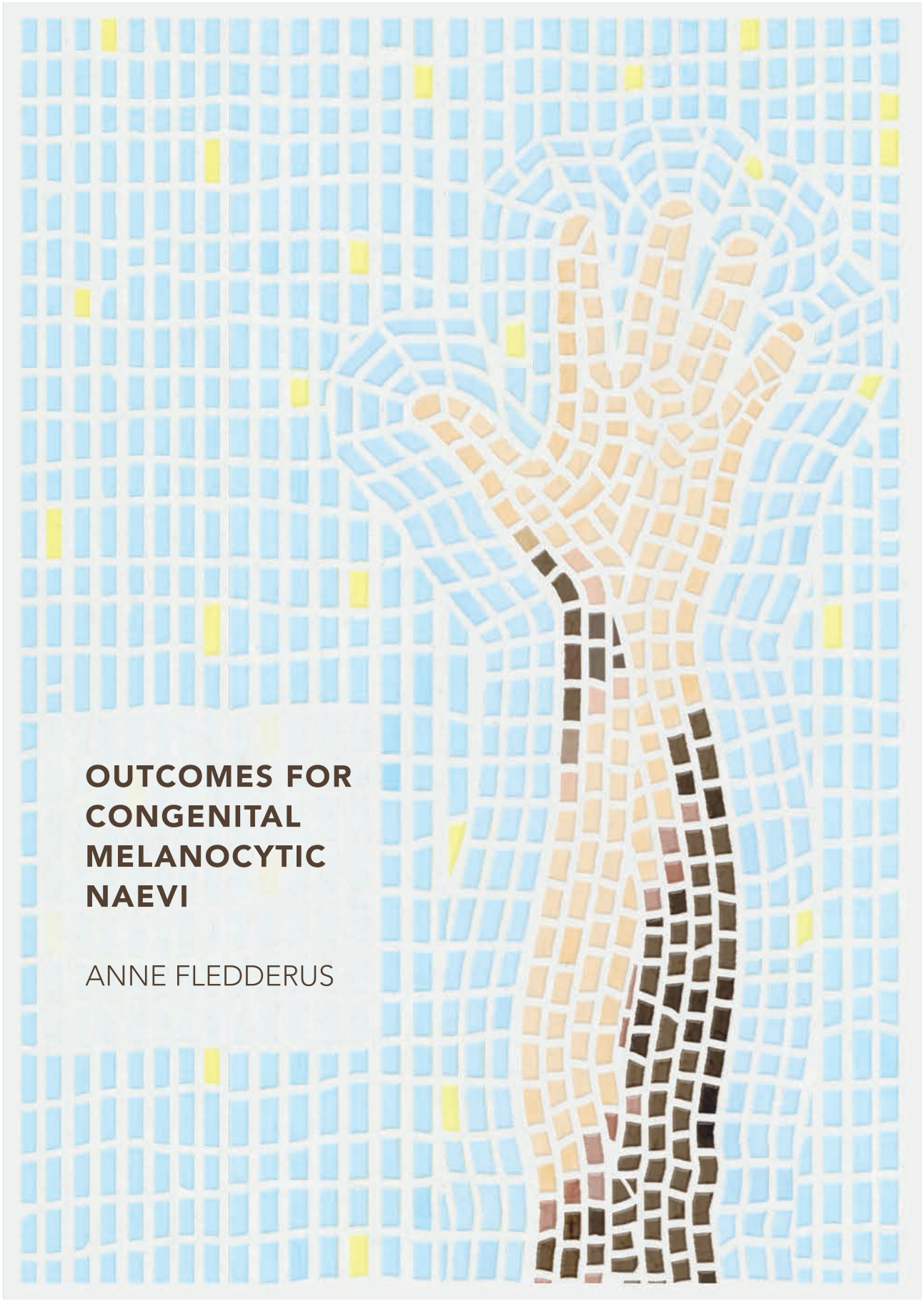

OUTCOMES FOR CONGENITAL MELANOCYTIC NAEVI

ANNE FLEDDERUS

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Outcomes for Congenital Melanocytic Naevi

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voor mijn ouders

TABLE OF CONTENTS

GENERAL INTRODUCTION

Antoni Gaudí

Mosaic at Park Güell, Barcelona

1914

Antoni Gaudí was a Catalan architect known for his innovative technical and decorative use of materials, such as his method of designing ceramic mosaics made of waste pieces in original and imaginative combinations, so-called 'Trencadís'.

As congenital melanocytic naevi are caused by a mosaic mutation, every chapter of this thesis will be preceded by a mosaic work of art.

1

GENERAL INTRODUCTION

Based on the book chapter:
'Il nevo melanocitico congenito gigante'
A.C. Fledderus, 2021 feb; pp 101-115.
Book: *'Colorati da natura'* ISBN: 9788898323623.

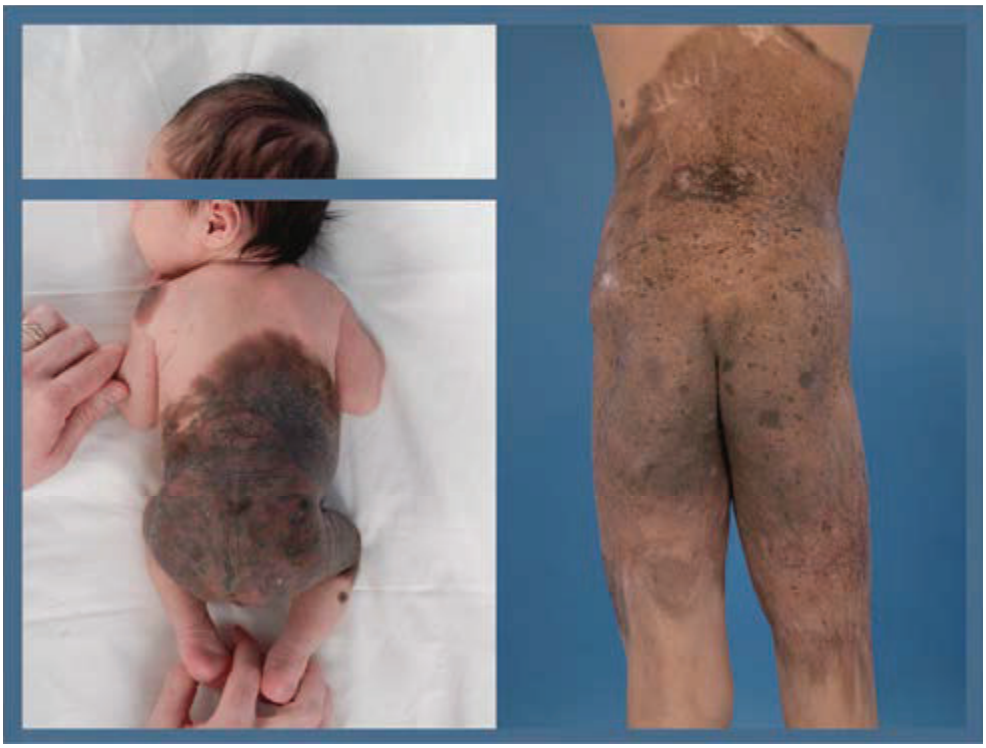
GENERAL INTRODUCTION

Congenital melanocytic naevi (CMN) are birthmarks present at birth or sometimes become visible in the first year of life ("tardive" CMN). They can be present anywhere on the skin or on the mucosa, including the oral cavity. They can be solitary, multiple, or they can appear as a large CMN accompanied by smaller so-called "satellite naevi".

