NEUROSURGICAL FOCUS

Neurosurg Focus 52 (5):E2, 2022

Multidisciplinary neurocutaneous syndrome clinics: a systematic review and institutional experience

Audrey Grossen, BA,[1,2] Theresa Gavula, PA-C,[3] Deepti Chrusciel, MD,[4] Alexander Evans, BS,[1,2] Rene McNall-Knapp, MD,[3] Ashley Taylor, PA-C,[3] Benay Fossey, MA, LMFT,[3] Margaret Brakefield, PT,[3] Carrick Carter, PsyD,[3] Nadine Schwartz, PA-C,[4] Naina Gross, MD,[5] Andrew Jea, MD,[1,2] and Virendra Desai, MD[1,2]

[1]Department of Neurosurgery, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; [2]Department of Pediatric Neurosurgery, Oklahoma Children's Hospital, Oklahoma City, Oklahoma; [3]Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; [4]Department of Pediatric Neurology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; and [5]Department of Pediatric Neurosurgery, Saint Francis Hospital, Tulsa, Oklahoma

OBJECTIVE Neurocutaneous syndromes have variable multisystem involvement. The multiorgan involvement, potential pathologies, and various treatment options necessitate collaboration and open discussion to ensure optimal treatment in any given patient. These disorders provide quintessential examples of chronic medical conditions that require a lifelong, multidisciplinary approach. The objectives of this study were to 1) perform a systematic review, thoroughly assessing different multidisciplinary clinic layouts utilized in centers worldwide; and 2) characterize an institutional experience with the management of these conditions, focusing on the patient demographics, clinical presentation, complications, and therapeutic strategies seen in a patient population.

METHODS A systematic review of studies involving multidisciplinary clinics and their reported structure was performed according to PRISMA guidelines using the PubMed database. Then a retrospective chart review of patients enrolled in the Oklahoma Children's Hospital Neurocutaneous Syndromes Clinic was conducted.

RESULTS A search of the PubMed database yielded 251 unique results. Of these, 15 papers were included in the analysis, which identified 16 clinics that treated more than 2000 patients worldwide. The majority of these clinics treated patients with neurofibromatosis (13/16). The remaining clinics treated patients with von Hippel–Lindau syndrome (n = 1), tuberous sclerosis complex (n = 1), and multiple neurocutaneous syndromes (n = 1). The most commonly represented subspecialties in these clinics were genetics (15/16) and neurology (13/16). Five clinics (31%) solely saw pediatric patients, 10 clinics saw a combination of children and adults, and the final clinic had separate pediatric and adult clinics. The retrospective chart review of the Neurocutaneous Syndromes Clinic demonstrated that 164 patients were enrolled and seen in the clinic from April 2013 to December 2021. Diagnoses were made based on clinical findings or results of genetic testing; 115 (70%) had neurofibromatosis type 1, 9 (5.5%) had neurofibromatosis type 2, 35 (21%) had tuberous sclerosis complex, 2 (1%) had von Hippel–Lindau syndrome, 2 (1%) had Gorlin syndrome, and the remaining patient (0.6%) had Aarskog-Scott syndrome. Patient demographics, clinical presentation, complications, and therapeutic strategies are also discussed.

CONCLUSIONS To the best of the authors' knowledge, this is the first detailed description of a comprehensive pediatric neurocutaneous clinic in the US that serves patients with multiple syndromes. There is currently heterogeneity between described multidisciplinary clinic structures and practices. More detailed accounts of clinic compositions and practices along with patient data and outcomes are needed in order to establish the most comprehensive and efficient multidisciplinary approach for neurocutaneous syndromes.

https://thejns.org/doi/abs/10.3171/2022.2.FOCUS21776

KEYWORDS neurocutaneous clinic; neurofibromatosis; tuberous sclerosis; multidisciplinary

Phakomatoses, or neurocutaneous syndromes, are a constellation of genetic diseases that have variable multisystem involvement. They tend to affect the CNS, skin, bones, and eyes—all of which derive from the same ectodermal origin. The most common neurocutaneous syndrome is neurofibromatosis type 1 (NF1), a single-gene disorder with an incidence of 1 in 3500 live births.[1] Other syndromes are rarer and include tuberous sclerosis complex (TSC), neurofibromatosis type 2 (NF2), von Hippel–Lindau (VHL), Sturge-Weber syndrome (SWS), and

ABBREVIATIONS ADHD = attention deficit hyperactivity disorder; ENT = ear, nose, and throat; NCSC = Neurocutaneous Syndromes Clinic; NF = neurofibromatosis; SWS = Sturge-Weber syndrome; TSC = tuberous sclerosis complex; VHL = von Hippel–Lindau.

SUBMITTED January 1, 2022. **ACCEPTED** February 23, 2022.
INCLUDE WHEN CITING DOI: 10.3171/2022.2.FOCUS21776.

various other disorders. While the pathogeneses of these syndromes differ, they all have the potential to affect multiple organ systems. Additionally, patients have a preponderance toward tumor formation with increased risk of malignant transformation, seizures, and various other neurological and systemic issues.

The multiorgan involvement, potential pathologies, and various treatment options necessitate collaboration and open discussion to ensure optimal treatment in any given patient. These disorders provide quintessential examples of chronic medical conditions that require a lifelong, multidisciplinary approach. A swift referral to specialists for appropriate imaging, monitoring, and possible intervention is essential for curtailing disease progression and morbidity. While multidisciplinary centers have become widespread, there is currently no established clinic model that provides the most comprehensive and efficient care through data-driven evidence. This study had two main objectives. The first was to perform a systematic review to thoroughly assess different multidisciplinary layouts utilized in centers worldwide. Additionally, we sought to characterize our institutional experience with the management of these conditions, focusing on the patient demographics, clinical presentation, complications, and therapeutic strategies seen in our patient population.

Methods

Eligibility Criteria

A systematic review of studies involving multidisciplinary care clinics and their reported structure was performed according to PRISMA guidelines. Articles were reviewed by one team member (A.G.), and interpretation was verified by a second team member (A.E.).

A search of the PubMed database was conducted through January 31, 2022, using the terms (neurocutaneous syndrome) AND (multidisciplinary clinic OR multidisciplinary unit). Studies were included if they 1) described an established clinic for patients that treated one or more neurocutaneous disorders, and 2) reported on their clinic structure, including subspecialties represented, clinic frequency (how many times per week or month the clinic is held), or referral patterns. Commentaries, letters to the editor, editorials, and articles not accessible in the English language were excluded. Papers that did not address clinic structure but presented studies or clinical trials that enrolled patients from multidisciplinary clinics were excluded from the systematic review but are included in the *Discussion* section.

Data Extraction

The following data points were extracted from each study: clinic location, subspecialties offered, clinic frequency, number of patients treated, patient diagnoses, and referral patterns. Each data point was extracted, reviewed, and agreed on by the two reviewers. The primary outcomes of our analysis were subspecialties that comprised the core teams of these clinics, referral patterns, and clinic frequency.

Institutional Experience

A retrospective chart review of patients enrolled in the Oklahoma Children's Hospital Neurocutaneous Syndromes Clinic (NCSC) from April 2013 to December 2021 was conducted. The following data points for each patient were collected: age, sex, race, address, insurance, median income (obtained using current census data by zip code), distance traveled, family history, comorbidities, diagnosis, and symptoms. General clinic data, including cancellation and no-show rates, were also recorded. We further collected information regarding neurosurgical interventions, including surgical management of brain and/or spine tumors and epilepsy. The 3-month period in which the clinic was canceled due to the COVID-19 pandemic (March 2020–May 2020) was omitted from analysis. Ethics approval for this study was granted by the institutional review board at the University of Oklahoma Health Sciences Center.

