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Comparing Congenital Melanocytic Nevus Treatment Effect on Children's Health-Related Quality of Life

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COMPARING CONGENITAL MELANOCYTIC NEVUS TREATMENT EFFECT

on CHILDREN'S HEALTH-RELATED QUALITY of LIFE

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Abstract

Surgical excision and laser are the two of the most commonly performed treatments for congenital melanocytic nevi, a type of birthmark present at birth or manifest infancy. Children with small to medium-sized congenital melanocytic nevi on the face and neck may elect treatment. However, there is no evidence-based guideline for the choice of treatment for small to medium-sized congenital melanocytic nevi that considers a child's quality of life. We propose a non-randomized, open-label trial to compare the functional effect of surgical excision and laser treatment on the holistic wellbeing of school-aged children with head and neck congenital melanocytic nevi of ≤10 cm. We will also use the Children's Dermatology Life Quality Index to evaluate pre- and post-procedural health-related quality of life. This proposed study is the first to compare the two common treatments for congenital melanocytic nevi, which will contribute to the evidence-based guidance for clinical practice.

Chapter 1 Introduction

1.1 Background

Congenital melanocytic nevi (CMN) are benign proliferations of neural crest melanocytes present at birth or manifest within the first few weeks of life.[119] A recently developed consensus-based standardized categorization scheme categorizes CMN into the following groups: small (<1.5 cm), medium (1.5-20 cm), large (>20-40 cm), and giant (>40 cm).[70] Medium CMN is further categorized into two subgroups: M1(1.5-10 cm) and M2 (≤10 -20 cm). Treatments used for CMN include surgical excision, dermatome shaving, curettage, dermabrasion, chemical peels, cryotherapy, electrosurgery, radiation therapy, and different laser treatment modalities.[54] However, to the best knowledge of the author, there is no current evidence-based guideline for the choice of treatment method for CMN. Treatment choices usually depend on the expertise and experience of the managing dermatologists and plastic surgeons, taking into consideration lesion size, location, and morphology; and ease of monitoring, cosmetic concerns, functional issues and anxiety of patients and their families.[58,87,101,109]

Empirically, surgical excision is recommended as the first-line treatment for CMN when treatment is indicated, since it theoretically reduces the risk of melanoma by complete or partial removal of the nevomelanocytes.[22,88,127] However, Arad and Zuker found no evidence that surgical treatment reduces melanoma risk in a recent literature review.[8] Mann proposed that melanoma may still occur after surgical excision due to the existence of melanocytes in subcutaneous fat, fascia and muscle.[84] Other studies found that a significant number of malignant melanoma arise outside the CMN and even the

skin.[63,66] Excision of the CMN will not reduce the risk of extracutaneous melanoma or neurocutaneous melanosis.[54,63]

Cosmetic outcome of surgery varies significantly across studies; surgical excision of small to medium-sized CMN usually result in better cosmetic outcome compared to large to giant CMN.[54,71,109] A large prospective study has shown that even though not all the cosmetic results were satisfactory, families of children with small to medium-sized CMN generally found the surgical excision overall worthwhile.[65] This was especially true for nevi on the head or neck; 95-96% families of the children with CMN on the head or neck deemed the surgical excision overall worthwhile. However, a follow-up study on the same population has shown that partial excision appeared to associate with less natural lightening of the original nevi and more development of new nevi over the years.[63] It is proposed that surgical interventions activate melanocytes, even though this phenomenon has not been confirmed by other studies. In addition, serial excision and tissue expansion before surgical procedures are frequently required for CMN >5cm, which could be a process for months and may contribute to reduced quality of life in school-aged children due to multiple operations, frequent clinical visits, and the cosmetic deformity and discomfort during the expansion process.[100] General risks of surgical interventions, including the risk of general anesthesia infection, bleeding, and post-operative impairment of functions, should also be factored in the general well-being of the children.[11,88] Post-surgical scars can be disfiguring and even affect function.[54] In some cases, there is also increased risk of distortion to adjacent structures.[100]

Laser is another commonly used treatment method for CMN, usually serves as an option when surgical excision is not feasible.[58,109] Laser treatment, usually if not always,

requires multiple sessions over months.[54,88] Post-operative darkening, crusting, blistering of the nevi are common and may temporarily worsen the cosmetic appearance.[9] Laser treatment often does not remove all nevomelanocytes, especially those in the deeper layer of the skin. Repigmentation after the procedure is common.[69,121] Therefore, laser treatment is not a definitive treatment and the treated CMN will require life-long follow up.[24] Woodrow and Burrows reported a case of malignant melanoma occurring at the periphery of a giant CMN previously treated with laser treatment.[132] They voiced the concern for the potential malignant conversion of CMN induced by the laser treatment, even though giant CMN was known to associate with heightened risk of melanoma.[128] Some case series reported malignant melanoma occurrence after laser treatment, but none was originated from a CMN. In fact, multiple studies have looked at the long-term effect of laser treatment on CMN and found no other documented malignant changes induced by laser, even though the quality of evidence was low.[38,46,56] Pseudomelanoma, a proliferative response to either laser or surgical excision was reported.[53,72,120] However, it is decided to be a benign process and represents recurrence of CMN. It is safe to say that the effectiveness and safety of laser treatment is not thoroughly understood, which limits its utilization.

Although laser treatment has a few drawbacks, it offers some unique advantages. Compared to surgical excision, laser treatment is less invasive and more selective. Post-procedure scaring may be minimized compared to surgical excision.[9,54,121] In older children and adults, laser treatment often requires only local anesthesia, which reduces potential anesthesia-related adverse events and side effects. Compared to surgical excision, laser treatment causes less irreversible changes to the skin. Patients with

unsatisfied laser treatment outcome can subsequently elect for surgical excision if appropriate. These may explain the finding in a recent study that for elective treatment to improve cosmetic outcome, most CMN patients (24/28) preferred laser treatment over surgery.[10]

Laser modalities that are commonly used in CMN treatment include ablative lasers and pigment-specific lasers. Ablative lasers target water molecules and nonspecifically vaporize tissue, which may lead to more scaring theoretically.[9] Pulse duration decides the amount of heat transmitted to the surrounding tissue; the longer the pulse duration, the high the chance of surrounding tissue injury and scar formation.[117] However, data have shown that scarring complication was more often seen in patients with large to giant CMN.[38] Pigment-specific lasers have specific wave lengths that fall in the absorption range of melanin. It targets nevus cells with selective photothermolysis and theoretically cause less scaring.[9] In a recent systemic review, Eggen and colleagues reported that combined ablative and Q-switched pigment-specific laser treatment achieves the best clearing of hyperpigmentation on both long and short term, with over 90% patients reported good to excellent clearing, although the quality of the evidence was low.[38] However, this study did not differentiate the types of ablative and pigment-specific lasers. Theoretically, the ablative laser removes the epidermal nevus cells and facilitates the penetration of the pigment-specific laser by exposing the deep-seated nevomelanocytes.[10,73,98] Two studies have reported that the addition of ablative laser to pigment-specific laser reduced the number of treatment sessions and shortens the therapeutic period needed for clearance of CMN.[10,98] Data have shown that scarring was negligible with the use of pigment-specific lasers, since pigment-specific lasers targeted

melanocytes and caused little damage to the surround tissue.[38] This suggests that the addition of pigment-specific laser to ablative laser may reduce scarring complication.

CO_2 laser is a type of ablative lasers. Q-switched Alexandrite laser (QSAL) is a type of pigment-specific laser. Both have been tested on CMN alone with good results. The combined CO_2 and QSAL is a new modality of combined laser treatment that has been tested on CMN with fair results in the recent years. Three studies reported a total of 41 patients who underwent combined CO_2 and QSAL treatment (Table 1).[10,34,62] Of note, these three studies are all case series, offering limited strength of evidence to support the effect of laser treatment on CMN.