CMN are usually larger than acquired naevi and they have a mixed morphology. CMN increase in size with the skin in proportion to the child's growth and are therefore classified based on the expected size at adulthood: the projected adult size (PAS). The PAS is calculated by using charts designed from paediatric growth charts and burns assessment charts, taking into account the age and location of the lesion.[1]

GENERAL CHARACTERISTICS OF CONGENITAL MELANOCYTIC NAEVI

Overall, CMN are relatively common, with an incidence of 1:100 in all neonates. However, large (>20 cm PAS) or giant (>40 cm PAS) CMN are quite rare, with an estimated prevalence of 1:20.000 and 1:500.000 in neonates.[2-4] The clinical threat of CMN is the risk of developing malignant melanoma or neurological complications.[5,6] In addition to these complications, the occurrence of CMN can lead



Congenital melanocytic naevi after birth and at adulthood

to psychosocial problems due to their appearance, fear of future complications, and the possible requirement for extra care.[7]

The colour of CMN is mostly light or dark shades of brown and can sometimes be reddish. CMN can be covered with hair and compared with the colour of the hair growing on the head, they can be darker, the same colour, or occasionally even lighter. Hair on the naevus can be absent at birth and may remain absent during life. Variations in the texture of the CMN are seen as well as the CMN can be smooth, wrinkled, or nodular.

The appearance of CMN can change, especially during the first years of life. It is commonly observed that a CMN darkens in the first year of life. During a lifetime, the colour of the CMN itself or of the hairs on the CMN can become lighter or darker. It is shown that lightening of CMN happens particularly in children with Fitzpatrick classification skin types 1 and 2.[8]

Benign skin complications in CMN include decreased ability or inability to perspire, with the potential risk of overheating. CMN can develop proliferative nodules that can grow rapidly and sometimes cause an abnormal cosmetic appearance. These nodules complicate the care of CMN because they are clinically as well as histopathologically difficult to distinguish from melanomas.[3] Skin-related discomfort caused by the CMN sometimes includes itching and spontaneous wounds, which occasionally leads to infections.

CMN CLASSIFICATION

CMN can be classified according to their size, location, number and appearance. Various methods of classifying CMN are available.[9] For instance, CMN size can be classified according to the percentage of the body surface area involved, the diameter of the CMN in centimetres or the diameter in centimetres in Projected Adult Size (PAS). International professionals specializing in CMN reached consensus on the following classification system developed by Krengel et al.[1]:

Projected adult size: Small (<1.5 cm), Medium M1 (1.5–10 cm), M2 (>10–20 cm), Large L1, (>20–30 cm), L2 (>30–40 cm), Giant G1 (>40–60 cm), G2 (>60 cm).
Multiple CMN: ≥3 medium without a single predominant CMN.
Location: Head (face, scalp), Trunk (neck, shoulder, upper back, middle back, lower back, breast, chest, abdomen, flank, gluteal region, genital region), Extremities (upper arm, forearm, hand, thigh, lower leg, foot).

Number of satellite naevi: S0 (0), S1 (<20), S2 (20–50), S3 (>50).
Colour heterogeneity: CO None, C1 Moderate, C2 Marked.
Surface rugosity: R0 None, R1 Moderate, R2 Marked.
Dermal or subcutaneous nodules: N0 None, N1 Scattered, N2 Extensive.
Hypertrichosis: H0 None, H1 Notable, H2 Marked.

GENETICS

CMN are caused by non-inheritable genetic mosaic mutations. Mosaic mutations are mutations found in some, but not all, body cells. The mutations responsible for CMN are found in affected skin or the nervous system.[10] It is likely that the timing of the mutation largely determines how extensively a CMN presents itself.[11] A mutation early in embryonic development leads to widespread distribution of naevus cells to the skin (giant CMN and multiple CMN) and also to the central nervous system, as both structures arise from the same embryonic layer, the ectoderm.[12] Most CMN are associated with NRAS gene mutations, but other mutations such as BRAF gene mutations, are found as well.[13] Both genes are important for the proteins that are involved in transmitting signals within cells. They are both part of the RAS/RAF/MEK/ERK pathway, involved in the growth, differentiation and survival of cells. Kinsler et al. showed that an NRAS mutation was found in 80% of the affected tissue of CMN patients.[12] In the same patients the same mutation was found to be present in several affected areas of the skin and the central nervous system, while it was absent in the unaffected areas or in the blood.[12] There may be more pathways involved in the pathogenesis of CMN than are currently described or known. Researchers are investigating the potential associations between specific gene mutations and different manifestations of CMN appearance, or the risk of developing melanoma or neurological complications.[14,15] Moreover, CMN patients may have gene mutations that are responsible for other aspects besides the CMN. For instance, various anatomical central nervous system abnormalities or typical facial features are found in CMN children.[16,17] These features may be part of a "CMN syndrome", i.e. the combination of cutaneous CMN and additional abnormalities.[17-19] More research is needed to investigate this potential syndrome.

MELANOMA

Melanoma in a CMN is a severe complication with generally fatal consequences.[20] A melanoma can develop from a CMN on the skin and in the central nervous system. The majority of these melanomas are reported in early childhood.[5] Melanoma in larger CMN (>20 cm PAS) seems to be more nodular and arises more often in the deeper layers of the skin.[21,22] Melanomas or premalignant stages in a CMN on the skin can present as a change in the CMN, such as hyper- or hypopigmentation, a papule or nodule, and sometimes ulceration or wounds. Unfortunately, CMN with benign noduli or colour heterogeneity are difficult to distinguish from melanoma.

