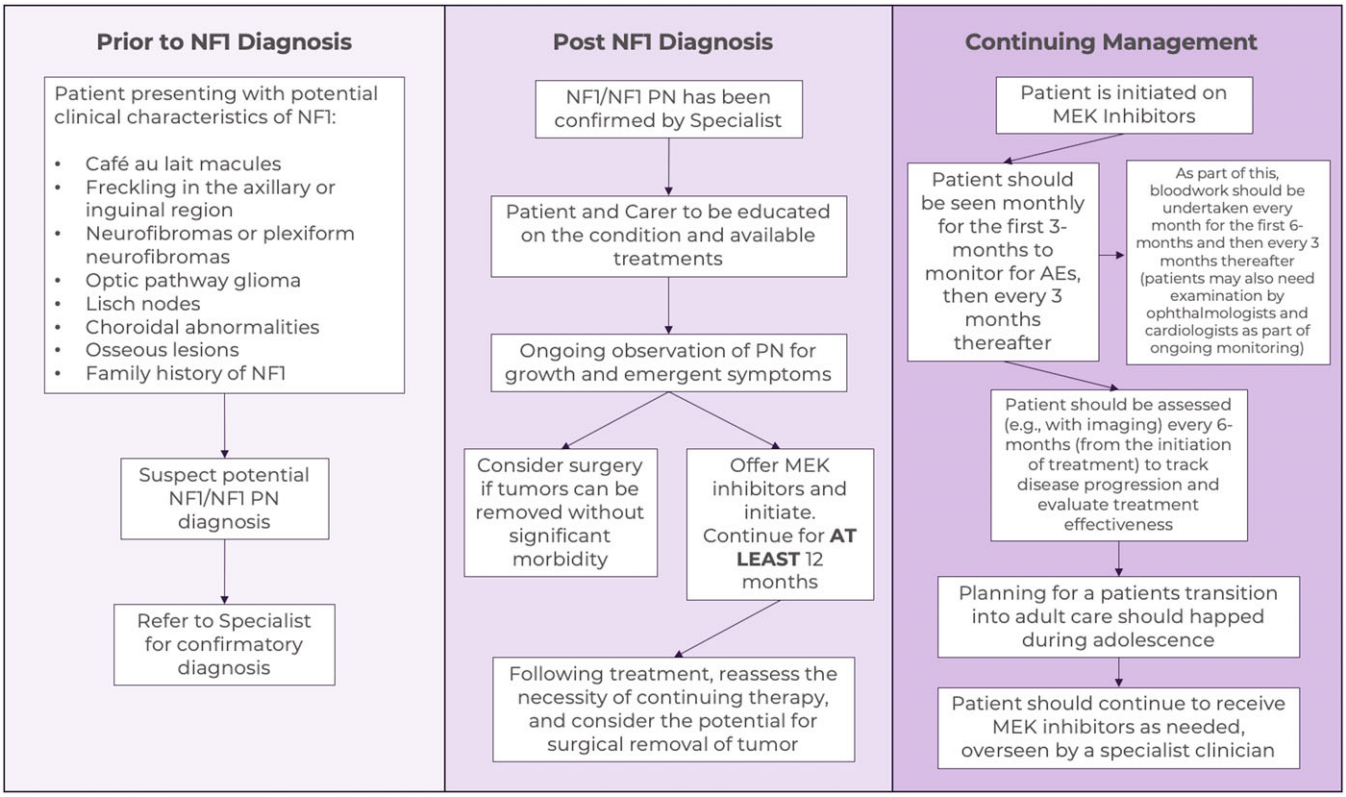

Figure 3. A proposed algorithm for the diagnosis, treatment and management of patients with NF1 and NF1-PN. NF1 = neurofibromatosis type 1; PN = plexiform neurofibromas; AEs = adverse events.

5. Patients who receive MEKi must undergo regular monitoring for response and potential toxicity.
6. Patients and their parents/carers should be educated on NF1 and the treatment options, including the signs and symptoms of adverse events.
7. Patients receiving MEKi should be able to receive ongoing access to treatment into adulthood.
8. Research needs to be undertaken to explore how NF1-PN evolves into adulthood and to assess the best approach to care for this population, including:

   - Short-term measures to ensure current patients receive appropriate care in line with current resources.
   - Long-term measures to raise disease awareness and develop clinician networks to improve the continuity of care when patients transition and to increase capacity in adult NF1 care.