Table 1. Summary of studies that report combined CO_2 laser and Q-switched Alexandrite laser treatment modality for congenital melanocytic nevus

Author	N	Mean age (range)	CMN size	CMN location	Laser modality	Mean number of treatments (range)	Result	Complication
August	14	18 (9–43) *	All medium Mean 5.45 cm (range 2–19 cm) *	Head/neck (n = 27) Trunk (n = 6) Extremities (n = 22) *	CO_2 (silk touch mode, 12–37W, spot size = 4–7 mm, multiple passes) QSAL (wavelength = 755nm, fluence = 6–10 J/cm^2, spot size = 2–3 mm) At 3-monthly interval	4.25	Excellent, >75% lightening (n = 7, 50%) Good, 50–75% lightening (n = 4, 29%)	Adverse effects (n = 2, 14%) Repigmentation (n = 1, 7%)
Chong	11	10.6 (3–21)	Small (n = 7) Medium (n = 4) Mean 2.13 cm (range 0.3–9 cm)	Face (n = 7) Extremities (n = 4)	CO_2 (pulse duration = 1 ms, fluence = 300 mJ/cm^2, 1–2 passes) QSAL (wavelength = 755nm, pulse duration = 60 ns, fluence = 6–7 J/cm^2, spot size = 5mm) At 6-week interval	3.9 (2–9)	Excellent, 79–95% lightening (n = 9, 81.8%) Good, 51–75% lightening (n = 2, 18.2%)	Hypertrophic scar (n = 3, 27.3%) Hyperpigmentation (n = 1, 9.1%)
Kim	16	8.9 (3 months-45 years)	Small (n = 5) Medium (n = 9) Giant (n = 1) The rest unknown	Face (n = 43) Trunk (n = 5) Extremities (n = 5)	CO_2 (super-pulsed mode, 2W) QSAL (wavelength = 755nm, pulse duration = 100ns, fluence = 8.0 J/cm^2, spot size = 3mm)	2.5 (1–4)	Excellent, >80% lightening (n = 14, 26.4%) Good, 61–80% lightening (n = 16, 30.2%) Moderate, 41–60% lightening (n = 14, 26.4%) Minimal, 21–40% lightening (n = 7, 13.2%) None, 0–20% lightening (n = 2, 3.8%) ¶	Texture change (n = 35, 66%) Depressed scar formation (n = 2, 3.8%) Hypertrophic scars (n = 4, 7.5%) Hypopigmentation (n = 17, 32.1%) Hyperpigmentation (n = 15, 28.3%) Repigmentation (n = 44, 83%) Absence of complication (n = 6, 11%) ¶

QSAL: Q-switched Alexandrite laser

CMN: congenital melanocytic nevi

N: sample size

* Data includes other treatment groups

¶ In this study, 37 participants were treated with QSAL alone, result is for CO_2+QSAL and QSAL alone

Melanoma prevention is a primary reason for children with CMN on head and neck and their families elect for treatment, primarily surgical excision.[39,121] The risk of malignant change of CMN appears proportional to the size of the lesion; the risk of melanoma arising from small and medium-sized CMN is less than 1% over a lifetime.[101,109] The low risk of malignant changes along with the new evidence aforementioned, that surgical excision may not reduce melanoma risk, may change the rationale of the treatment choices for CMN in children.

Another primary reason for elective treatment for CMN is to diminish disfigurement associated with CMN.[39] One underlying goal for appearance correction with elective treatment is to improve the children's psychosocial wellbeing.[112] However, traditional outcome measures, including cosmetic outcome, do not capture the full range of the impact of CMN and the interventions on the children.[67] Health-related quality of life (HRQOL) is a progressively recognized measure to assess the broader effect of the health and psychosocial wellbeing of the children. In a recent case series, two out of four patients with mild CMN recurrence on nasal ala treated with laser were content to leave the recurrence as it was.[135] This suggests that contrary to popular belief, the improvement of quality of life may not rely on the complete removal of the CMN. Managing and lightening the exposed CMN lesions with periodic laser therapies, instead of definite surgical excision, may lead to equal or possibly better outcome in quality of life.

1.2 Statement of the Problem

About 14% of CMN present on the head and neck.[89] CMN on head and neck are highly visible and aesthetically important. Studies have shown that head and neck CMN

was associated with significant psychological sequelae.[15,116] School-aged children with head and neck CMN are at higher risk of negative psychosocial experience. Previous studies have shown that school-aged children with head and neck CMN reported reduced HRQOL and increased perceived stigmatization, compared to younger children.[90,91] Many factors may contribute to this phenomenon. Firstly, appearance-related teasing is a common phenomenon in school. Adolescent with facial difference reported more perceived teasing than their peer without facial difference.[41] In addition, school-aged children spend more time outside their familiar environment compared to younger children and are exposed to the reactions of strangers. Finally, school-aged children may be more aware of their condition compared to their younger counterpart.[90]

School-aged children with head and neck CMN and their families may decide on elective procedures to improve the children's cosmetic outcome and their quality of life. However, the effect of medical procedures on quality of life is not totally benign. Besides the risk of treatment failure and complication, treatment may have additional negative psychosocial effect on children with CMN. Some believe a scar is more socially acceptable than a congenital lesion.[68] Krengel and Marghoob summarized that three out of four older children and adolescents preferred a surgical scar over the original nevus.[69] However, Patrick and colleagues discovered that adolescents with acquired facial lesions, such as burns, were more likely to report negative self-image and negative emotions than adolescents with congenital facial lesions, including facial CMN.[99] Strauss and colleagues also reported that adolescents with acquired facial lesions experienced more staring from others, compared to those with congenital facial lesions.[116] This suggests that scar-generating treatments may have a negative psychological impact on the

children, compared to no treatment. The true psychological effect of scar-generating procedures to remove existing head and neck CMN is unclear, and likely depends on the size and quality of both the original nevi and the scars. In addition, the process of treatment itself may affect children's psychologic health. Small children dislike being restrained and older children become fearful and anxious due to the anticipation of pain associated with the procedures.[112] The anticipation of medical procedures with the use of anesthesia may also generate anxiety in the children and their families. A recent study by Wramp and colleagues investigated the effect of the evolution of the nevi and prior treatment experience on the quality of life in children with CMN aged 4-16.[39] However, it is difficult to isolate the effect of the treatment from the effect of the nevi since there was no comparison before and after the treatment.

1.3 Goals

To navigate the clinical decision on choosing elective treatment for head and neck CMN of ≤10 cm in school-aged children, this study aims to compare the functional effects of surgical excision and laser treatment on HRQOL in this population. Among school-aged children with head and neck CMN of ≤10 cm, we hypothesize that compared to the surgical group, there will be a statistically significantly greater improvement of HRQOL in the laser group, measured as the mean change of the Children's Dermatology Life Quality Index, before and after the procedures in six months.