Statistical Analyses

Statistical analyses were conducted using IBM SPSS Statistics for Windows (version 27.0, IBM Corp.).

Results

Systematic Review

A search of the PubMed database using our criteria yielded 251 unique results. Of these, 15 papers were ultimately included in the analysis (Fig. 1). A total of 16 clinics were identified that treated more than 2000 patients worldwide (Table 1). The majority of these clinics treated patients with neurofibromatosis (NF) (13/16). The remaining clinics treated patients with VHL (n = 1), TSC (n = 1), and multiple neurocutaneous syndromes (n = 1). The most commonly represented subspecialties in these clinics were genetics (15/16) and neurology (13/16). Five clinics (31%) solely saw pediatric patients, 10 clinics saw a combination of children and adults, and the final clinic had separate pediatric and adult clinics.

Institutional Experience

Between April 2013 and December 2021, 164 patients had been enrolled and seen in the comprehensive NCSC. Table 2 outlines general characteristics of the clinic and its patients. The mean patient age at first encounter was 9.9 years (range 0.17–23.92 years). The majority of patients (60%) had Medicaid as their primary insurance. The average median income of patients and/or their families was $54,774. The clinic cancellation rate was 4.3% and the no-show rate was 4.1%. The mean distance traveled was 62.4 miles. The clinic serves patients located throughout the state of Oklahoma (Fig. 2).

Diagnoses of the 164 patients seen in our clinic were made based on clinical findings or results of genetic testing; 115 (70%) had NF1, 9 (5.5%) had NF2, 35 (21%) had TSC, 2 (1%) had VHL, 2 (1%) had Gorlin syndrome, and the remaining patient (0.6%) had Aarskog-Scott syndrome. Table 3 further categorizes patient demographics and concomitant medical issues by diagnosis (NF1, NF2, TSC, Gorlin syndrome, and Aarskog-Scott syndrome).

Table 4 outlines tumor prevalence and treatment in our patient population. Table 5 illustrates epilepsy rates in each syndrome and the utilization of different treatment modalities.

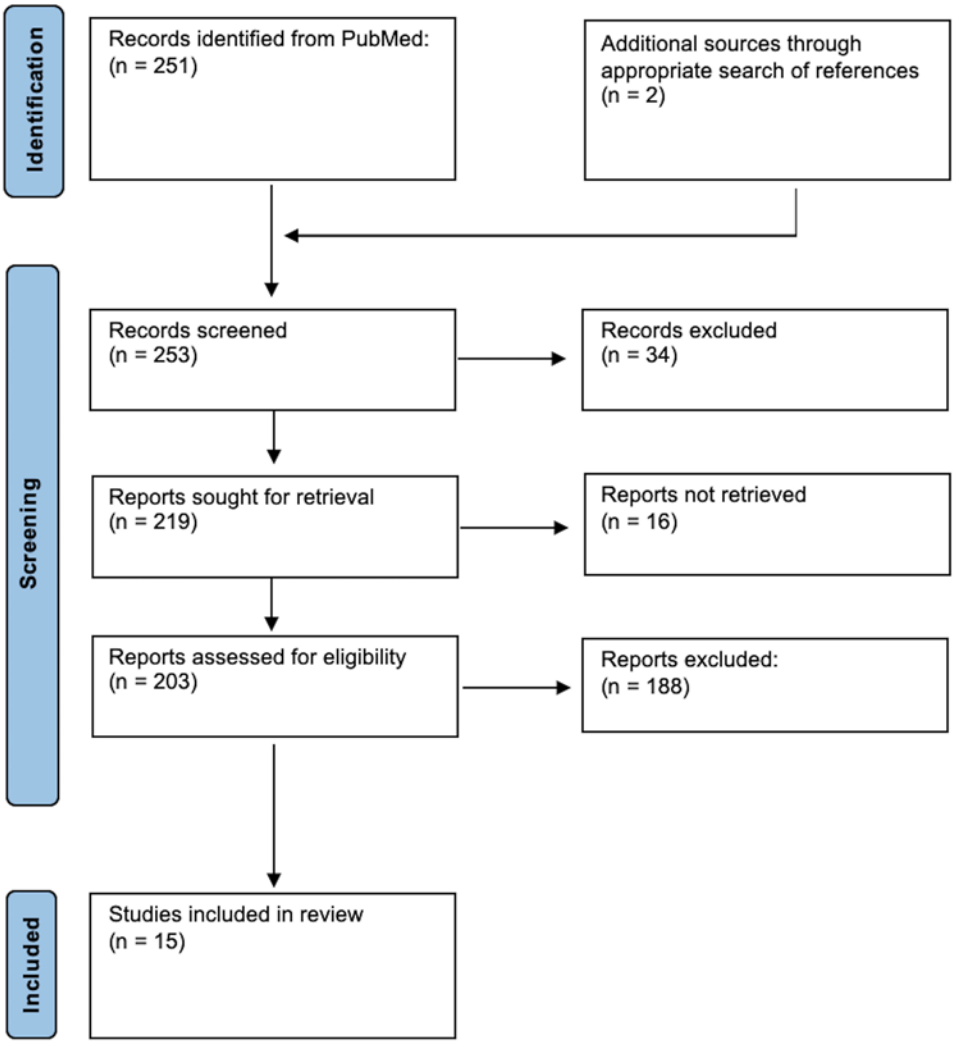

FIG. 1. Identification of studies via PRISMA guidelines. Data added to the PRISMA template (from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CT, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71) under the terms of the Creative Commons Attribution License.

Discussion

Our Multidisciplinary Clinic Layout

The comprehensive NCSC was established in the spring of 2013 at Oklahoma Children's Hospital after a need was recognized for these multidisciplinary services. The clinic stemmed from and was modeled after the comprehensive brain tumor clinic. In the 1st year, 32 patients were enrolled and seen in the clinic. Today, that number has grown to 164. This clinic is held twice per month. Together, the combined expertise from all specialties promotes collaboration and discussion regarding the best plan of action for patients. Services range from establishing care for annual evaluation for screening and anticipatory guidance to medical and surgical intervention for conditions such as tumors and epilepsy.

The core specialties represented in the clinic include neurology, neurosurgery, genetics, neuro-oncology, psychiatry, and physical therapy (Fig. 3). This core team of providers meets the patient at the first encounter and acts as a gatekeeper to other medical specialties and further workup. After a thorough history is obtained and a physical examination is conducted, appropriate imaging is obtained, and referrals to endocrinology, orthopedic surgery, dermatology, otorhinolaryngology (ear, nose, and throat [ENT]), ophthalmology, and plastic surgery are commonly made.