Aspects of these recommendations can be integrated by following the proposed treatment algorithm (Figure 3). These recommendations, and the resultant treatment algorithm, are in line with current international thinking,[8,9] while providing further guidance on management practices.

Strengths and limitations

This study had a good response rate (48%) and very high levels of agreement. While there was a bias toward neuro-oncology, there was representation across roles, and respondents had high levels of experience. The study utilized paired statements to allow for a more precise understanding of HCP thoughts regarding the timings of care. Additional research could be undertaken to explore areas of contention with further paired statements.

The structure of the Delphi statements that were developed could be biased due to the practices of the SC. However, high levels of agreement would suggest that other Canadian clinicians agree with this approach. The agreement levels could indicate that the statements were too agreeable and that the respondent group was biased. However, these HCPs were chosen as they are directly involved in NF1 management. Reaching out to HCPs who do not treat this disease would have lessened the impact and validity of the results. The 4-point Likert scale was chosen to avoid middle option bias, but it could have reduced the nuance in the results. While the survey was predominantly aimed at establishing a care pathway for pediatric NF1, it did touch on the transition of care for patients. However, the respondents were predominantly pediatric specialists; therefore, future work should explore the transition of care from the perspective of adult specialists. Representation across provinces was skewed but thought to reflect the number of specialists in these regions. Low responses from certain provinces reduced the reliability of geographic comparisons, and the cause of certain trends was unclear. While it is standard for Delphi surveys to be quantitative, it would be useful in future research to allow for qualitative feedback. Furthermore, due to the rarity of the disease, additional questions to explore the levels of experience of practitioners assessing NF1-PN and using MEKi could help to strengthen the basis of future consensus work.

Conclusion

This study was able to achieve strong agreement from a national panel of 56 HCPs currently involved in the management of NF1-PN for all but 2 of the 43 statements. These results were used to generate recommendations that help to broaden the consensus on

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approaches to management of NF1-PN, not just nationally in Canada but globally. The results of the consensus are in line with those from international experts, which validates the consensus findings beyond Canada and enforces how its results may contribute to developing international clinical practice. There is clearly an understanding of patient needs, but there are highlighted educational gaps that need addressing. The results show very strong levels of agreement regarding key timings for treatment and management. These have been used to develop a series of actionable recommendations and a treatment algorithm. This Delphi exercise forms a framework for the construction of future guidelines informing the management of this vulnerable and evolving patient population. Future research using cross-national panels of clinicians and further exploring the utility of surgery in the era of MEKi would help strengthen the current recommendations.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/cjn.2025.10409.

Availability of data and materials. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions. VR, SP and LLC developed the initial statements, distributed the survey, contributed to the analysis and discussion of results and read, edited and approved the final manuscript. DS facilitated the project, managed group discussions, helped to identify key topics and generate consensus statements, conducted the initial data analysis and provided editorial support for the manuscript. KL conducted the literature review, helped to identify key topics and generate consensus statements and drafted, edited and finalized the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests. All authors received no honoraria from Alexion, AstraZeneca Rare Disease Canada, while undertaking this study. The authors state the following conflicts of interest: VR has received consulting fees and honorarium from Alexion and Servier. SP has received fees for advisory boards from Alexion, AstraZeneca, Bayer and Eisai and research support from Bayer, Novartis and Roche. LLC has received consultancy fees and advisory board fees from Alexion, DayOne biopharmaceutical and Servier. DS and KL worked on behalf of Triducive Partners Limited, who were funded by Alexion, AstraZeneca Rare Disease Canada, for the project; however, they received no personal payments or honoraria for this study.

Ethical standards. This study did not require registration because neither the assigned interventions nor the outcomes assessed were related to the health of participants. All respondents involved in the survey within the study were informed of the research purpose and that their data would remain anonymous. Their consent was assumed through the completion and submission of their survey responses.

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