We focus on small to M1 CMN (≤10 cm) because the majority of CMN are less than 3 to 4 cm; larger CMN are substantially rarer.[6] The size of the CMN appears to correlate with the depth of nevomelanocytes; small to medium-sized CMN usually

present clinically and histologically similar.[14] Although one may think that small CMN have minimal effect on children's HRQOL, if the children and their families are concerned enough to elect for cosmetic procedures, the nevi and treatment choice likely will have an impact on children's HRQOL. Other categories of CMN will not be included, such as M2, large and giant CMN (>10 cm) and multiple small to medium-sized CMN.[70] These lesions are likely to have a heightened malignant risk profile.[6] In addition, due to the increased body surface area these larger CMN cover, their treatment generally requires special considerations and is a greater management challenge.[8]

We will exclude CMN on the scalp and the posterior neck, because CMN on these locations may be covered by hair and are less visible. We will also exclude periorbital and periauricular CMN. CMN on these anatomical significant locations requires special treatment considerations to preserve organ function and improve cosmetic outcome, which has been described by many.[16,20,33,37,52,57,78,83,133,134] Most head and neck CMN are on the front rather than on the back of head and neck.[64] Periorbital and periauricular CMN are also very rare.[37,136]

We will exclude CMN with empirically suspicious or concerning features that warrant excision. These clinically suspicious features are well delineated in the literature.[88,109] Other variants of congenital or acquired melanocytic disorders are also excluded, such as nevi spilus, dysplastic nevi, blue nevi, Spitz nevi, café-au-lait macules and patches, Mongolian spots, nevi of Ito, nevi of Ota, acquired melanocytic nevi and lentigines.

1.4 Objectives

This study is the first to compare the psychological effect of two major treatment choices for head and neck CMN, surgical excision and laser treatment. Instead of the cosmetic outcome of the treatments, this study will focus on the general psychological wellbeing of school-aged children, which can be a product of the cosmetic outcomes and the children's and their families' perception and tolerance of the treatments. The study result will provide a data-driven patient-centered guidance for the treatment choice of small to M1 CMN on head and neck in school-aged children.

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Chapter 2 Literature Review

2.1 Health-Related Quality of Life and its Assessment

The definition of health-related quality of life (HRQOL) has continued to evolve since its introduction in 1970s. At least four definitions were reported in the literature.[61] The Centers for Disease Control and Prevention defines HRQOL as a broad concept that "encompass those aspects of overall quality of life that can be clearly shown to affect health—either physical or mental, which includes physical and mental health perceptions (e.g., energy level, mood) and their correlates—including health risks and conditions, functional status, social support, and socioeconomic status."[29]

Dermatological diseases often have a strong psychosocial and functional impact on the patients,[2,43,122] and children are particularly vulnerable to the negative psychosocial impact caused by dermatological diseases.[17,68,86,91,129] HRQOL synthesizes objective functional status and subjective perception of wellbeing in physical, mental, and social domains and focuses on their impacts on the perceptions of life satisfaction and quality,[94] therefore it is an all-inclusive measure to inform the degree of impairment, the need for treatments, and the effectiveness of interventions in pediatric patients with dermatological diseases.[26,42,129] The European Academy of Dermatology and Venereology Task Force summarized a wide range of potential benefits of measuring HRQOL in dermatological practice, including to inform clinical decisions, promote clinician-patient communication, promote awareness of skin disease burden, inform consultation, and clinical service administration.[44] For these benefits, life quality measures have rapidly gained interest in pediatric dermatology in recent years.[44,47] As interest in HRQOL grew, an increased number of valid and reproducible HRQOL

instruments were developed in an attempt to better capture HRQOL specific to pediatric patients with dermatological conditions.[26,30,31,40,60,76,77,114]

Children's Dermatology Life Quality Index (CDLQI) is a standardized instrument to assess HRQOL among pediatric dermatological patients.[76] Developed in 1995 by Lewis-Jones and Finlay, it was based on the result of an open-ended questionnaire among children aged 3–16 years attending a pediatric dermatology clinic. The questionnaire identified 111 different aspects of life affected by the children's dermatological conditions, which were sorted into different topics. From these topics the most identified aspects were elected to form the ten questions that constitute the CDLQI. These ten questions focus on children's perception of the impact of their skin conditions on different aspects of their HRQOL in the past week, covering symptoms, emotions, friendship, clothes, social activities, physical activities, school work, perception of stigmatization, sleep, and treatment. Each question is scored on a four-point Likert scale to represent the impact of the skin condition on the children's everyday life, with 0 being the least and 3 being the most impact. Children can achieve a CDLQI score of a minimum of 0 and a maximum of 30. Higher scores represent greater impairment of the children's HRQOL.

CDLQI is the first dermatology-specific quality of life measure specifically for children with skin disease, and was developed to parallel the Dermatology Life Quality Index (DLQI), the first dermatology-specific quality of life measure designed for adults.[76] CDLQI was validated among children aged 4–16 years with dermatological conditions, including congenital melanocytic nevus (CMN). CDLQI is widely used and available in more than 50 languages.[27,35,59,103,131] It was also expanded to include a cartoon version for

young patients.[50] However, a significant drawback of CDLQI is that its self-reported nature does not allow for the measurement of objective functional status, even though it assesses self-reported functions. Some recent comments advocate that only perceived wellbeing, not functional assessment, should be used to determine quality of life because quality of life is inherently subjective.[94] The lack of objective measures may be justified that the degree of impairment and the need for intervention will be perceived by the children and not by their doctors.

Although CDLQI is a widely-used measure for patients with many pediatric dermatological diseases, its use in CMN research is limited. To our knowledge, only six studies have reported CDLQI scores among children with moles or nevi. The older terms moles and nevi are used in the past to refer to abnormal skin with increased melanocytes, which include CMN and other lesions with similar appearances.[130] In the initial validation of CDLQI, Lewis-Jones and Finlay included 29 children with moles and reported CDLQI (SD) = 2.3 (2.9) in this sample.[76] In the validation of the Cantonese version of CDLQI, Chuh reported CDLQI (SD) = 2.33 (2.08) in three children with moles and nevi.[35] Beattie and colleagues look at CDLQI among 56 children aged 5-15 years with nevi, and reported CDLQI (SD) = 1.46 (3.04).[17] In a study of the impact of cosmetic camouflage, Salsberg and colleagues reported CDLQI (SD) = 6.82 (1.28) in 22 children with various dermatological diseases; only one child had CMN.[106] Another cosmetic camouflage study reported mean CDLQI = 5 among four children with nevi, without reporting SD.[102] The most recent study reporting CDLQI scores among children with congenital nevi is by Wramp et al.; however, the reported data was aggregate and the mean was not reported.[39]

Besides the HRQOL measures in CDLQI, a few studies have focused on other significant predictors of HRQOL among children. Older age, female sex, and lower family socioeconomic status were found to be predictors of lower HRQOL among children and adolescents.[48,85,97] A recent study in Netherland showed that the most significant determinants of HRQOL among general children aged 4-11 were the use of healthcare (including office visit, hospitalization, and medication) and the number of physical and mental disorders or complaints.[51] A Dutch study also showed that chronic physical or mental conditions associate with lower HRQOL among school aged children.[12]

2.2 Surgical Interventions and Laser Treatments Affect HRQOL

Previously, few studies have looked at the relationship between treatment options and quality of life among children with head and neck CMN. The comparison of laser treatment and traditional surgery in other craniofacial disease entities may provide some insights for the treatment choices for head and neck CMN. A study compared postoperative HRQOL and pain among patients who underwent oral soft tissue surgery with either laser or cold blade.[45] The result showed that laser group had significantly better HRQOL and lower postoperative pain compared with the surgery group. Another study also revealed better postoperative comfort for frenectomy patients with laser treatment compared to surgery.[3] The advantage of laser treatment may be associated with the precise control of the depth and diameter of thermal injury. Compared to traditional surgeries, laser treatment induces less bleeding, minimal damage to the surrounding tissue, and reduced immediate postoperative pain due to nerve endings sealing by laser

irradiation.[3] However, these advantages of laser treatment over surgical excision has not yet been tested among children with CMN.