Subspecialties

Genetics

On the first visit, the geneticist completes or reviews a genetic questionnaire and family pedigree. Genetic testing, if not previously performed, is then generally offered to the patient and their family. During this stage of workup, it is not uncommon for family members to also be diagnosed within the clinic. Genetic counseling is also made available to patients at every clinic encounter to dis-

TABLE 1. Other described neurocutaneous clinics

Authors & Year	Location	Disease(s) Treated	No. of Patients	Pediatric/ Adult	Frequency	Clinic Structure
Beckman & Akbarnia, 1988[59]	St. Louis, MO	NF	150	Both	Monthly	Core team: clinic coordinator, genetics, neurology, orthopedic surgery, ophthalmology, social work
Obringer et al., 1988[60]	Philadelphia, PA	NF	—	Both	—	Core team: clinic coordinator, genetics, neurology, hematology-oncology
Schorry et al., 1989[61]	Cincinnati, OH	NF	78	Both	—	Core team: genetics, neurology, orthopedic surgery, social work One of the core team providers assigned as case worker for each patient Family physician is available to examine adult family members
North, 1993[62]	Campertown, Australia	NF	200	Both	2 times/wk	Core team: genetics, neurology Ophthalmology clinic held on the same day for easy referral
Habiby et al., 1995[31]	Chicago, IL	NF	—	Pediatric	—	Core team: genetics, pediatrics, ophthalmology
Cnossen et al., 1997[32]	Rotterdam, the Netherlands	NF	122	Pediatric	—	Core team: genetics, pediatric neurology, pediatrics, dermatology, ophthalmology
Ramanjam et al., 2006[63]	Cape Town, South Africa	NF	48	Pediatric	—	Core team: genetics, neurology, neurosurgery, neurodevelopment Open referral policy to ophthalmology, dermatology, plastic surgery, orthopedic surgery
Noble et al., 2007[64]	Melbourne, Australia	NF	130	Pediatric	Monthly	Core team: genetics, neurology, ophthalmology Subspecialties affiliated w/ clinic: neuropsychology, endocrinology, oncology, nephrology, plastic surgery Many children see a separate pediatrician btwn visits Referrals: any medical provider can refer to the clinic; referrals are also accepted directly from patients/families w/ NF1
Mansouri et al., 2017[65]	Toronto, Ontario, Canada	NF	66	Both	Biweekly	Core team: genetics, neurology, neurosurgery, nurse practitioner
Lloyd & Evans, 2018[57]	Manchester, UK	NF	256	Both	Varies by clinic	Core team: clinic coordination, genetics, neurology, otolaryngology, neurosurgery, pediatrics, audiology, radiology, psychology, physical therapy, nursing Additional subspecialties if needed: plastic surgery, ophthalmology, oncology
	Oxford, UK		143			
	Cambridge, UK		121			
	London, UK		168			
Peron et al., 2018[39]	Milan, Italy	TSC	250 (~1/3 pediatric & 2/3 adult)	Separate affiliated pediatric & adult clinics	Weekly	Pediatric core team: genetics, pediatric neurology, pediatric psychiatry, pediatrics, nephrology, pulmonology (starting at age 16 yrs), dermatology, ophthalmology, dentistry, psychology, social work, molecular lab At affiliated hospital: radiology, neurosurgery, epilepsy surgery Adult core team: genetics, neurology, psychiatry, internal medicine, nephrology, pulmonology, dermatology, ophthalmology, radiology, dentistry, gynecology, psychology, social work, molecular lab At affiliated hospital: neurosurgery, epilepsy surgery
Kokkinou et al., 2019[66]	Athens, Greece	NF, TSC, SWS	157	Pediatric	Monthly	Core team: genetics, neurology, dermatology, oncology, ophthalmology, orthopedic surgery, neuroradiology, neuropsychology, social work Plan to expand services to adult patients
Toledano-Alhadef et al., 2020[41]	Israel	NF	—	Both	—	Core team: genetics, neurology, neurosurgery, ophthalmology, orthopedic surgery, oncology, radiology, psychology, social work
	Tübingen, Germany	NF	—	Both	—	Core team: genetics, neurology, neurosurgery, dermatology

CONTINUED ON PAGE 5 »

» CONTINUED FROM PAGE 4

TABLE 1. Other described neurocutaneous clinics

Authors & Year	Location	Disease(s) Treated	No. of Patients	Pediatric/ Adult	Frequency	Clinic Structure
Nishida et al., 2021[67]	Nagoya, Japan	NF	246	Both	—	Core team: genetics, pediatrics, neurosurgery, orthopedic surgery
Yoon et al., 2022[3]	Seoul, Korea	VHL	50	Both	—	Core team: endocrinology, urology, general surgery, neurosurgery, ophthalmology, otolaryngology, radiology

UK = United Kingdom; — = unknown.

cuss disease progression, inheritance patterns, and reproductive questions. This is especially important as patients reach reproductive age and consider having children of their own.

Our review showed that 15 of 16 described clinics had genetics represented as a core component of their clinic team. Studies have shown long-term surveillance to be a vital component of neurocutaneous management.[2] In their cohort of VHL patients, Yoon et al.[3] found the multidisciplinary model to be an effective means of providing long-term surveillance and genetic counseling. They reported that most visceral tumors in their clinic were asymptomatic and diagnosed incidentally on routine imaging surveillance.[3] They also found that patients diagnosed with VHL who were not followed up in their clinic had significantly lower rates of ophthalmological examination, audiometry testing, and pheochromocytoma-related hormone tests.[3] In a 10-year prospective follow-up study, Cnossen et al.[4] found that the mean number of minor disease features was significantly higher in patients 6 years of age or younger who were later diagnosed with NF1. They advocated for routine surveillance and documentation of these features (macrocephaly, short stature, hypertelorism, and thorax abnormalities) from a young age as they serve as predictors of NF1 diagnosis.[4]

Neurology

Many of the manifestations of neurocutaneous disorders require medical treatment. Neurologists provide management for conditions such as headaches, epilepsy, and pain. In our patient cohort, roughly half of all patients complained of headache. Of the total clinic patient population, 33.5% had a history of at least one seizure. The majority (69%) were medically treated with a mean of 1.3 antiepileptic drugs. In epilepsy, early management is key to decrease of the chances of developing cognitive dysfunction or other psychiatric disorders.[5]

Infantile spasms seen in TSC are generally treated with vigabatrin as a first-line agent and adrenocorticotropic hormone as a second-line option. Neurologists also manage vascular malformations, and the use of antiplatelet therapy in SWS may be considered.

Neuro-Oncology

The role of the neuro-oncologist is invaluable for managing benign and malignant brain tumors. Oncologists and surgeons have the opportunity to collaborate and formulate the best management strategy for patients, be it surgery or chemoradiotherapy. Advances in molecularly targeted treatment and potential immunological treatment of these tumors continue to be studied for this purpose. One of the most commonly used pharmaceuticals is everolimus, a mechanistic target of rapamycin (mTOR) inhibitor. Studies have shown everolimus to be an effective option for inducing stabilization or shrinkage in recurrent or progressive NF1-associated low-grade glioma.[6] Additionally, clinical trials have demonstrated that adjunctive everolimus is a well-tolerated option in pediatric patients with medically refractory epilepsy due to TSC, showing a sustained seizure reduction at 1 year.[7,8] MEK inhibitors have also been tested in clinical trials.[9,10] They were found to have a favorable profile and deemed safe in neurocognitive functioning in NF1 clinical trials.[11]

Neurosurgery

Perhaps the most predominant roles for neurosurgical intervention in these patients include CNS tumors and refractory epilepsy. Other associated conditions that could potentially require intervention include Chiari malformation, tethered cord, scoliosis, vascular malformations, and hydrocephalus necessitating ventriculoperitoneal shunt placement.