The risk of developing melanoma was formerly estimated to be up to 40%. Fortunately, this risk has now been shown to be much lower.[5] The risk of developing melanoma in a solitary smaller CMN (<20 cm PAS) is only slightly increased compared with the general population (<1%).[3,23] In patients with larger CMN (>20 cm PAS) the estimated increased risk is 1–3%.[3,23] In giant CMN, however, the estimation of the risk is much higher, estimated to be up to 8–14%.[3,23] Note that these risk estimations are based on relatively low-quality studies which reported on small patient groups due to the rarity of giant CMN, thus also implicating selection bias. The lack of universally accepted classifications and the lack of standard reporting of outcomes complicate the comparison and combination of these low-powered studies.

NEUROLOGICAL COMPLICATIONS

Having a CMN on the skin or mucosa can be associated with neurological manifestations. Neurocutaneous melanocytosis, an excessive amount of naevus cells in the central nervous system, can sometimes be revealed by an MRI scan of the brain and spine.[6,24] Apart from melanocytosis, incidental abnormalities on the MRI are also found in individuals with CMN.[17] Having abnormalities on the MRI is associated with a broad variety of clinical outcomes, ranging from mortality to a lack of symptoms or signs at all.[25,26] Complications that have been reported are epileptic seizures, neurodevelopmental problems, motor disorders, an excessive amount of liquid in the brain (hydrocephalus), spinal cord compression, benign spinal or brain tumours, melanoma or a rapidly growing quantity of naevus cells (proliferative melanocytosis).[25-27] If there are neurological complaints, an MRI scan is important to identify the nature of the abnormality and whether there are possible therapeutic options.[7] Screening MRI scans in CMN patients without neurological symptoms or signs could theoretically be of added value by intervening early in the event of abnormalities, or by recording the initial situation which might result in better detection of changes later in life. There is clinical uncertainty in the literature about the value of screening MRI examinations in patients with an increased risk of neurological involvement. Waelchli et al. recommend an MRI scan of the central nervous system (brain and spine) in any child with two or more CMN of any size or at any site.[17] However, others argue that routine MRI screening in asymptomatic patients is not needed. It is unclear how clinical management could be adapted substantially on the basis of the results of routine MRI screening at a young age. There is currently no treatment for abnormalities found by an MRI scan in asymptomatic patients. There are also some disadvantages of routine MRI screening, including extra costs, sedation of young children and false-positive and false-negative results. If routine neurological examination by a specialist is performed, MRI screening may not be needed[3].

The exact risk of developing neurological complications associated with having a CMN is unclear. It has been shown that patients with larger (>20 cm PAS) and/or multiple CMN (>1,5 cm PAS) are at greater risk of having naevus cells in the central nervous system.[27] Individuals with single, smaller CMN (<20 cm PAS) have a minor risk of having neurological complications associated with the CMN. Some rare cases have been reported of patients having small or no CMN and yet having melanocytosis in the central nervous system.[28,29]

IMPACT ON MENTAL HEALTH

Children growing up with CMN can have psychological issues relating to their appearance, skin-related discomfort, invasive treatments required and (fear of) developing melanoma or neurological complications.[7,30] Important aspects of health-related quality of life are emotional, social and physical functioning. Especially social and emotional functioning can be influenced by the unusual appearance of the CMN. People with CMN can be picked on, ridiculed, or commented on by others. Therefore, they can experience stigmatization and a negative body image, leading to emotional distress (sadness, anxiety and anger). Participation in social activities can be hindered by these emotions. Physical functioning is mainly influenced by neurological complications.[30] Treatments can influence physical functioning as well. For instance, mobility can be impaired during the healing

process of operated CMN. It is of great importance to take into consideration the mental health of people with CMN and their families. CMN can have a great impact on parents due to the fear of complications, the burden of treatment, the affected quality of life of their child, and the feeling of guilt towards the child with CMN.[31] Siblings can experience psychological issues as well, due to the teasing and ridiculing of their affected sibling or because they receive less attention compared with their brother or sister with CMN.

The influence of the appearance of CMN on mental health differs among individuals. The influence on mental health depends on the child's personality and ability to cope, and on the support received from family, friends and patient support groups. Psychological support from a psychologist may be helpful for patients and their families. Moreover, patient support groups are considered to be very helpful by patients and parents; they can share their experience and find mental support. Currently, there are around twenty different international patient support groups for CMN and new national support groups are still being formed. Naevus Global is an umbrella organization for national CMN patient organizations. They provide an overview of the international patient organizations (www.naevusglobal.org).

All the same, people can become self-confident with their CMN and their CMN may even be considered as a part of their identity.[31] Young people are proudly sharing their CMN pictures on social media and people with CMN are pursuing modelling careers. The exhibition named How Do You C Me Now? In London in 2019 raised awareness of CMN by presenting photos of people with giant CMN showing their skin. The dissemination of photos of people with CMN helps other individuals with CMN to accept their skin "abnormalities". Nonetheless, CMN can still have a great impact on mental health. It is therefore of great importance that professionals monitor the mental health of people with CMN and their families and advise consulting a (paediatric) psychologist for patients with a CMN and their parents.

MULTIDISCIPLINARY CARE OF CMN

Management of CMN requires a multidisciplinary approach. A team of professionals specialized in CMN care should be consulted, including a dermatologist to examine the skin, a plastic surgeon to give advice on possible surgical treatments, a dermal pathologist for histopathological examination, a paediatrician to examine the development of the child, and a neurologist if any neurological complications are suspected or present. A clinical geneticist can be included to advise on genetic findings and see if there is a relation to a known syndrome.[32] A (paediatric) psychologist may be involved in the multidisciplinary team or consulted separately in the close environment of the family. Patient outcome measurement instruments that measure emotional, social, and physical functioning can be used to screen patients and parents for mental health issues and, if needed, to offer them psychological help. Furthermore, a radiologist specialized in central nervous system MRI analysis or an oncologist specialized in melanoma treatment can be consulted. The multidisciplinary care in a CMN-dedicated expert centre is especially important for people with an elevated risk of melanoma or neurological complications, i.e. multiple CMN or CMN >20 cm PAS.[3]

INDICATION FOR INTERVENTIONAL TREATMENT

One decade ago, removal of the CMN was thought to be the first choice of treatment in order to prevent the development of melanoma, and it had to be performed as early as possible.[33] However, the risk of melanoma now appears to be lower than was assumed before.[5] Moreover, there is no clinical evidence that removing the CMN is a better treatment for preventing melanoma or neurological complications compared with watchful monitoring. Thus, interventional treatment may be indicated more for "cosmetic" reasons to prevent psychosocial problems.[33] An international survey showed that a scar is more accepted than a CMN.[34] However, the child can be taught how to cope with his or her "different" skin and to accept the CMN. Excision is still always indicated when there is a suspicion of melanoma; at least the suspected part of the CMN should be removed.[3]