Among dermatological diseases, laser treatment was shown to improve HRQOL among patients with vitiligo[4,107,137], port-wine stain[110,113], atopic dermatitis[13], rosacea[118], and acne scars[126]. Laser treatment also reduced DLQI scores within one to two months postoperatively among women with facial hirsutism.[82] However, long-term quality of life improvement was not found in this study. The short-term only quality of life improvement was likely associated with a high rate of reappearance of facial hirsutism. It may also imply that laser treatment has little immediate negative impact on patient's quality of life, even given its potential side effects. Indeed, even though reappearance was very common, many patients were satisfied and willing to undergo further treatment. The quality of life improvement effect of laser treatment among women with facial hirsutism was replicated by a later study.[92]

The immediate side effects of laser treatment were described in a prospective cohort study focusing on the effect of pulsed dye laser on port-wine stain.[81] Tightness, soreness, and burning are common early post-operative complaints. Symptoms were resolved on the day of treatment in most patients. But in some the symptoms lasted a maximum of 3 days. Post-operative swelling, weeping, crusting, and bruising were also reported. These skin changes that may temporarily worsen the cosmetic appearance lasted up to 36 days. Post-operative purpura and hyperpigmentation were also reported among patients with atopic dermatitis treated with lasers.[13]

An ongoing Swiss prospective cohort study (ClinicalTrials.gov Identifier: NCT02280889) seeks to understand how surgical excision of CMN affects children's

quality of life. However, this study is in the recruitment phase and interim analysis is not yet available.[123] The results from a systematic review suggested that facial cosmetic surgeries improve self-esteem and quality of life.[55] However, the systematic review did not include cosmetic surgery for CMN or other skin diseases. Facial cosmetic surgeries reported to improve patients' HRQOL include rhinoplasty,[32,36,80,105,108,111] otoplasty,[19,23,93,115] facial palsies reconstruction,[21,49,79] and orthodontic surgery.[7]

Many factors may affect the HRQOL changes after facial cosmetic surgery. A prospective cohort study showed that the age of the patient, preoperative expectations, and the origin of the decision for surgery (particularly in adolescents) significantly affect post-operative psychosocial improvement.[74] Sex may also confound the relationship between facial cosmetic surgery and HRQOL. Nicodemo and colleagues found that females have improved self-esteem and decreased depressive symptoms after orthognathic surgery, while males show no changes with surgery.[95]

CMN is unique compared to other craniofacial defects, and CMN patients may have unique responses to surgical excision. Most facial cosmetic surgeries improve not only the cosmetic and psychosocial outcomes, but also physical functions. Though the skin of the nevus is often dry and prone to irritation and itching, CMN alone usually does not affect physical functions. Therefore, CMN patients may have less postoperative HRQOL improvement. Vivar and Kruse speculated that surgical excision may have little effect on self-esteem among children with CMN because the cosmetic outcome from surgical excision varies and is sometimes undesirable.[125] Antoun and colleagues found that orthodontic surgery significantly improves physical pain, psychological discomfort, and psychological disability among malocclusion adolescents, but not among adolescents

with cleft lip and/or palate.[7] It is believed that the prolonged management of a cleft lip and/or palate, the dissatisfaction with upper lip and nose after surgery, and the need for further surgery contribute to the less improvement of HRQOL among adolescents with cleft lip and/or palate. This implies that the response to surgical excision may also vary among CMN patients because the number of surgeries and the cosmetic outcome greatly depend on the location and morphology of the nevus.

HRQOL improvement is more likely to be seen in 6 months than in 2 months after facial cosmetic surgeries, likely due to the immediate postoperative skin changes such as the healing wound, erythema, residual edema and bruising.[55] There are also postoperative problems and complication associated with surgical excision of CMN, such as dressing changes, immobilization, failure to remove the entire lesion, impaired wound healing, dehiscence, and scar formation.[39,54]

Surgery and laser treatment are inherently different procedures with different mechanisms. Both interventions are shown to improve HRQOL among patients with other diseases; for some diseases, laser treatment seems to result in more HRQOL improvement than surgery. As treatment options for CMN, surgical excision and laser treatment may affect the patient's HRQOL in different ways. Compared to surgery, laser treatment is associated with less postoperative pain and faster healing. While temporary postoperative skin changes from laser treatment rarely last for more than one month, skin changes from surgery may last for more than two months. Postoperative skin changes including scarring may also be less prominent in laser patients since laser treatment tends to be less traumatic and invasive. As facial scaring has a negative social, emotional and functional impact on the patient,[25,75] this choice of treatment may subsequently affect the

patient's quality of life. Besides the immediate effects of the treatment, the potential differences between surgery and laser treatment that are clinically relevant include the cosmetic outcome, complications, negative emotion and stigmatization associated with the treatment, the time and the cost required by the treatment, and the number of clinical visits.[18] As discussed in Chapter 1, the cosmetic outcome, complications and psychosocial response greatly vary among the two interventions. Laser treatment tends to require more clinical visits, and studies have shown that number of clinical visits is negatively associated with children's HRQOL.[51] Without existing studies comparing the two treatments and detailing how they affect HRQOL, the need for examining the different effect of surgery and laser treatment among school-aged children with head and neck CMN is significant.

2.3 References

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Chapter 3 Study methods

3.1 Study Design

This international, multicenter, non-randomized, open-label clinical trial will recruit school-aged children (6-14 years) with congenital melanocytic nevus (CMN) of ≤10 cm on head and neck who elect for cosmetic treatment. The study will be conducted by a consortium of clinical and research centers in the United States, Canada, Mexico, Europe and the Middle East. Physician and other healthcare professional members of the Pediatric Dermatology Research Alliance (PeDRA) will be invited to participate in this collaborative study. Protocol for this study will be submitted for review by the PeDRA Birthmarks group and the Institutional Review Board at each participating center.

3.2 Study Population and Recruitment

Eligible children will be referred to the study from their pediatricians, dermatologists, and/or plastic surgeons. We expect to enroll 128 children, with 64 children in the surgical and laser group, respectively.

3.2.1 Inclusion Criteria

Patients must meet all following criteria to be enrolled in the study:

1. Male or female who are 6-14 years of age at the time of screening.
2. Patients must have a clinically documented diagnosis of single CMN on the head and neck which was present at birth or before the first birthday.[1]
3. The CMN is ≤10 cm at largest diameter.

4. The CMN is completely or partially above the jugular notch, or completely or partially exposed when patient wears a crew-neck T-shirt.
5. Patients must not have any previous surgical or dermatological treatment for CMN, including surgical excision, laser treatment, dermabrasion, curettage, and chemical peel.
6. Patients must be currently enrolled in a primary school or middle school as full-time students, who present to school five days per week during school terms.
7. Patients and their caregivers must express a desire to improve cosmetic outcome via medical procedures.
8. Patients and their caregivers must be able to provide concordant informed consent or assent.
9. Patients must have public or private health insurance coverage.

3.2.2 Exclusion Criteria

Patients who meet the following criteria will be excluded from the study:

1. Patients have CMN >10 cm or more than one small to medium-sized CMN on head and neck.
2. Patients have CMN with spontaneous regression.
3. The CMN has empirically suspicious or concerning features that may warrant excision,[109] or the managing clinicians have medical concerns other than cosmetic consideration, such as malignant changes and post-procedural function loss.
4. Patients have evidence or documented diagnosis of melanoma or symptomatic/complicated neurocutaneous melanosis.

5. Patients have Fitzpatrick skin type V or VI. As Alexandrite laser has been proven to be less safe in Fitzpatrick skin type VI.[5]
6. Patients are unable to understand and follow instructions and complete the questionnaires with the help of an adult.
7. Patients have a history of psychiatric or psychological disorders that could have an impact on either the interventions and the study outcomes. Examples include, but not limited to, body dysmorphic disorder and autism spectrum disorder.
8. Patients have contraindications for surgery or laser treatment, including but not limited to coagulation disorders, immunodeficiency disorders, active infections, and photosensitivity disorders.
9. Patients have any condition that, in the opinion of the investigators, may compromise the patient's safety or compliance, preclude successful conduct of the study or interfere with interpretation of the results.