Both brain and spinal tumors are frequently encountered in the neurocutaneous clinic (Table 3) and may require surgical intervention in addition to chemotherapy and/or radiation therapy. Studies from databases housed by multidisciplinary clinics have documented the rates

TABLE 2. General clinic data

Characteristic	Value
No. of patients	164
Age at 1st encounter, yrs	9.9 ± 5.54
Insurance, n (%)	
Private	56 (34)
Medicaid	98 (60)
Uninsured	10 (6)
Median income	$54,774 ± 16,511
Distance traveled, miles	62.40 ± 52.86
Cancellation rate	4.3%
No-show rate	4.1%

Mean values are given as mean ± SD.

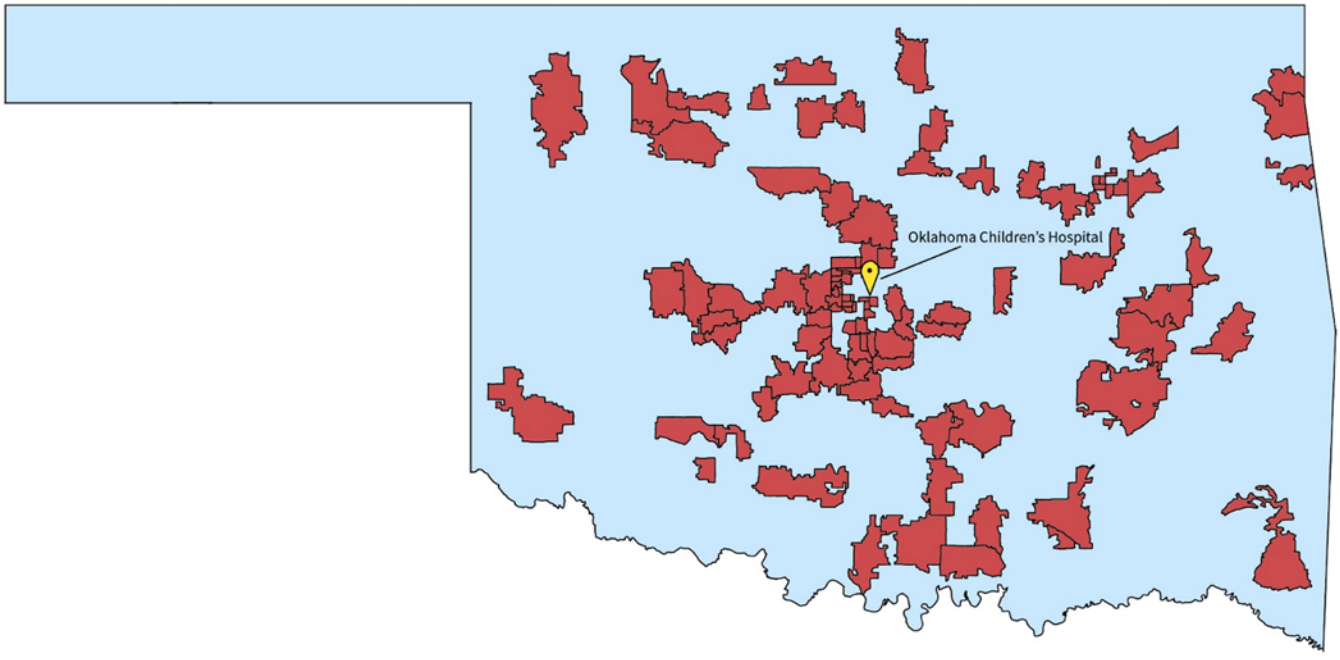

FIG. 2. Oklahoma zip codes represented at the NCSC. *Red color-coded areas* are zip codes of patients enrolled in the clinic. The *yellow pin* represents the location of Oklahoma Children's Hospital. One patient traveling from Kansas was excluded from this illustration. Created with Adobe Fresco.

TABLE 3. Demographics and comorbidities characterized by diagnosis

	NF1, n = 115	NF2, n = 9	TSC, n = 35	VHL, n = 2	Gorlin Syndrome, n = 2	Aarskog-Scott Syndrome, n = 1
Age at 1st encounter, yrs	10.1 ± 5.2	12.8 ± 5.6	8.4 ± 6.1	16.9 ± 0.5	7.7 ± 10.2	4.9
Sex						
Male	70 (61)	7 (78)	16 (46)	1 (50)	2 (100)	1 (100)
Female	45 (39)	2 (22)	19 (54)	1 (50)	0 (0)	0 (0)
Race						
White	86 (75)	8 (89)	29 (83)	2 (100)	2 (100)	1 (100)
African American	14 (12)	0 (0)	5 (14)	0 (0)	0 (0)	0 (0)
American Indian or Alaska Native	11 (9.6)	1 (11)	1 (3)	0 (0)	0 (0)	0 (0)
Asian	4 (3.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ethnicity						
Hispanic	11 (9.6)	3 (33)	7 (20)	0 (0)	0 (0)	0 (0)
Positive family history	65 (57)	3 (33)	14 (40)	1 (50)	1 (50)	1 (100)
Headache	66 (57)	5 (56)	7 (20)	1 (50)	2 (100)	0 (0)
Hypertension	16 (14)	1 (11)	8 (23)	0 (0)	0 (0)	1 (100)
Scoliosis	38 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tethered cord	7 (6)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)
Chiari malformation	3 (3)	0 (0)	1 (3)	0 (0)	1 (50)	1 (100)
ADHD/learning disability	85 (74)	6 (67)	27 (77)	0 (0)	1 (50)	0 (0)
Anxiety/depression	20 (17)	2 (22)	6 (17)	0 (0)	0 (0)	0 (0)

Values are given as n (%) or mean ± SD unless otherwise indicated.

TABLE 4. Tumor management

	Monitor	Op	CRT	Op + CRT
Plexiform neurofibroma, n = 46	28 (61)	5 (11)	6 (13)	7 (15)
MPNST, n = 3	0 (0)	1 (33)	0 (0)	2 (67)
Meningioma, n = 6	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)
Schwannoma, n = 10	7 (70)	2 (20)	1 (10)	0 (0)
Ependymoma, n = 4	3 (75)	0 (0)	1 (25)	0 (0)
SEGA, n = 23	13 (57)	2 (9)	5 (22)	3 (13)
Glioma, n = 31	20 (65)	0 (0)	7 (23)	4 (13)
Optic pathway glioma, n = 51	34 (67)	1 (2)	16 (31)	0 (0)
Medulloblastoma, n = 1	0 (0)	0 (0)	0 (0)	1 (100)

CRT = chemoradiotherapy; MPNST = malignant peripheral nerve sheath tumor; n = number of patients with confirmed tumor; SEGA = subependymal giant cell astrocytoma.
Values are given as n (%).

of plexiform neurofibromas and other thoracic tumors causing spinal compression in NF1 within their own clinics.[12,13]

Epilepsy is another common neurological manifestation of neurocutaneous disorders. One systematic review found the lifelong prevalence of epilepsy in NF1 to be 5.4%.[14] This value is significantly higher in TSC, as tubers, hamartomas, subependymal giant cell astrocytomas, and epilepsy are hallmarks of the disorder. This patient population presents unique challenges in epilepsy treatment and has known indications for surgery and laser ablation.[15–22] SWS has also been shown to be associated with increased rates of drug-refractory epilepsy.[23]

Although there is no known pathophysiological relationship between NF and tethered cord, there seems to be a correlation between the two. One study found the rate of tethered cord in NF patients to be as high as 13%.[24] In our cohort, this value was 6.5% and all of our patients underwent surgical correction.