INTERVENTIONAL TREATMENT OPTIONS

The goal of interventional treatment is to remove as much of the CMN as possible with a satisfactory aesthetic result and minimal visible scarring, preserving anatomical structure and function, again with as few complications as possible. There are two different types of surgical treatment to remove a CMN:

(1) *Partial-thickness treatment* is a treatment where only the superficial layer of the CMN is removed. The deeper layers of the skin, including the hair follicles, remain untouched. Partial thickness treatment includes dermabrasion, curettage and laser therapy. Dermabrasion and curettage were used after a coincidental finding. A newborn with a CMN on the scalp was delivered with forceps. The forceps removed a part of the CMN. This part healed spontaneously without scarring or repigmentation.[35] The first curettage of CMN was performed and reported in 1987.[36] Few studies have been published about the long-term cosmetic results of dermabrasion or curettage.[3,37] Unfortunately, repigmentation and scarring are frequently seen after these treatments. One case has been presented in which no difference was later found between the non-treated areas and the areas treated with curettage.[8] Important complications are blood loss, postoperative pain, and infection.[3] Since the indication of CMN removal has now shifted from melanoma prophylaxis to a more cosmetic reason, dermabrasion and curettage are no longer advised due to the poor cosmetic results and the potential major complications.[37]

Various laser devices and combinations of lasers have been used for the treatment of CMN, including pigment-specific and ablative lasers. Although most studies report initial improvement of the appearance of the CMN after laser therapy, repigmentation is common and complications such as scarring, hypopigmentation, or wound infections can occur after laser therapy.[38] Lasers may be useful for reducing irregular texture of the CMN or for removing dark hairs on the CMN.[38] There are some concerns that laser therapy might increase the risk of melanoma. However, there are no reports of melanomas occurring in a CMN after laser therapy.[38]

(2) *Full-thickness treatment* is a technique in which the CMN is fully removed, including the deeper layers of the skin. Often the ensuing defect will require reconstruction. There are several plastic surgery techniques used to close the defect, ranging from primary wound closure to more-sophisticated reconstructive techniques, often following the reconstructive ladder.[39] Smaller CMN

(<5 cm) can generally be successfully excised in one stage.[40] Larger CMN or CMN on an anatomically challenging location such as the eyelids – so-called "kissing naevi" – are typically approached in one of the following ways: serial excision, excision and grafting, or tissue expansion.[3,41]

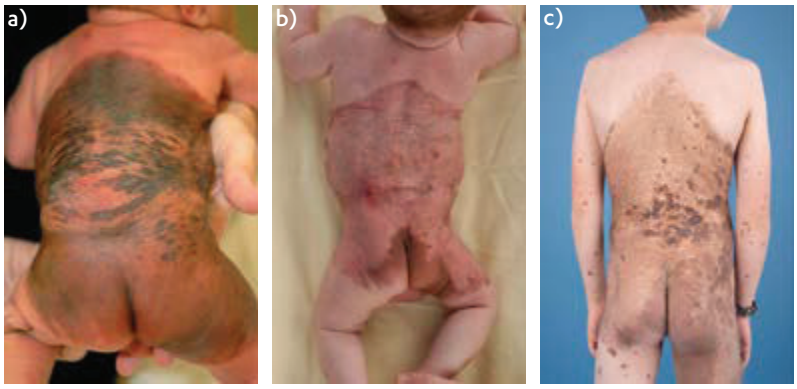
Serial excision involves a technique in which portions of the CMN are removed through staged operations. Between each operation the scar and tissue will be allowed to heal and stretch, enabling re-excision and closure with less tension on the scar.

Excision and grafting involve the removal of the complete CMN and closure with skin obtained from a donor site on another body part. To close the defect of a completely excised, larger CMN, a full-thickness skin graft, including superficial and deeper layers of the skin, gives the best cosmetic results. However, full-thickness skin grafts are limited by the donor site that is available. When there is not enough donor site for a full-thickness graft, a split-thickness skin graft might be used, i.e., using only the superficial parts of the skin, but this is associated with poorer cosmetic outcomes. Another option is to use artificial dermis (Integra®) in combination with a split-thickness skin graft, but this is a costly technique[42]. Excision and grafting allow for rapid removal of the CMN with fewer operations. However, skin grafts can leave more significant scarring when compared with tissue expansion or serial excision.

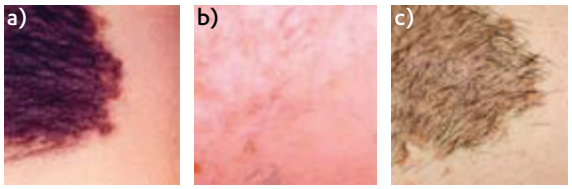
A tissue expander is a "balloon" that is placed under the skin to obtain extra skin.[43] By regularly filling the tissue expander with sterile saline, the skin will be expanded. When the skin is sufficiently expanded, generally after a couple of months, the extra skin can be used as a flap to close the defect after removing the CMN. It is possible to use multiple expanders, depending on the size and location of the CMN. However, in larger CMN this procedure may need to be repeated to achieve complete excision of the CMN.

The optimal surgical management of larger CMN is challenging. Multiple, major operations and a combination of techniques are often required. The studies on surgical treatment of CMN are of low methodological quality, as most are retrospective case series with a high risk of selection bias, with only a few descriptions of outcomes, limited patient-reported outcomes, and unvalidated outcome measures.[3] Also, the patient characteristics are not always clear (size and location of the CMN), and the studies are often heterogenous.[3]

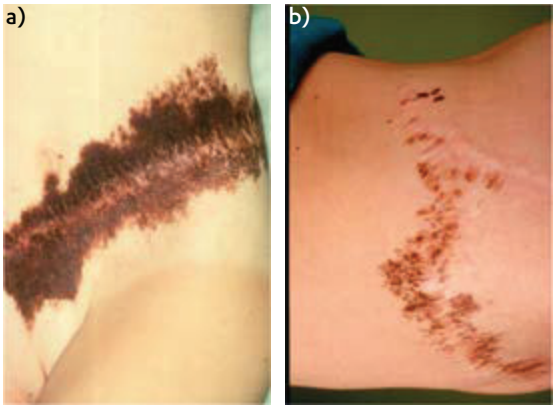
According to the Dutch guideline, full-thickness treatment is the first choice due to the good cosmetic results and the greatest reduction of melanoma risk.[3] Which technique should be chosen to close or reconstruct the wound depends on the size of the CMN, its location, the wishes of the patients/parents, and the experience of the surgeon. As the indication of surgical treatment is mainly indicated for improvement of appearance, the risks of excision should be weighed against the benefits. It is of great importance that patients and their families are informed about the advantages and disadvantages of different treatment options to enable shared decision-making.