3.3 Subject Protection and Confidentiality

Patients and their legal guardians will be counselled regarding the risks, benefits and, alternatives of surgical excision and laser treatment. Written informed consent will be obtained prior to all procedures. All patients have the right to exit the study any time. All adverse events will be reported. In case of severe adverse events, the principle investigators and the physicians who perform the interventions will jointly decide whether to withdraw the patient from the study in a case-by-case basis.

Patients and their legal guardians will be informed of the purpose of the study and assured of the confidentiality of the data. Research materials will be stored in locked

cabinets and shredded before discarding. Digital data will be stored and analyzed only on properly encrypted devices. All personal identifiable information will be deidentified prior to analysis to ensure confidentiality. Only the study investigators and their affiliated institutes will have access to the data set. Individual study participation will be entered into the patient's Electronic Medical Record (EMR). Once placed in the patients' EMR, these results are accessible to all providers who participate in the EMR system. Information within the EMR may also be shared with others who are appropriate to have access to the patient's EMR (e.g. health insurance company, disability provider).

3.4 Interventions

After obtaining written informed consent at initial visit, pre-treatment CMN lesions will be measured and photographed. Eligible children and their families will be offered two treatment options, surgical excision and laser treatment. All procedures will be performed under general anesthesia. Children in the laser treatment group will have the option to undergo surgical excision one year after the last laser treatment session, if the children and the families elect to.

3.4.1 Surgical Excision

Patients in the surgical group will undergo one to two scheduled surgeries performed by plastic surgeons specialized in craniofacial reconstruction. The performing surgeon will independently evaluate the CMN and choose the surgical techniques suitable for the lesions. Techniques that are commonly used by craniofacial plastic surgeons for

CMN removal includes, but not limited to, excision with primary closure, serial excision, excision with flap reconstruction, and excision with skin graft.

3.4.2 Laser Treatment

Patients in the laser group will undergo a combined laser treatment modality that include carbon dioxide (CO_2) laser and Q-switched Alexandrite laser, at six-week intervals for maximal six sessions. If optimal result is obtained before six sessions, the patient should return for each follow-up visit, but may choose to skip one or more sessions. Laser treatments will be performed by clinicians trained in laser treatments. During laser treatment session, the CMN will be first treated with a single pass or multiple passes of the CO_2 laser with a pulse duration of one millisecond and a fluence of 300 mJ/cm^2. During ablation, carbonized tissue on the skin surface will be wiped off with a gauze soaked in normal saline. After the epidermis peels off, a further treatment will be followed with the single-pass Q-switched Alexandrite laser, with a pulse duration of 60 nanoseconds, a fluence of 8 J/cm^2, a spot size of 3mm^2.

3.5 Outcome and Covariates

3.5.1 Primary Outcome

The primary outcome is the change of health-related quality of life (HRQOL) before and six months after the last intervention, which will be assessed with the Children's Dermatology Life Quality Index (CDLQI) questionnaire. A brief review of CDLQI is included in Chapter 2.

3.5.2 Secondary Outcomes

The secondary outcomes are the changes of HRQOL one week and one month after each intervention. These secondary outcomes will also be measured by CDLQI.

3.5.3 Other Covariates

3.5.3.1 Sociodemographic Variables

Patients' age, sex, race, ethnicity, and household annual income per family member will be recorded in the initial study. Race includes Caucasian/White, African American/Black, Asian and Pacific Islander. Ethnicity includes Hispanic/Latino and non-Hispanic/non-Latino.

3.5.3.2 Other Dermatological Variables

CMN morphologies (size, color, hair-bearing, flat or raised) and CMN locations (forehead, nose, cheeks, chin/jaw, and neck) will be described by the assessing dermatologists in the initial visit prior to any interventions. Post-procedural site color, size, healing status, repigmentation, and complications (pain, infection, hypertrophic scarring) will be assessed in each follow-up visit.

Patients' native skin color will be classified with Fitzpatrick skin phototype scale in the initial visit by the assessing dermatologists.[104]

3.5.3.3 Other Health-Related Burdens

To estimate other health-related burdens, we will also record other physical or mental comorbidities, annual healthcare visit frequency, number of healthcare visits last year, number of hospitalizations last year, current number of medications taken, maximal number of medication taken last year. Other physical or mental comorbidities will be listed out. To ascertain annual healthcare visit frequency, patients will be asked to choose from one of the four categories: never, sometimes, often, always.

3.6 Data Collection and Statistical Considerations

3.6.1 Data Collection

Data will be collected via CDLQI questionnaires, sociodemographic surveys, physician's notes and digital photographs. A baseline CDLQI questionnaire will be administered at the initial visit, before any intervention. Patients should complete the CDLQI questionnaires independently; caregivers may clarify the wording of the questions but should not answer the questions for the patients. Sociodemographic data and covariates will also be collected at the initial visit in a written survey; caregivers may answer this survey with the patients. Post-procedure CDLQI questionnaire will be administered at one week and one month after each procedure, and six months after the last procedure. This will allow us to investigate both the short term and long term effect of the treatment. CMN and post-procedural site characteristics will be abstracted from physician's notes in each visit. Clinical photographs of CMN will be taken at all visits under similar digital camera settings.

3.6.2 Sample Size Calculation

In the existing literature, reported CDLQI scores among children with CMN range from 2.30 to 6.82, with the standard deviation (SD) ranges from 2.08 to 3.04.[17,35,76,102,106] As mentioned previously in Chapter 2, the reported data do not differentiate CMN with other lesions with similar morphologies, which may cause the SD of CDLQI scores in the samples to be overestimated. However, to be even more conservative, we assume a SD for CDLQI score among children with CMN to be 4. We also assume a mean difference of CDLQI scores in the laser group is 2 points higher than in the surgery group, because half a SD has been shown to be the smallest detectable difference for changes in HRQOL for chronic diseases.[96] With a SD of 4 and a mean difference of 2, we will need to study 64 children in each group (128 children in total) to be able to reject the null hypothesis that the population means of the surgery and laser groups are not significantly different with the power of 80% and the Type I error probability 0.05.

No previous study has reported attrition data in this population. We expect low attrition due to the nature of the elective cosmetic procedures. Children and their families are expected to be highly motivated, especially when they are concerned enough to request consultation for nevus removal. In addition, prior to each visit, researchers will utilize phone calls and email messages to remind patients and families.

3.6.3 Data Analysis

Descriptive statistics will be used to summarize patient demographic and CMN characteristics. Student's t test will be used to compare the distribution of the primary and secondary outcomes in the surgical group and the laser group. Multiple linear regression model will be used to control for confounding. We will report 2-sided p-value. A p-value of < 0.05 is considered statistically significant.

3.7 Timeline

The study consists of two logistic phases: Phase 1 is recruitment and data collection and Phase 2 is data analysis. Phase 1 is planned to complete in two years (Figure 1). The first six months is subject recruitment. Surgeries and laser treatments can start as soon as patients qualify and consent for the study. The last intervention procedure of any patient should conclude six months prior to the end of Phase 1, allowing the six-month postoperative data collection. Data will be collected throughout Phase 1.