Psychiatry

It is well known that neurocutaneous syndromes are associated with cognitive impairment and higher rates of concomitant psychiatric disorders. This is especially true of attention deficit hyperactivity disorder (ADHD), learning disabilities, behavioral problems, anxiety, and depression.[25] In our patient population, 74% of patients had ADHD and/or a learning disability, and 17% were diagnosed with anxiety and/or depression.

Psychologists screen for mental health diagnoses, problems with learning, neurocognitive deficits, family stressors, and health maintenance behaviors. They also provide psychoeducation and brief behavioral interventions related to mental health, school accommodations, and health maintenance behaviors, as well as referrals for counseling, psychiatry, and neuropsychological testing.

One well-studied area in neurocutaneous disorders is the mental health of adults living with TSC. Multiple studies have shown that these patients report a decreased quality of life and require continued monitoring into adulthood.[26–28]

Physical Therapy

Physical therapy can greatly improve the quality of life and function of some patients. However, a standard of care has yet to be established in pediatric and adult patients.[29]

Pertinent areas in which physical therapy can intervene are evaluating coordination and strength and identifying and treating gait abnormalities. Tillmann et al. described the experience of their multidisciplinary hospital team in managing transient hemiparesis in SWS, in which physical therapy played a vital role.[2]

TABLE 5. Epilepsy management

	Cases of Epilepsy	No Intervention	Treated Medically	Mean No. of AEDs	Treated Surgically
NF1, n = 115	20 (17)	8 (40)	12 (60)	1.5	0 (0)
NF2, n = 9	1 (11)	0 (0)	1 (100)	1	0 (0)
TSC, n = 35	32 (91)	5 (16)	24 (75)	1.65	3 (9)
VHL, n = 2	0 (0)	NA	NA	NA	NA
Gorlin syndrome, n = 2	1 (50)	0 (0)	1 (100)	1	0 (0)
Aarskog-Scott syndrome, n = 1	1 (100)	1 (100)	0 (0)	0	0 (0)

AED = antiepileptic drug; NA = not applicable.
Values are given as n (%) unless otherwise indicated.

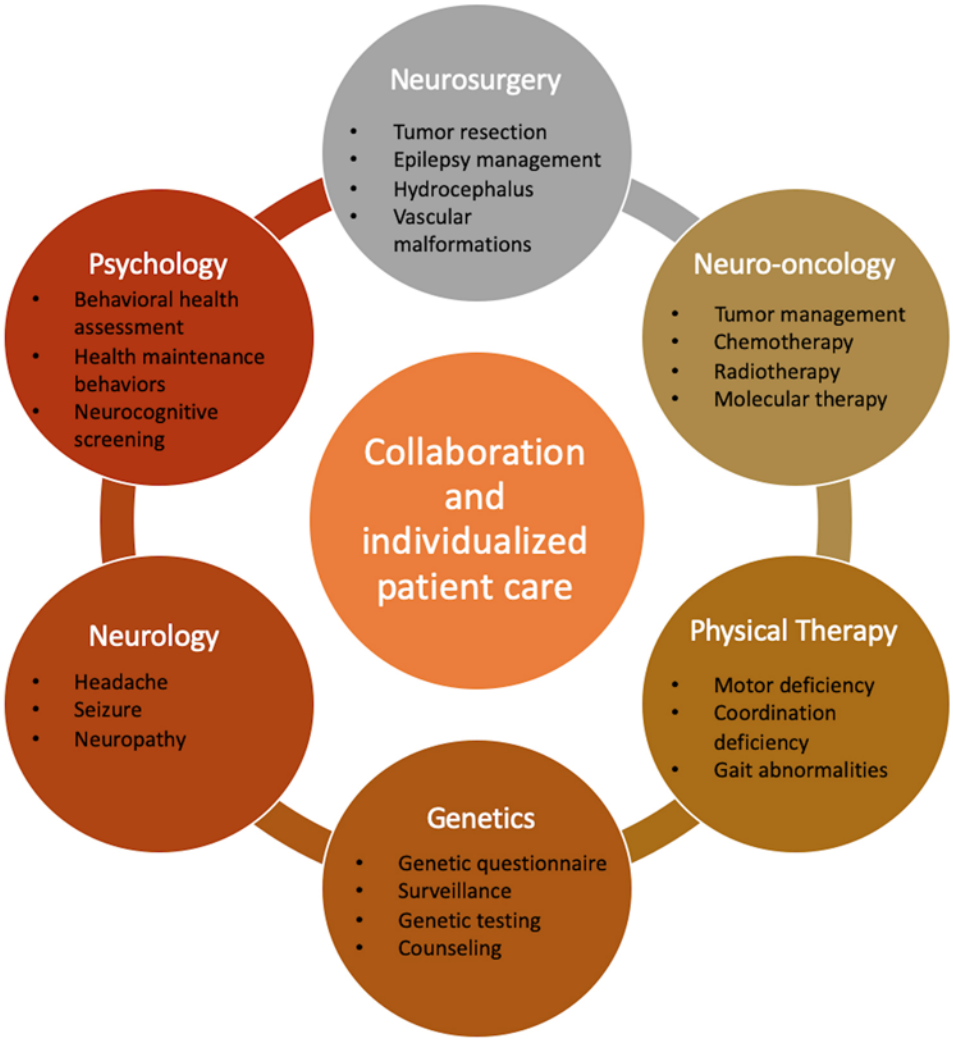

FIG. 3. Oklahoma Children's Hospital NCSC core clinic team.

Referrals

Ideally, as many subspecialties as possible are incorporated into a multidisciplinary clinic. However, this is often not feasible. At our institution, this is especially true for the specialties that comprise the bulk of referrals from the clinic—ophthalmology, endocrinology, and ENT.

Ophthalmology referrals are warranted for evaluation of optic pathway gliomas and Lisch nodules in NF1. In TSC, this subspecialty monitors for retinal hamartomas and sequelae of vigabatrin treatment, which can cause retinal toxicity. In particular, optic pathway gliomas are highly prevalent and are estimated to affect between 15% and 20% of patients with NF1.[18,30] Habiby et al. described 11 patients with concomitant optic pathway tumors and precocious puberty in their comprehensive NF1 clinic.[31]

Guidance from endocrinology is often sought with cases of precocious puberty, amenorrhea, gigantism/acromegaly, and short stature. Cnossen et al.[32] demonstrated the prevalence of endocrine complications in NF1.

ENT is especially helpful in cases of vestibular schwannomas, which can lead to hearing loss. There have been multiple reports of cochlear implantation in multidisciplinary NF2 clinics.[33–35] There are strong proponents of adding these subspecialties to the direct care of neurocutaneous disorders.[36]

Clinic Workflow Options

There are a variety of different clinic layouts that could function effectively in neurocutaneous management. There is currently no established model for optimal multidisciplinary treatment, including which subspecialties should comprise the core team, referral requirements, or collaboration with other centers. Much of the time, logistics, funding, and institutional resources dictate how a clinic is arranged.

At our institution, patients with a variety of neurocutaneous disorders are seen in the same clinic. This is partly due to scheduling and logistics within the hospital. However, there is also rationale in this approach, as patients with differing disorders require evaluation from many of

the same subspecialties. This also allows for those few patients in our clinic with VHL syndrome (n = 2), Gorlin syndrome (n = 2), or Aarskog-Scott syndrome (n = 1) to be included in a comprehensive clinic.