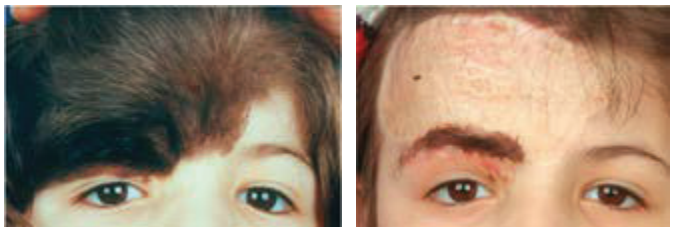
Results of curettage. (a) Preoperative view of a giant CMN. (b) Short terms results of curettage. (c) Long term results of curretage after a follow-up of 13 years.



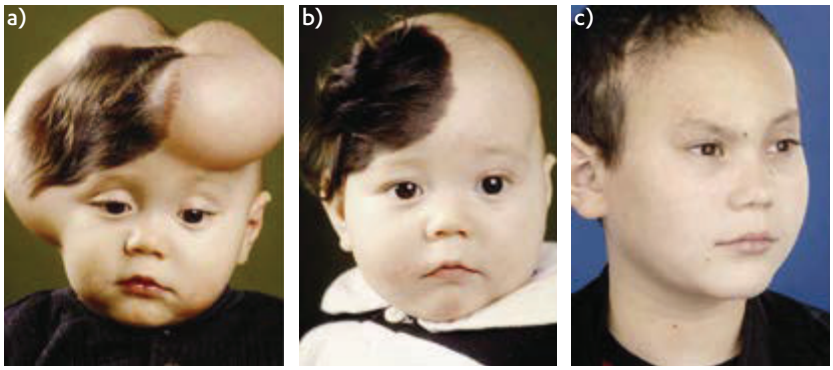
Results of laser therapy. (a) Results after 15 sessions of laser therapy. (b) Recurrence of the lesion after 15 years of follow up.



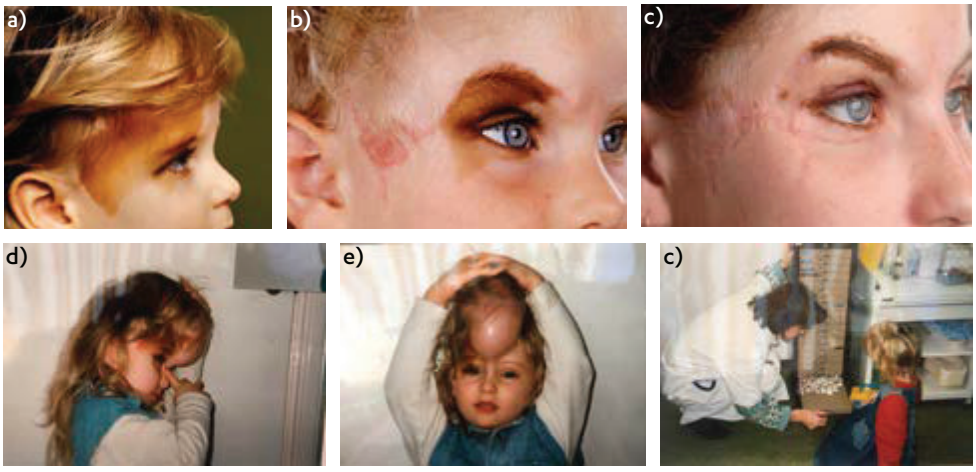
Results of serial excision. (a) Partial excision of a giant CMN (b) Complete excision with repigmentation of the scar.



Results of a split-thickness skin graft from the upper extremity after a follow up period of 2 years.



Results of tissue expanders. (a) Two tissue expanders (16 x 10 cm and 8 x 6 cm) are placed at the subgaleal plane. (b) Results after a follow-up of 8 months. (c) Results after a follow-up period of 10 years.



Results of a combination of tissue expansion and skin grafting. (a) Preoperative view of a 3-year-old girl with a CMN on the face, including the eyelids. (b) Results after excision and tissue expansion. (c) Results after tissue expansion and a full-thickness skin graft on the eyelids. (d) Lateral view of the tissue expander. (e) Frontal view of the tissue expander. (d) Visit to the outpatient clinic of the Academic Medical Center in Amsterdam for the tissue expander filling procedure.

EXPERIMENTAL PHARMACOLOGICAL TREATMENTS

Currently, novel treatments are being investigated to treat CMN with medication. One case is described in which regression of the CMN took place in a child treated with trametinib, an anti-cancer drug.[44] In four cases, trametinib reduced the symptoms of the central nervous system melanoma.[45] Furthermore, a preclinical study proposed endothelin-1 receptor antagonists as a therapeutic approach for CMN.[46] Moreover, anti-senescence peptides are now being investigated as a therapeutic option in CMN by the University of Leiden. Anti-senescence agents are promising to prevent and treat ageing-associated diseases, but they might also be used as a therapeutic approach for CMN and melanoma. Large clinical studies to verify these medications have not yet been performed. These therapies have the potential for use as an alternative, non-surgical approach to CMN treatment. Clinical studies should be performed to investigate the effect and safety of these pharmacological therapies and their long-term outcomes.

SUMMARY OF MANAGEMENT ACCORDING TO THE DUTCH GUIDELINE

The Dutch CMN guideline was developed by a group of national specialists and national patient associations.[3] The Dutch guideline provides classifications for groups of CMN patients requiring diverse standard care, based on the level of risk of complications, prognostic factors, and surgical complexity. A follow-up schedule was developed for every risk group, based on the data in the literature combined with the expert opinion of the guideline working group (Table 1).

The most important aspect of the care given by the dermatologist is to monitor changes in the CMN. New lesions, fast-growing lesions, changing noduli, and ulcerations or bleeding require extra attention. Anamnesis, inspection, and palpation are of great importance. Although dermatoscopy does not have added value in evaluating the melanoma risk in CMN, it might help in choosing the most suspected part of the lesion in the CMN for diagnostic excision. In patients with larger CMN (>20 cm PAS) it is advised to palpate the lymph nodes for lymphadenopathy.

A paediatrician and, if indicated, a neurologist should monitor a child with CMN at risk for neurological complications. An MRI scan with contrast medium should be performed in patients with any suspicion of neurological involvement and then evaluated by a specialized radiologist and/or neurologist. If there are no neurological symptoms, a screening MRI of the central nervous system is not advised.