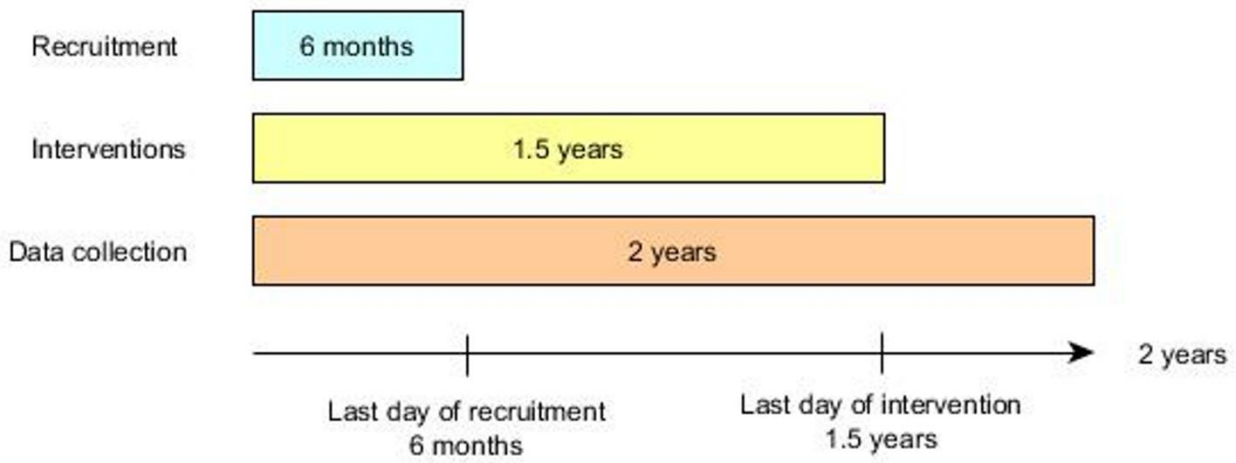

Figure 1. Timeline of Phase 1 (recruitment and data collection)

3.8 References

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Chapter 4 Discussion

4.1 Advantages and Disadvantages

Congenital melanocytic nevus (CMN) treatment may help to mitigate the negative impact of exposed CMN on a patient's general wellbeing and health-related quality of life (HRQOL); yet, it is unknown how the choice of treatment affects a patient's HRQOL. Due to the complexity of how CMN is affecting this population, school-aged children are of particular concern. It is essential that we provide evidence-based recommendations to children and their families who seek CMN treatment. However, few studies have focused on how treatment affect the general wellbeing among school-aged children with head and neck CMN. No previous study has directly compared the functional effect of surgical excision and laser therapy, the two common treatment choices for CMN. Our study is designed to address this gap in knowledge using a reliable and valid HRQOL measurement instrument. With the result of this study, we will determine the choice of treatment to achieve a better HRQOL effect among school-aged children with small to M1 CMN of the head and neck. As Children's Dermatology Life Quality Index (CDLQI) covers different HRQOL domains, we may also learn more details about how the treatments are affecting HRQOL among this clinically important population.

This study has several limitations. First, school-aged children who have health insurance coverage and have access to pediatricians and other healthcare specialists may be psychosocially different from their counterpart and have a different response to the interventions. However, we decided against expanding the sample due to the high cost of interventions. Second, a double-blind, randomized controlled trial is the best study design

for a treatment question. However, given the interventions are elective procedures, randomizing the children to a certain intervention group, regardless of the preference of the patients and the families, would be difficult, would likely hinder enrollment and increase attrition. The procedural differences between laser treatment and surgical excision prevent the blinding of the patients, their families and the investigators. A non-randomized open-label trial inevitably has increased risk of bias; including selection, reporting and performance biases. Third, the standard deviation (SD) we used for sample size calculation may not be an accurate reflection of the SD among the true study population. The SD of CDLQI scores among the study population was extracted from six previous studies that reported CDLQI scores among children with moles or nevi. However, it is unclear whether the participants had CMN or other melanocytic lesions, such as acquired melanocytic nevi and lentigines, in some of the six studies. The location and the size of the lesions were also not reported in most studies. The SD estimate greatly influenced the sample size calculation, not only because it was a part of the sample size formula, but also because it was used to derive the minimally detectable effect size, which also affect the sample size calculation. However, there is no better-quality study in the literature to provide us with a more accurate SD estimate. In order to provide sufficient power to detect a small effect difference between laser treatment and surgical excision, we conservatively calculate the sample size with a larger SD estimate than the reported values.

4.2 Clinical Significance

Previous studies have mainly focused on the cosmetic outcome of treatment options; few studies have looked at the relationship between treatment options and quality of life among children with CMN. To our knowledge, this proposed study is the first study that attempts to compare the effect of two common treatment options on HRQOL among school-aged children with head and neck CMN of ≤10 cm. HRQOL captures patient's perspectives of disease and treatment, their perceived need for health care, and their preferences for treatment and outcomes.[28] Using HRQOL rather than solely relying on physical outcome reflects a growing appreciation of patient-centered care in the medical field.[124] This study will re-examine the choice of treatment plan for school-aged children with small to medium-sized head and neck CMN. It will also inform clinicians, patients, and families, contribute to future evidence-based guidelines and improve decision-making in clinical practice.

4.3 References

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Appendices

Appendix I Sample Parental Consent Form

ID Code:

PARENTAL CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL: SAINT RAPHAEL CAMPUS

Study Title: COMPARING CONGENITAL MELANOCYTIC NEVUS TREATMENT EFFECT on CHILDREN'S HEALTH-RELATED QUALITY of LIFE

Principal Investigator: Yunru Lai, PA-III, Richard Antaya, MD

Funding Source: Pending

Invitation to Participate and Description of Project

Your child is invited to participate in a research study designed to look at the effect of different treatments on health-related quality of life among school-aged children with head and neck congenital melanocytic nevi. Congenital melanocytic nevi are birthmarks that you may notice at birth or in early infancy. Health-related quality of life measures a person's general wellbeing related to health and diseases. Your child has been asked to participate because s/he is a full-time student between 6–14 years, have one or more congenital melanocytic nevi on head and neck, and seek treatments. We expect to enroll 128 children in total across all study sites.

In order to decide whether or not you wish your child to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish your child to participate; if so, you will be asked to sign this form. Your child will also be asked to sign an assent form if s/he is 7 years or older.

Description of Procedures

When your child comes to the initial visit, s/he will fill out a form with your assistance for us to better know her/him. We will measure and photograph your child's birthmark.

If your child is deemed eligible, you may choose one from the two treatment options offered. The two treatment options include surgery and laser. All procedures will be performed under general anesthesia.

If you choose **surgery**, your child will receive one (1) to two (2) scheduled surgeries performed by plastic surgeons specialized in craniofacial reconstruction. Your child's surgeons will independently evaluate the birthmark and choose the surgical techniques suitable for her/his birthmark. Techniques that are commonly used by craniofacial plastic surgeons for the removal of this type of birthmark includes but not limits to excision with primary closure, serial excision, excision with flap reconstruction, and excision with skin graft.

If you choose **laser**, your child will receive a maximum of six (6) monthly combined laser treatment sessions. All laser sessions are performed by clinicians trained in laser treatments. You and your child may choose to skip one or more sessions if satisfied result is obtained. However, your child should still return for each scheduled follow-up visit. The laser used in each session include CO_2 laser and Q-switched Alexandrite laser. Your child will have the option to have surgeries after the trial, if you wish to.

Regardless of the treatment chosen, your child will return for follow-up in one (1) week, one (1) month, and six (6) months after each treatment session. If your child is in the laser group, s/he may schedule her/his follow-up for the previous treatment session and the new treatment session in the same visit.

In each treatment and follow-up session, the site of the birthmark will be assessed by a physician. Your child will be asked to independently complete a Children's Dermatology Life Quality Index questionnaire. This questionnaire consists of 10 questions about different aspects of her/his life in the past week. You may read the questions to your child and clarify words, but you child should be the one who answers all the questions without prompts.