Pearls of Multidisciplinary Clinics

Removing Barriers to Access

The convenience of seeing a multitude of specialists during one clinic visit is invaluable to patients and their families. This is particularly true for those who live in rural areas and states with few, large academic centers who travel long distances for these appointments. These centers often provide health services to a larger number of uninsured and low-income patients and have the opportunity to advocate for patient funding.[37]

Clinics also play a role in the transition of care from childhood into adulthood for many patients.[38,39] Peron et al. described a TSC clinic model in which they house both pediatric and adult clinics.[39] When the patient transitions into adult care, administrative staff simply transfer records between the two clinics. Pediatric and adult staff meet every 4 months to discuss patients and make the process even more seamless.

Decreased Cancellation and No-Show Rates

The ability for patients to see many providers at one visit has increased our reach within the state. When reviewing general clinic data, cancellations were defined as notification by the patient or their care provider if they were unable to keep their scheduled appointment within 24 hours of the appointment time. "No-shows," or missed appointments, were defined as failure to keep the appointment with no prior notification. Our clinic had 4.3% and 4.1% cancellation and no-show rates, respectively. Even condensing these values into a combined cancellation and no-show rate (8.4%), this rate was much lower than those reported in previous studies of pediatric clinics, in which no-show rates have been reported to be as high as 26%.[40] Not only does this hinder patients from receiving necessary services, but it also comes at a cost to the healthcare system. One analysis of the lost costs of no-shows in a pediatric neurology clinic showed that annual losses were more than $250,000.[40]

Social Support

It would be hard to overstate the impact of the relationships formed in the clinic. Connections are formed between patients, within families, and with patients and their providers. One specific way that multidisciplinary clinics have the opportunity to do this is through the family-centered care approach. This method implements the patient's family in treatment and has been proven effective in improving healthcare services, particularly in treating chronic conditions in the pediatric and adolescent populations.[41] Multidisciplinary clinics have also been shown to improve patient satisfaction and patient outcomes.[42]

Guidelines and Protocols

The teams of experts who comprise multidisciplinary clinics are up to date on current guidelines and ever-evolving protocols of various syndromes.[43–47] Multidisciplinary meetings also occur in which providers meet to discuss, refine, and create protocols.[48,49]

The multidisciplinary nature of clinics is especially useful in cases of dual diagnoses in which management must be further individualized. In our clinic, there have been cases of craniosynostosis, moyamoya, osteosarcoma, type 1 diabetes, and Klinefelter syndrome that have required additional care and discussion.

Academics and Research

There is ongoing research in various fields of neurocutaneous disorders. Large academic centers have an opportunity to contribute largely to this research, as they have a higher concentration of rare diseases and more academic funding. It is the hope of many that this continued research will lead to earlier patient referrals to multidisciplinary clinics, better pediatric-to-adult transition of care, and prolonged life expectancy.

Multidisciplinary centers have furthered academics by participating in numerous clinical trials and studies.[4,50,51] The formation of clinic databases has allowed centers to perform their own clinical trials and studies as well as to participate in national databases.[52] Perhaps the best examples of these are the Neurofibromatosis Clinic Network and the Tuberous Sclerosis Alliance (TOSCA).[53–56]

Potential Pitfalls of Multidisciplinary Clinics

Scheduling Limitations

Our clinic sees patients twice a month. Each clinic is 4 hours in length. Typically, 6 to 8 patients are seen within one clinic. This limitation of volume does not allow for the scheduling of patients with less complex cases who are typically followed in individual clinics. Additional clinic time would provide more appointment slots. Our providers tend to see patients together or in tandem, rather than seeing them individually. This allows more patients to be seen in one clinic session.

Personnel Rotations

Consistent personnel at each clinic visit enables providers to establish rapport with patients and become familiar with patients and their families. However, personnel rotations sometimes become inevitable, which results in less knowledge regarding the patient and their care. In order to mitigate this, our clinic keeps a fixed staff.

Future Directions

Multidisciplinary care and individualized patient treatment are areas of interest, not only for neurocutaneous disorders, but also for the healthcare field at large. These models provide opportunities for data sharing, research collaboration, and the formation of regional networks. Lloyd and Evans[57] described a supraregional network of clinics established by the United Kingdom that provides a prime example of the latter. Through the implementation of four "hospital hubs" that function autonomously under a regional umbrella, they have created a uniform, national coordination of care.[57,58]

It is of great interest to us to further examine our own

patient cohort, in addition to collaborating with other facilities to examine how multidisciplinary clinics affect time to treatment, number of interventions, patient satisfaction, and life expectancy.

Study Limitations

There are limitations to this study. Systematic reviews are vulnerable to limitations, as they are retrospective in nature. There is the potential to miss relevant studies due to the choice of search terms and an inability to access certain articles or journals. There is also the potential for reporting bias. In this review, there were a substantial number of papers that were not accessible in the English language.

A limitation of many multidisciplinary clinics, including our own NCSC, is the inability to include more subspecialties within the clinic. This can be due to factors such as scheduling conflicts or limited relative value unit (RVU) generation, given low patient numbers. Specifically, RVU-driven specialties and hospitals have much less incentive for multidisciplinary clinics. However, more data demonstrating multidisciplinary clinics leading to decreased no-show and cancellation rates and/or higher surgical yield as RVU generators may change this.

Another limitation of this study was the inability to compare the patient outcomes prior to and following initiation of treatment in the clinic.

Conclusions

To the best of our knowledge, this is the first detailed description of a comprehensive pediatric neurocutaneous clinic in the US that serves patients with multiple syndromes. We endorse the referral of patients with known neurocutaneous disorder to a comprehensive clinic. From there, the decision can be made if the patient can be appropriately managed in individual clinics or by a comprehensive team with further imaging, routine clinic monitoring, and/or referral to other specialties as needed. There is currently heterogeneity between described multidisciplinary clinic structures and practices. We were unable to accurately quantify the benefits of a multidisciplinary neurocutaneous clinic given that the varied pathologies seen in isolated clinics, with low numbers of neurocutaneous patients for each, limited proper cross-analysis. More detailed accounts of clinic compositions and practices along with patient data and outcomes are needed from national and international clinics in order to establish the most efficient multidisciplinary approach for neurocutaneous syndromes.