It is not recommended that a CMN that appears benign should be removed for melanoma prophylaxis. Indications for removal could be a CMN that is difficult to follow up or removal for cosmetic indications. The cosmetic result should be weighed against the risks of the procedure.

When the CMN has an impact on the psychosocial wellbeing of the patient and/or the parents, referral to a (paediatric) psychologist is required. All patients and their parents should be informed about the added value of the patient association, apart from the care delivered by the CMN-specialized expert team.

Table 1. Risk groups

	Single CMN			Multiple CMN	
	I CMN <10 cm PAS	**II CMN 10-20 cm PAS**	**III CMN >20 cm PAS**	**IV CMN >20 cm PAS + satellites**	**V ≥3 CMN 1.5-20 cm PAS**
Risk of cutaneous melanoma	low (<1%)	low (<1%)	possibly slightly increased	elevated (2-3%, >60cm PAS ± 9%)	unknown
Risk of neurological complications (NCM, melanoma)	low	low	low	increased*	increased*
Surgical complexity	low	complex	very complex	very complex	possibly complex

*The risk of NCM is difficult to estimate due to different definitions of NCM and different classifications of CMN used in the literature.
cm: centimetres; NCM: Neurocutaneous Melanocytosis; PAS: Projected Adult Size

Table 1. Guidlines for follow up

	Single CMN			Multiple CMN	
	I CMN <10 cm PAS	**II CMN 10-20 cm PAS**	**III CMN >20 cm PAS**	**IV CMN >20 cm PAS + satellites**	**V >2 CMN 1.5-20 cm PAS***
Dermatologist (or another main practitioner)					
	not standard, but with CMN change or concerns of patient	periodic evaluation	periodic evaluation	periodic evaluation	periodic evaluation
Need to be seen in an expert centre	no	only the first time*	only the first time*	yes	yes
Frequency	when needed	0-1 years: 2x/ year >1 years: every 2 years or 1/year**	0-1 years: 2x/ year >1y years: every 2 years or 1/year**	0-1 years: 3,6,12 months >1 years: Lifetime check-ups 1-2x/ year	0-1 years: 3,6,12 months >1 years: Lifetime check-ups 1-2x/ year
Plastic surgeon***					
	when there are questions about surgery	information about treatment	information about treatment	information about treatment	information about treatment
Need to be seen in an expert centre	no	expert centre is advised	yes	yes	expert centre is advised

Table 1. continued

	Single CMN			Multiple CMN	
	I **CMN <10 cm** **PAS**	**II** **CMN 10-20 cm** **PAS**	**III** **CMN >20 cm** **PAS**	**IV** **CMN >20 cm** **PAS + satellites**	**V** **>2 CMN 1.5-20 cm** **PAS***
Frequency	when needed	at least once	at least once	yearly evaluation	at least once
Paediatrician					
	not needed, regular developmental check-ups by the national children health centre is enough****			periodic evaluation until the age of 5 years	
Need to be seen in an expert centre	not applicable			no	
Frequency	not applicable			once a year	
Psychologist					
when needed can be seen in an expert centre					
Skin therapist					
when needed					
Neurologist, pathologist, radiologist, oncologist					
when complication occur generally in an expert centre					

* Evaluation in an expert centre is indicated when the location or texture of the CMN complicates monitoring of the CMN

** Depending on the clinical manifestations, the dermatologist should decide if lifetime follow-up is needed

*** When the CMN is difficult to excise due to its location, the classification for surgical complexity should be moved to a higher category according to this classification scheme

**** In the Netherlands, monitoring development of children is done by a special health care service.

cm: centimetres; NCM: Neurocutaneous Melanocytosis; PAS: Projected Adult Size.

CASE REPORT

The case report below demonstrates the clinical care of CMN and the still-existing clinical dilemmas encountered by professionals, patients, and parents.

Patient: A 1-month-old girl with a CMN was taken by her parents to visit a CMN expert centre to consult a dermatologist, a plastic surgeon, a paediatrician, a neurologist, and a clinical geneticist.

History: There were no complications during pregnancy, birth, or the weeks after birth. There were no developmental problems and the parents did not notice any symptoms that might suggest seizures or other problems. Soon after birth multiple birthmarks were diagnosed, the largest birthmark being found on her left leg. The child was developing well. There were no melanomas or CMN in the family. The quality-of-life PROMs revealed no abnormalities in the child. However, the PROMs for the mother showed emotional distress, which the mother explained during

the consultation. She was anxious about malignancy because after the birth of her child a clinician in the hospital had told her that the CMN could become malignant. She felt guilty because she thought that the CMN had developed because of something she had done during her pregnancy.

Physical examination by the dermatologist and plastic surgeon: It was a happy, healthy-looking neonate. The largest diameter of the CMN was 9 cm. The projected adult size of such a CMN was calculated as 25 cm. The CMN was located on her left upper leg, right above the knee. She had one CMN of 2 cm on her left arm and two small CMN of 1 cm on her right hand and trunk. The colour of all the CMN was dark brown, with some lighter shades of brown. The texture was smooth and there were no nodules. Hair was growing out of the CMN, the colour of this hair being the same as the hair on her head. According to the Krengel classification, the CMN was classified as follows: Large 1 (>20–30 cm projected adult size), located on the extremities, number of satellites S1 (<20 CMN), colour heterogeneity C1 (moderate), rugosity R0 (none), nodules N0 (none), hypertrichosis H1 (notable).

Physical examination by the paediatrician or neurologist: There were no abnormalities found on neurological physical examination.

Physical examination by the clinical geneticist: There were no signs of a CMN-associated syndrome.

Clinical considerations of the multidisciplinary specialized CMN expert team

First of all, the dermatologist explained that the chance of developing malignancy is much lower than thought previously. The increased risk of this large CMN was estimated at around 1–3%. In comparison, the lifetime risk of developing breast cancer is around 12 % in all women. Furthermore, there were no factors known that could have caused the CMN during pregnancy – a CMN develops by chance. The mother was offered psychological support. She indicated that the explanation by the dermatologist was sufficient and that she did not need psychological treatment.

In this patient, there were no signs for melanoma or premalignant stages of melanoma. According to the Dutch guideline, this patient should be monitored at least twice a year as she has a large CMN with multiple smaller CMN. When she is older, the frequency of monitoring can be discussed with the parents. If the parents detect any changes, they should contact the dermatologist. The skin will be examined and, if needed, the dermatologist or plastic surgeon will remove the changed part of the skin for pathological examination to investigate any histological sign of malignancy or premalignancy.