All treatments will be completed roughly in a year from the first treatment session. All data collection will be completed roughly in 18 months from the first treatment session.

Risks and Inconveniences

Surgical operations including laser treatment all involve RISKS OF COMPLICATIONS, SERIOUS INJURY, OR DEATH, from both known and unknown

causes. Potential complications of surgeries include pain, bleeding, infection, scarring, unsatisfactory results including incomplete removal of the nevus (birthmark), and injury to the nearby structures. Potential complications of laser surgeries include skin irritation including redness, swelling, itching, blistering, pain; change in skin color; unsatisfactory results including repigmentation (birthmark initially lightens but darkens over time); burns; scarring; and infection.

General anesthesia also carries its own risks; potential complications associated with the administration of anesthetic drugs include, but not limit to, drowsiness, nausea, vomiting, pain, hematoma, phlebitis, numbness, swelling, bleeding, bruising, allergic reaction and death.

Benefits

Potential benefits from treatments include improvement of cosmetic outcome, improvement of psychosocial wellbeing, and reduction of cancer risk.

Economic Considerations

The cost of treatment involves several charges, including fees charged by the physician, the cost of pre- and post-operative skin care medications, surgical supplies, laboratory tests, possible hospital charges, and assisting personnel if applicable, depending on the type of procedure performed. Additional costs may occur should complications develop from the treatment.

Your child's health insurance plan will likely partially or completely cover congenital melanocytic nevus removal surgery and laser treatment, because it involves removal of a potentially cancerous lesion with or without the reconstruction of the area. You may be responsible for the copayment and/or deductible, per your child's health insurance plan. In the rare case that your child's health insurance plan does not cover the procedures, you will be responsible for the full payment. Discounts may be applicable on a case by case basis.

Treatment Alternatives/Alternatives

The most common treatment alternatives to having surgeries or laser treatments include curettage, dermabrasion, and chemical peels. Observation without interventions and cosmetic camouflage are common non-treatment alternatives.

Confidentiality

Research materials will be stored in locked cabinets and shredded before discarding. Digital data will be stored and analyzed only on properly encrypted devices. All identifiable information will be deidentified prior to analysis to ensure confidentiality. When the results of the research are published or discussed in conferences, no information will be included that would reveal your child's identity unless your specific consent for this activity is obtained.

Information about your child's study participation will be entered into her/his Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of the providers who participate in the EMR system. Information within your child's EMR may also be shared with others who are appropriate to have access to her/his EMR (e.g. health insurance company, disability provider.)

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to refuse your child's participation in this study. Refusing to participate will involve no penalty or loss of benefits to which your child is otherwise entitled (such as your child's health care outside the study, the payment for your child's health care, and your child's health care benefits). However, your child will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow the use of your child's information as part of this study.

If your child does become a subject, your child is free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw your child from participating in the research if necessary. Conditions under which a subject might be withdrawn from the research include, but not limit to, when the subject is no longer a suitable candidate for a treatment plan due to health, the subject develops serious side effects or complications, or the subject is unable to comply to treatments or follow-up visits.

Withdrawing from the study will involve no penalty or loss of benefits to which your child is otherwise entitled. It will not harm your child's relationship with her/his own doctors or with the affiliated institute including Yale-New Haven Hospital.

When you withdraw your child from the study, no new health information identifying your child will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

Parent/legal guardian Authorization

I, the parent or legal guardian, have read (or someone has read to me) this form and have decided for my child to participate in the project described above. Its general purposes, the particulars of my child's involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name: _____ Signature: _____

Relationship to subject: _____ Date: _____

_____ _____

Signature of Principal Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator (Yunru Lai, 937-344-8842).

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix II Sample Consent Form

ID Code:

CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

For ages 13-14 years

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL: SAINT RAPHAEL CAMPUS

Study Title: COMPARING CONGENITAL MELANOCYTIC NEVUS TREATMENT EFFECT on CHILDREN'S HEALTH-RELATED QUALITY of LIFE

Principal Investigator: Yunru Lai, PA-III, Richard Antaya, MD

Funding Source: Pending

Invitation to Participate and Description of Project

You are invited to participate in a research study designed to look at the effect of different treatments on health-related quality of life among school-aged children with head and neck congenital melanocytic nevi. Congenital melanocytic nevi are birthmarks that you may notice at birth or in early infancy. Health-related quality of life measures a person's general wellbeing related to health and diseases. You have been asked to participate because you are a full-time student between 6–14 years, have one or more congenital melanocytic nevi on head and neck, and seek treatments. We expect to enroll 128 children in total across all study sites.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, possible benefits and possible alternative treatments. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form. Your legal guardian(s) will also be asked to sign a consent form to give permission to your participation in this study.

Description of Procedures

When you come to the initial visit, you will fill out a form for us to better know you. We will also measure and photograph your birthmark.

If you are deemed eligible, you may choose one from the two treatment options offered. The two treatment options include surgery and laser. All procedures will be performed under general anesthesia.

If you choose **surgery**, you will receive one (1) to two (2) scheduled surgeries performed by plastic surgeons specialized in craniofacial reconstruction. Your surgeons will independently evaluate the birthmark and choose the surgical techniques suitable for her/his birthmark. Techniques that are commonly used by craniofacial plastic surgeons for the removal of this type of birthmark includes but not limits to excision with primary closure, serial excision, excision with flap reconstruction, and excision with skin graft.

If you choose **laser**, you will receive a maximum of six (6) monthly combined laser treatment sessions. All laser sessions are performed by clinicians trained in laser treatments. You may choose to skip one or more sessions if satisfied result is obtained. However, you should still return for each scheduled follow-up visit. The laser used in each session include CO_2 laser and Q-switched Alexandrite laser. You will have the option to have surgeries after the trial, if you wish to.

Regardless of the treatment chosen, you will return for follow-up in one (1) week, one (1) month, and six (6) months after each treatment session. If you are in the laser group, you may schedule your follow-up for the previous treatment session and the new treatment session in the same visit.

In each treatment and follow-up session, the site of the birthmark will be assessed by a physician. You will be asked to independently complete a Children's Dermatology Life Quality Index questionnaire. This questionnaire consists of 10 questions about different aspects of your life in the past week.

All treatments will be completed roughly in a year from the first treatment session. All data collection will be completed roughly in 18 months from the first treatment session.

Risks and Inconveniences

Surgical operations including laser treatment all involve RISKS OF COMPLICATIONS, SERIOUS INJURY, OR DEATH, from both known and unknown causes. Potential complications of surgeries include pain, bleeding, infection, scarring, unsatisfactory results including incomplete removal of the nevus (birthmark), and injury to the nearby structures. Potential complications of laser surgeries include skin irritation including redness, swelling, itching, blistering, pain; change in skin color; unsatisfactory results including repigmentation (birthmark initially lightens but darkens over time); burns; scarring; and infection.

General anesthesia also carries its own risks; potential complications associated with the administration of anesthetic drugs include, but not limit to, drowsiness, nausea,

vomiting, pain, hematoma, phlebitis, numbness, swelling, bleeding, bruising, allergic reaction and death.

Benefits

Potential benefits from treatments include improvement of cosmetic outcome, improvement of psychosocial wellbeing, and reduction of cancer risk.

Economic Considerations

The cost of treatment involves several charges, including fees charged by the physician, the cost of pre- and post-operative skin care medications, surgical supplies, laboratory tests, possible hospital charges, and assisting personnel if applicable, depending on the type of procedure performed. Additional costs may occur should complications develop from the treatment.