References

1. Al-Otibi M, Rutka JT. Neurosurgical implications of neurofibromatosis Type I in children. *Neurosurg Focus*. 2006;20(1):E2.
2. Tillmann RP, Ray K, Aylett SE. Transient episodes of hemiparesis in Sturge Weber Syndrome—causes, incidence and recovery. *Eur J Paediatr Neurol*. 2020;25:90-96.
3. Yoon SJ, Kwon WK, Hong G, et al. Genetic counseling and long-term surveillance using a multidisciplinary approach in von Hippel-Lindau disease. *Ann Lab Med*. 2022;42(3):352-357.
4. Cnossen MH, Moons KG, Garssen MP, et al. Minor disease features in neurofibromatosis type 1 (NF1) and their possible value in diagnosis of NF1 in children < or = 6 years and clinically suspected of having NF1. Neurofibromatosis team of Sophia Children's Hospital. *J Med Genet*. 1998;35(8):624-627.
5. Vignoli A, La Briola F, Turner K, et al. Epilepsy in adult patients with tuberous sclerosis complex. *Acta Neurol Scand*. 2021;144(1):29-40.
6. Ullrich NJ, Prabhu SP, Reddy AT, et al. A phase II study of continuous oral mTOR inhibitor everolimus for recurrent, radiographic-progressive neurofibromatosis type 1-associated pediatric low-grade glioma: a Neurofibromatosis Clinical Trials Consortium study. *Neuro Oncol*. 2020;22(10):1527-1535.
7. Curatolo P, Franz DN, Lawson JA, et al. Adjunctive everolimus for children and adolescents with treatment-refractory seizures associated with tuberous sclerosis complex: post-hoc analysis of the phase 3 EXIST-3 trial. *Lancet Child Adolesc Health*. 2018;2(7):495-504.
8. Franz DN, Lawson JA, Yapici Z, et al. Everolimus dosing recommendations for tuberous sclerosis complex-associated refractory seizures. *Epilepsia*. 2018;59(6):1188-1197.
9. Weiss BD, Wolters PL, Plotkin SR, et al. NF106: a Neurofibromatosis Clinical Trials Consortium Phase II Trial of the MEK inhibitor mirdametinib (PD-0325901) in adolescents and adults with NF1-related plexiform neurofibromas. *J Clin Oncol*. 2021;39(7):797-806.
10. Fisher MJ, Shih CS, Rhodes SD, et al. Cabozantinib for neurofibromatosis type 1-related plexiform neurofibromas: a phase 2 trial. *Nat Med*. 2021;27(1):165-173.
11. Walsh KS, Wolters PL, Widemann BC, et al. Impact of MEK inhibitor therapy on neurocognitive functioning in NF1. *Neurol Genet*. 2021;7(5):e616.
12. Pollack IF, Colak A, Fitz C, Wiener E, Moreland M, Mulvihill JJ. Surgical management of spinal cord compression from plexiform neurofibromas in patients with neurofibromatosis 1. *Neurosurgery*. 1998;43(2):248-256.
13. Schorry EK, Crawford AH, Egelhoff JC, Lovell AM, Saal HM. Thoracic tumors in children with neurofibromatosis-1. *Am J Med Genet*. 1997;74(5):533-537.
14. Bernardo P, Cinalli G, Santoro C. Epilepsy in NF1: a systematic review of the literature. *Childs Nerv Syst*. 2020;36(10):2333-2350.
15. Iyer RR, Strahle JM, Groves ML. Neurosurgical considerations of neurocutaneous syndromes. *Neurosurg Clin N Am*. 2022;33(1):81-89.
16. Harter DH, Bassani L, Rodgers SD, et al. A management strategy for intraventricular subependymal giant cell astrocytomas in tuberous sclerosis complex. *J Neurosurg Pediatr*. 2014;13(1):21-28.
17. Desai VR, Jenson AV, Hoverson E, Desai RM, Boghani Z, Lee MR. Stereotactic laser ablation for subependymal giant cell astrocytomas: personal experience and review of the literature. *Childs Nerv Syst*. 2020;36(11):2685-2691.
18. Doddamani RS, Meena R, Sawarkar D, Singh PK, Chandra PS. Stereotactic guided ablation for subependymal giant cell astrocytomas: does it change the surgical indications? *Childs Nerv Syst*. 2021;37(3):735-736.
19. Doddamani RS, Meena R, Samala R, Agrawal M, Tripathi M, Chandra PS. Expanding the horizons of mTOR inhibitors for treating subependymal giant cell astrocytomas with obstructive hydrocephalus. *Pediatr Neurosurg*. 2021;56(1):102-104.
20. Kuzan-Fischer CM, Parker WE, Schwartz TH, Hoffman CE. Challenges of epilepsy surgery. *World Neurosurg*. 2020;139:762-774.
21. Hoffman CE, Parker WE, Rapoport BI, Zhao M, Ma H, Schwartz TH. Innovations in the neurosurgical management of epilepsy. *World Neurosurg*. 2020;139:775-788.