There is no clinical evidence that removal of the CMN by a plastic surgeon will be a better treatment to prevent melanoma or neurological complications when compared to watchful monitoring. However, removing the CMN might prevent psychological issues.[34] The parents should decide for their child whether the CMN should be treated for cosmetic reasons. It is therefore of great importance that parents are informed about all the benefits and disadvantages of different surgical treatments to enable a shared decision process between the CMN expert team and the parents.

A generally high satisfaction rate of patients and parents is shown for surgical treatment.[47] The disadvantages of all surgical treatments are possible complications, such as bleeding, wound-healing problems, infection, post-operative pain, and scar-related problems. These complications

could affect the child's health and cosmetic/functional outcomes. Because the CMN is located immediately above her knee, her knee function may be impaired if contraction of the scar takes place. Surgical treatment may cause a burden of care for both the patient and her parents due to the need for multiple visits to the hospital, the recovery time, and the psychological burden of treatment. Furthermore, all interventions require general anaesthesia and some of the interventions require multiple surgical sessions.

If the parents wish to have the CMN removed, excision of the CMN is the first choice for interventional treatment.[7] Excision of the CMN with primary closure cannot be performed due to the size of this CMN. Serial excision is complicated by the fact that the skin on the legs is very tight, causing a risk of contraction on the scar which would result in wide scars or expanded CMN skin. Total excision with reconstruction may therefore be performed. Fair results have been shown when reconstruction with tissue expanders has been performed on the lower extremities.[48] However, this location has an increased risk of developing complications due to the mobility of the legs. Although tissue expanders have the best results in young children, complications will increase when this patient starts crawling and walking.[43] Therefore, it might be wiser to wait until she reaches a certain age when it can be explained to her how she should behave with the tissue expander (around 8 years). Excision with reconstruction with a skin graft or with artificial skin (Integra®) may be an option as well. However, the cosmetic results may not always be favourable.

Age of treatment

The principle of removing a CMN as soon as possible to prevent melanoma is now obsolete.[33] However, the skin of a younger child is elastic/stretchable, which might be advantageous for the cosmetic results.[7] Moreover, removal at a young age may reduce or even prevent stigmatization and psychosocial problems. The parents can also choose to wait until the child is old enough to decide for herself whether she wants to be operated. The colour of the CMN can become lighter over time spontaneously and the child might accept the CMN.[8] Parents should be aware that she will then miss school or work due to the operations and post-operative recovery time. There is ongoing discussion as to whether repeated general anaesthesia in young children affects their neurological development.[3,49,50] The advice of the Dutch Association for Anesthesiology says: "preferably no elective procedures before the age of 3 years".[7]

This girl has an elevated risk of having neurological involvement due to her large CMN accompanied by multiple smaller CMN and should therefore be monitored for neurological symptoms and signs. Currently, there is no international consensus on routine MRI screening to diagnose melanocytosis. The team of experts, including neurologists, who compiled the Dutch national CMN guideline advise the following procedures. First, routine MRI screening is not needed in asymptomatic patients. However, all children with an elevated risk, large/giant CMN (>20 cm PAS) or multiple CMN should be screened annually by a paediatrician, at least during the first five years of life. Nonetheless, if there is any suspicion, even a low one, of a neurological complication, an MRI scan of the central nervous system should be performed and evaluated by a CMN expert centre.[3]

The clinical geneticist explains that the mutation of CMN occurs by chance after conception. The mutation is only present in the affected cells and is not in her reproductive cells, so she cannot pass on the mutation to her children.

Molecular analysis of the CMN skin can be done to investigate DNA mutations. At the moment, there are no clinical consequences based on the DNA mutation. Advancing knowledge about the different molecular characteristics of CMN might help in the future to estimate the risk of melanoma or neurological complications.[51] Moreover, new pharmacological therapies may be developed that can be offered to patients with a certain DNA mutation. Skin removal has to take place in order to perform DNA analyses and these analyses are therefore recommended if the skin is removed for other indications.

Uniformity in CMN care and research

The clinical dilemmas demonstrated in this introduction and case report show that there is a need to improve CMN care and research. Different management strategies have been described for CMN. However, high-level evidence regarding the best management options is lacking.

The reason for the low quality of studies is twofold: (1) limited research and low-powered studies due to the rarity of larger CMN; and (2) heterogeneity in current care and research, meaning that there is a lack of uniformity regarding classification, study populations, treatment descriptions, management strategies, the measurement instruments used and the reported outcomes.[38,52] This has precluded pooling and comparison of data in the small number of low-powered studies reported. In order to accomplish high-level evidence studies on larger CMN, it is important to attain uniformity in international care and research.[53] Recently, a Dutch guideline for CMN care was developed through consensus among multidisciplinary national specialists and patient associations.[3] The experts who compiled the Dutch guideline concluded that there was a need to develop internationally accepted standard outcomes and uniformity in CMN care and research. This was internationally supported by experts in the field, including the European Reference Network SKIN.

This thesis aims to conduct the first steps towards homogeneity in international CMN research. We present the Outcomes for Congenital Melanocytic Naevi (OCOMEN) project aiming to develop a Core Outcome Set (COS), i.e. a consensus-based agreed minimum set of outcomes that should be measured and reported in all clinical care of and research on medium, large, and giant CMN.[54] This includes those patients with M1 (1.5–10 cm PAS) on the face or M2 (>10–20 cm PAS) elsewhere, either single or multiple. This COS is intended for the following interventions: surgical (laser/curettage/dermabrasion/excision) and conservative (watchful waiting).

The COS will be developed according to the guidelines of the Core Outcome Measures in Effectiveness Trials (COMET) initiative, the Cochrane Skin Core Outcomes Set Initiative (CS-COUSIN) and Consensus-based Standards for the selection of health Measurement Instruments (COSMIN).

The COS will be developed by working together with patients and professionals to decide *what* should be measured (domains and outcomes) and *how* this should be measured (outcome measurement instruments).[55] Once all researchers and clinicians are using standard classifications, baseline characteristics, and outcomes, care and research will become more homogenous and

reporting bias will be reduced, resulting in data that can be compared in care and research. By means of this project, we are attempting to improve future CMN care and research by developing standard outcome measures.

AIMS AND OUTLINE OF THE THESIS

PART II: CLINICAL CONSIDERATIONS

The first part of this thesis explains how we searched the medical literature to answer important questions regarding CMN management. **Chapter 2** evaluates neurological involvement in CMN patients by means of a systematic review of the literature. Clinicians responsible for the care of CMN patients struggle with the management strategies regarding neurological involvement in this patient group due to the rarity of this condition. To inform these clinicians, we estimated the prevalence of neurological symptoms and signs and provided an overview on what specific neurological symptoms and signs and MRI abnormalities are reported in the literature in order to identify what abnormalities should or could be expected in this patient group. In addition, we summarized and evaluated the recommendations on routine MRI screening reported in the literature.