Your health insurance plan will likely partially or completely cover congenital melanocytic nevus removal surgery and laser treatment, because it involves removal of a potentially cancerous lesion with or without the reconstruction of the area. You may be responsible for the copayment and/or deductible, per your health insurance plan. In the rare case that your health insurance plan does not cover the procedures, you will be responsible for the full payment. Discounts may be applicable on a case-by-case basis.

Treatment Alternatives/Alternatives

The most common treatment alternatives to having surgeries or laser treatments include curettage, dermabrasion, and chemical peels. Observation without interventions and cosmetic camouflage are common non-treatment alternatives.

Confidentiality

Research materials will be stored in locked cabinets and shredded before discarding. Digital data will be stored and analyzed only on properly encrypted devices. All identifiable information will be deidentified prior to analysis to ensure confidentiality. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may

also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)

Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects) may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.

Voluntary Participation and Withdrawal

Participating in this study is voluntary. You are free to refuse to participate in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow the use of your information as part of this study.

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. Conditions under which a subject might be withdrawn from the research include, but not limit to, when the subject is no longer a suitable candidate for a treatment plan due to health, the subject develops serious side effects or complications, or the subject is unable to comply to treatments or follow-up visits.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with the affiliated institute including Yale-New Haven Hospital.

When you withdraw from the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

Questions

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully—as long as you feel is necessary—before you make a decision.

Patient Authorization (For children ages 13-14 years)

I, _____, have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Signature: _____ Date: _____

Parent/legal guardian Authorization

I, the parent or legal guardian, have read (or someone has read to me) this form and have decided for my child to participate in the project described above. Its general purposes, the particulars of my child's involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name: _____ Signature: _____

Relationship to subject: _____ Date: _____

_____ _____

Signature of Principal Investigator Date

or

_____ _____

Signature of Person Obtaining Consent Date

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator (Yunru Lai, 937-344-8842).

If, after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203-432-5919. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.

Appendix III Sample Child Assent Form

ID Code:

CHILD ASSENT FORM

for ages 7-12 years

(To be read aloud to child)

My name is _____ (identify yourself to the child by name). I am doing a study trying to learn more about which birthmark treatment makes children feel better. The two treatments we are comparing are surgeries and laser. By agreeing to be in this study, you may be helping other kids who also have birthmarks choose the treatment that works better for them.

If you agree to help us, you will be asked to come to the clinic for treatments and answer some questions to tell us how you feel. There are no right or wrong answers. If there is a question you don't want to answer, just leave it blank.

If you agree to help us, we will keep all your answers private, and will not show them to your classmates and teachers. Only people from Yale University working on the study will see them.

Please talk this over with your parents before you decide if you want to be in my study or not. You should know that you do not have to be in this study if you do not want to. You won't get into any trouble if you say no. I will also ask your parents to give their permission for you to be in this study, but even if your parents say "yes," you can still say "no" and decide not to be in the study. You may also stop being in the study after we begin, that's okay, too.

You can ask any questions you have, now or later. If you think of a question later, you or your parents can call me at _____ (phone number).

Sign this form or Answer "Yes" only if you:

- have understood what you will be doing for this study,
- have had all your questions answered,
- have talked to your parent(s)/legal guardian about this project, and
- agree to take part in this research

_____

Your Signature Printed Name Date

_____

Signature of Assenting Researcher Date

* Child may verbally assent. Only a definite "Yes" may be taken as assent to participate.

Appendix IV Sample Sociodemographic Survey

ID Code:

SOCIODEMOGRAPHIC SURVEY

(To be completed by child, with the assistance of parents/caregivers)

Name: _____ **Date of Birth:** __ / __ / ____

Education level & Grade:

☐ Elementary school: _____

☐ Middle school: _____

☐ Home schooling: _____

☐ Others: _____

Sex:

☐Male ☐ Female

Race:

☐ Caucasian/White ☐ African American/Black

☐ Asian and Pacific Islander ☐ Native Americans and Alaska Natives

☐ Others: _____

Ethnicity:

☐Hispanic/Latino ☐Non-Hispanic/non-Latino

Household Annual Income: _____

☐ Less than $25,000 ☐ $25,000 to $49,999

☐ $50,000 to $99,999 ☐ $100,000 or more

Number of Family members: _____

Appendix V Sample Health-Related Burdens Survey

ID Code:

HEALTH-RELATED BURDENS SURVEY

(To be completed by child, with the assistance of parents/caregivers)

Today's Date: _____

Today's visit:

☐ Initial visit ☐ One-week follow-up

☐ One-month follow-up ☐ Six-month post-intervention follow-up

Doctor's visits:

How often have you visited the doctor's office **in the past year**?

☐ Always ☐ Often

☐ Sometimes ☐ Never

How many times have you been hospitalized for **in the past year**? _____

How many days have you been hospitalized for **in the past year**? _____

Medications:

How many different medications are you routinely taking **currently**? _____

What is the maximal number of different medications you have routinely taken **in the past year**? _____

Co-morbidities:

List all the diagnosis of **physical conditions** you have had:

_____

_____

List all the diagnosis of **mental conditions** you have had:

_____

_____

Appendix VI Sample Lesion Characteristics Report

ID Code:

LESION CHARACTERISTIC REPORT

(To be completed by clinician)

Today's Date: _____

Today's visit:

☐ Initial visit ☐ One-week follow-up

☐ One-month follow-up ☐ Six-month post-intervention follow-up

Complete only in initial visit:

Fitzpatrick Skin Phototype:

☐ I ☐ II ☐ III

☐ IV ☐ V ☐ VI

Complete in all visits:

Lesion Location (choose all that apply):

☐ Central (vertical area in-between outer canthi) ☐ Lateral

☐ Forehead ☐ Nose ☐ Cheeks

☐ Chin/Jaw ☐ Neck ☐ Others: _____

Lesion Size (cm × cm): _____

Lesion Colors (choose all that apply):

☐ Uniform ☐ Multicolored

☐ Skin-colored ☐ Tan ☐ Brown

☐ Black ☐ Purple ☐ Pink

☐ Others: _____

Morphologies (choose all that apply):

☐ Uniform ☐ Irregular ☐ Ulcerated

☐ Flat ☐ Raised ☐ Hairless

☐ Mildly hair-bearing ☐ Moderately hair-bearing ☐ Dense hair-bearing

☐ N/A (s/p surgical excision)

Complete only in follow-up visits:

Pigmentation Clearance:

☐ 0-24% ☐ 25-49% ☐ 50-74%

☐ 75-100%

Wound Healing Impression (choose all that apply):

☐ Normal healing ☐ Delayed healing

☐ Abnormal surrounding skin color ☐ Well-defined Edges

☐ Undermining ☐ Exudate ☐ Induration

Wound Bed Tissue Type:

☐ Closed wound ☐ Epithelial ☐ Granulation

☐ Slough ☐ Necrosis

Complications (choose all that apply):

☐ Infection ☐ Bleeding ☐ Hypertrophic scar

☐ Hyperpigmentation ☐ Hypopigmentation

☐ Others: _____

Pain: _____ / 10

☐ Improved over time ☐ Same ☐ Worsen over time

Appendix VII Sample Children's Dermatology Life Quality Index Questionnaire

ID Code:

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

(To be completed independently by child)

Name: Age: CDLQI SCORE:

Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it□□□ **school time?** **OR** was it **holiday time?**	**If school time**: Over □□□the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday?**	Prevented school Very much Quite a lot Only a little Not at all Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

10.	Over the last week, how much of a problem has the **treatment** for skin been?	Very much	☐
		Quite a lot	☐
		Only a little	☐
		Not at all	☐

Please check that you have answered EVERY question. Thank you.

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