22. Treiber JM, Curry DJ, Weiner HL, Roth J. Epilepsy surgery in tuberous sclerosis complex (TSC): emerging techniques and redefinition of treatment goals. *Childs Nerv Syst*. 2020; 36(10):2519-2525.
23. Bianchi F, Auricchio AM, Battaglia DI, Chieffo DRP, Massimi L. Sturge-Weber syndrome: an update on the relevant issues for neurosurgeons. *Childs Nerv Syst*. 2020;36(10): 2553-2570.
24. Quinsey CS, Krause K, Baird LC, Sayama CM, Selden NR. Incidence of symptomatic tethered spinal cord in pediatric patients presenting with neurofibromatosis types 1 and 2. *J Neurosurg Pediatr*. 2018;21(5):456-459.
25. Payne JM, Haebich KM, MacKenzie R, et al. Cognition, ADHD symptoms, and functional impairment in children and adolescents with neurofibromatosis type 1. *J Atten Disord*. 2021;25(8):1177-1186.
26. De Sautu De Borbón EC, Guerra Vales JM, Lumbreras Bermejo C, et al. Clinical, genetic and quality-of-life study of a cohort of adult patients with tuberous sclerosis. *Orphanet J Rare Dis*. 2021;16(1):243.
27. Waltereit R, Beaure d'Augères G, Jancic J, et al. Involvement of mental health professionals in the treatment of tuberous sclerosis complex-associated neuropsychiatric disorders (TAND): results of a multinational European electronic survey. *Orphanet J Rare Dis*. 2021;16(1):216.
28. Bachour K, House AA, Andrade DM, et al. Adults with tuberous sclerosis complex: a distinct patient population. *Epilepsia*. 2022;63(3):663-671.
29. Adams RB, Dudley JT, Struessel TS. Physical therapy to address fall risk in an individual with neurofibromatosis. *Physiother Theory Pract*. Published online January 26, 2021. doi:10.1080/09593985.2021.1875523
30. de Blank PMK, Fisher MJ, Liu GT, et al. Optic pathway gliomas in neurofibromatosis type 1: an update: surveillance, treatment indications, and biomarkers of vision. *J Neuroophthalmol*. 2017;37(suppl 1):S23-S32.
31. Habiby R, Silverman B, Listernick R, Charrow J. Precocious puberty in children with neurofibromatosis type 1. *J Pediatr*. 1995;126(3):364-367.
32. Cnossen MH, Stam EN, Cooiman LC, et al. Endocrinologic disorders and optic pathway gliomas in children with neurofibromatosis type 1. *Pediatrics*. 1997;100(4):667-670.
33. Tolisano AM, Baumgart B, Whitson J, Kutz JW Jr. Cochlear implantation in patients with neurofibromatosis type 2. *Otol Neurotol*. 2019;40(4):e381-e385.
34. Emmanouil B, Houston R, May A, et al. Progression of hearing loss in neurofibromatosis type 2 according to genetic severity. *Laryngoscope*. 2019;129(4):974-980.
35. Harris F, Tysome JR, Donnelly N, et al. Cochlear implants in the management of hearing loss in Neurofibromatosis Type 2. *Cochlear Implants Int*. 2017;18(3):171-179.
36. Janssens de Varebeke S, Van de Heyning PH, Willems P, Koekelkoren E. Place of the otorhinolaryngologist in the multidisciplinary approach to neurofibromatosis. Article in Dutch. *Acta Otorhinolaryngol Belg*. 1992;46(4):411-420.
37. Van Lierde A, Menni F, Bedeschi MF, et al. Healthcare transition in patients with rare genetic disorders with and without developmental disability: neurofibromatosis 1 and Williams-Beuren syndrome. *Am J Med Genet A*. 2013;161A(7):1666-1674.
38. Bar C, Ghobeira R, Azzi R, et al. Experience of follow-up, quality of life, and transition from pediatric to adult healthcare of patients with tuberous sclerosis complex. *Epilepsy Behav*. 2019;96:23-27.
39. Peron A, Canevini MP, Ghelma F, Di Marco F, Vignoli A. Healthcare transition from childhood to adulthood in tuberous sclerosis complex. *Am J Med Genet C Semin Med Genet*. 2018;178(3):355-364.
40. Guzek LM, Gentry SD, Golomb MR. The estimated cost of "no-shows" in an academic pediatric neurology clinic. *Pediatr Neurol*. 2015;52(2):198-201.
41. Toledano-Alhadef H, Mautner VF, Gugel I, et al. Role, function and challenges of multidisciplinary centres for rare diseases exemplified for neurofibromatosis type 1 syndrome. *Childs Nerv Syst*. 2020;36(10):2279-2284.
42. Villegas MA, Okenfuss E, Savarirayan R, et al. Multidisciplinary care of neurosurgical patients with genetic syndromes. *Neurosurg Clin N Am*. 2022;33(1):7-15.
43. Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. *Genet Med*. 2021;23(8):1506-1513.
44. Sabeti S, Ball KL, Bhattacharya SK, et al. Consensus statement for the management and treatment of Sturge-Weber syndrome: neurology, neuroimaging, and ophthalmology recommendations. *Pediatr Neurol*. 2021;121:59-66.
45. Ahlawat S, Ly KI, Fayad LM, et al. Imaging evaluation of plexiform neurofibromas in neurofibromatosis type 1: a survey-based assessment. *Neurology*. 2021;97(7 Suppl 1): S111-S119.
46. Northrup H, Aronow ME, Bebin EM, et al. Updated international tuberous sclerosis complex diagnostic criteria and surveillance and management recommendations. *Pediatr Neurol*. 2021;123:50-66.
47. Pozetti M, Belsuzarri TAB, Belsuzarri NCB, Seixas NB, Araujo JFM. Neurofibromatosis type 1 and Chiari type 1 malformation: a case report and literature review of a rare association. *Surg Neurol Int*. 2016;7(Suppl 16):S469-S472.
48. Azizi AA, Walker DA, Liu JF, et al. NF1 optic pathway glioma: analyzing risk factors for visual outcome and indications to treat. *Neuro Oncol*. 2021;23(1):100-111.
49. De la Torre AJ, Luat AF, Juhász C, et al. A multidisciplinary consensus for clinical care and research needs for Sturge-Weber syndrome. *Pediatr Neurol*. 2018;84:11-20.
50. Mansfield Smith S, Makam R, Sullivan L, Sandford R, Allen L. Is ultra wide-field retinal imaging alone appropriate for retinal angioma screening in lower risk subjects attending Von Hippel-Lindau (VHL) clinics? *Ophthalmic Genet*. 2019; 40(5):403-406.
51. Créange A, Zeller J, Rostaing-Rigattieri S, et al. Neurological complications of neurofibromatosis type 1 in adulthood. *Brain*. 1999;122(Pt 3):473-481.
52. Richard S, Beigelman C, Gerber S, et al. Does hemangioblastoma exist outside von Hippel-Lindau disease? Article in French. *Neurochirurgie*. 1994;40(3):145-154.
53. Sauter M, Belousova E, Benedik MP, et al. Rare manifestations and malignancies in tuberous sclerosis complex: findings from the TuberOus SClerosis registry to increAse disease awareness (TOSCA). *Orphanet J Rare Dis*. 2021; 16(1):301.
54. de Vries PJ, Belousova E, Benedik MP, et al. Natural clusters of tuberous sclerosis complex (TSC)-associated neuropsychiatric disorders (TAND): new findings from the TOSCA TAND research project. *J Neurodev Disord*. 2020;12(1):24.
55. de Vries PJ, Belousova E, Benedik MP, et al. TSC-associated neuropsychiatric disorders (TAND): findings from the TOSCA natural history study. *Orphanet J Rare Dis*. 2018; 13(1):157.
56. Kingswood JC, Belousova E, Benedik MP, et al. Renal angiomyolipoma in patients with tuberous sclerosis complex: findings from the TuberOus SClerosis registry to increase disease Awareness. *Nephrol Dial Transplant*. 2019;34(3):502-508.
57. Lloyd SK, Evans DG. Neurofibromatosis type 2 service delivery in England. *Neurochirurgie*. 2018;64(5):375-380.
58. Raffalli-Ebezant H, George KJ, Burkitt-Wright E, et al. Neurosurgical contribution within a complex NF1 supraregional service. *Clin Neurol Neurosurg*. 2019;180:18-24.
59. Beckman E, Akbarnia BA. The Cardinal Glennon Children's

Hospital Neurofibromatosis Clinic model. *Neurofibromatosis*. 1988;1(3):134-136.
60. Obringer AC, Zackai EH, Meadows AT. The Neurofibromatosis Clinic of the Children's Hospital of Philadelphia. *Neurofibromatosis*. 1988;1(3):179-181.
61. Schorry EK, Stowens DW, Crawford AH, Stowens PA, Schwartz WR, Dignan PS. Summary of patient data from a multidisciplinary neurofibromatosis clinic. *Neurofibromatosis*. 1989;2(2):129-134.
62. North K. Neurofibromatosis type 1: review of the first 200 patients in an Australian clinic. *J Child Neurol*. 1993;8(4):395-402.
63. Ramanjam V, Adnams C, Ndondo A, Fieggen G, Fieggen K, Wilmshurst J. Clinical phenotype of South African children with neurofibromatosis 1. *J Child Neurol*. 2006;21(1):63-70.
64. Noble F, Kornberg AJ, Elder JE, Delatycki MB. Retrospective analysis of patients attending a neurofibromatosis type 1 clinic. *J Paediatr Child Health*. 2007;43(1-2):55-59.
65. Mansouri A, Ghadakzadeh S, Maqbool T, et al. Neurofibromatosis clinic: a report on patient demographics and evaluation of the clinic. *Can J Neurol Sci J Can Sci Neurol*. 2017;44(5):577-588.
66. Kokkinou E, Roka K, Alexopoulos A, et al. Development of a multidisciplinary clinic of neurofibromatosis type 1 and other neurocutaneous disorders in Greece. A 3-year experience. *Postgrad Med*. 2019;131(7):445-452.
67. Nishida Y, Ikuta K, Natsume A, et al. Establishment of in-hospital clinical network for patients with neurofibromatosis type 1 in Nagoya University Hospital. *Sci Rep*. 2021;11(1):11933.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this publication.

Author Contributions

Conception and design: Desai, Grossen, Chrusciel, McNall-Knapp, Taylor, Fossey, Brakefield, Carter, Schwartz, Gross, Jea. Acquisition of data: Grossen, Gavula, Chrusciel, Evans, Taylor, Fossey, Brakefield, Carter, Schwartz, Gross. Analysis and interpretation of data: Grossen, Evans. Drafting the article: Grossen, Chrusciel, Evans. Critically revising the article: Desai, Gavula, Chrusciel, McNall-Knapp, Taylor, Fossey, Brakefield, Carter, Schwartz, Gross, Jea. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Desai. Statistical analysis: Grossen. Administrative/technical/material support: Grossen, Gavula. Study supervision: Desai, Jea.

Correspondence

Virendra Desai: University of Oklahoma Health Sciences Center, Oklahoma City, OK. virendra-desai@ouhsc.edu.