To be able to assist patients and their families in deciding which treatment suits their personal needs best, adequate information is needed regarding different surgical strategies. **Chapter 3** presents the results of a literature search evaluating the safety and effectiveness of surgical excision of medium-to-giant and/or difficult-to-excise CMN.

PART III: UNIFORMITY IN OUTCOME MEASURES AND INSTRUMENTS

Given the heterogeneity found in CMN care and research, the principal aim of this thesis was to work towards uniformity in outcomes measures for CMN. The Congenital Melanocytic Naevi (OCOMEN) project aimed to develop a "core outcome set" (COS) for medium-to-giant CMN care and research. A COS is a consensus-based (i.e. developed by patients and professionals) agreed minimum set of outcomes that are recommended to be measured in all research on a certain condition. A COS comprises a core domain set (CDS, *what* to measure) and a core outcome measurement set (COMS, *how* to measure).[56]

The first step of this project was to develop a protocol for the development of the CDS, as shown in **Chapter 4**. In addition, this chapter shows the findings of seven focus group sessions enabling patients and parents to specify what outcomes are important to them.

In **Chapter 5**, a systematic review of the literature was performed to identify the outcomes and measurement instruments used for CMN care and research.

Chapter 6 describes the procedure followed with internationally relevant stakeholders (patients/parents and professionals) who aimed to reach consensus on the CDS of care and research. The outcomes identified during the focus group sessions and the systematic reviews given in Chapter 4 and Chapter 5 were classified into domains. Through e-Delphi surveys, relevant stakeholders iteratively rated the importance of domains and outcomes. An online consensus meeting attended by patient representatives and professionals reached consensus on the core domains of the CDS.

To select the appropriate measurement instruments, the domains of the CDS were specified by outcomes. **Chapter 7** shows a second consensus procedure followed with relevant stakeholders to reach consensus on the outcomes describing these domains.

Chapter 8 presents the first step followed towards developing the COMS. We performed a systematic review to identify and describe the outcomes and instruments used in previously published studies. This was an update of the previously performed systematic review presented in Chapter 5. However, this update focuses only on the core outcomes of the COS and their instruments. In addition, Chapter 8 presents a systematic literature search to evaluate the quality of the measurement instruments developed or validated for the domains and outcomes of the COS of CMN.

In summary, this thesis has the following specific aims:

- Chapter 2: Evaluate the prevalence and management regarding neurological involvement in CMN patients.
- Chapter 3: Evaluate the safety and effectiveness of surgical excision of medium-to-giant and/or difficult-to-excise CMN.
- Chapter 4: Provide a protocol for the core domain set for CMN care and research and find outcomes important to patients by means of focus groups.
- Chapter 5: Identify the outcomes and instruments used in CMN care and research.
- Chapter 6: Reach consensus on the core domains of the core domain set.
- Chapter 7: Reach consensus on the core outcomes describing the domains of the core domain set.
- Chapter 8: Identify the core outcomes and their instruments used in CMN research and evaluate the quality of their measurement properties.

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CLINICAL CONSIDERATIONS

Iris Roskam

Skatepark Zeeburgereiland, Amsterdam

2020

In the summer of 2020, the largest skatepark in the Netherlands opened in Amsterdam. The Danish designer of this park assigned Iris Roskam to create artwork for the park referencing typically Dutch Delftware. Roskam drew different skate- and Amsterdam-themed artworks with a ballpoint pen 'the way the way we made scathes in class, when we were bored'. The artwork exists out of 40.000 different tiles in this 4000 square meter skate park. The park is recognized as an important spot for athletes to train, as skating has been selected as an Olympic sport since last year.

2

NEUROLOGICAL SYMPTOMS, SIGNS AND MRI ABNORMALITIES IN CONGENITAL MELANOCYTIC NAEVI PATIENTS AND EVALUATION OF ROUTINE MRI-SCREENING: SYSTEMATIC REVIEW AND META-ANALYSIS

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Submitted

ABSTRACT

Background

A congenital melanocytic naevus (CMN) is a rare skin condition that can be associated with abnormalities of the central nervous system (CNS). These anomalies can sometimes cause severe complications, and incidentally death. Adequate information about aetiology and management is therefore crucial. To identify how to monitor CMN patients, we aimed to estimate the prevalence of neurological involvement in CMN patients and to summarize what specific neurological symptoms and signs and MRI abnormalities are reported in the medical literature. In addition, we summarized and evaluated the recommendations regarding MRI-screening reported in the medical literature.

Methods

This review was registered in PROSPERO and reported according to the MOOSE checklist. A search was conducted in EMBASE (Ovid), PubMed, and the Cochrane Library. We included studies with 10 or more CMN patients, reporting on neurological symptoms and signs or CNS MRI.

Study selection, data extraction and methodological quality assessment were performed by two independent reviewers. A meta-analysis was used to assess the prevalence of neurological symptoms and signs.

Results

Out of 1287 studies, we included fourteen studies. The meta-analysis revealed neurological symptoms and signs in 6.26 % (95%CI: 3.85-10%) of patients with a CMN > 6 cm. Neurodevelopmental delay and seizures were most frequently reported symptoms and signs. CNS melanocytosis and hydrocephalus were the most frequently reported MRI abnormality. It was not possible to estimate the increased risk of neurological involvement in CMN patients due to low quality of evidence and clinical heterogeneity.

Conclusion

Standardization in CMN studies and a multi-centre prospective study are needed to evaluate neurological involvement. Based on current literature, it is not possible to make strong recommendations on routine MRI-screening. For now, every clinical centre should decide on its own policy and weigh the advantages and disadvantages of routine MRI.

Keywords: Congenital melanocytic naevi; neurocutaneous; MRI; neuroimaging; pigment cell; brain; central nervous system; melanoma; melanocytes; melanocytosis.

INTRODUCTION

Congenital melanocytic naevi (CMN) are melanocytic skin lesions that sometimes cover large areas of the body. CMN can have a great impact on patients' lives due to their appearance and risk of development of melanoma or neurological complications.[1-3] The incidence is 1:100 in infants, but large (>20 cm Projected Adult Size (PAS)) and giant CMN (>40 cm PAS) are rare and have an incidence of 1:20.000 and 1:50.000 infants, respectively[4]. CMN are caused by a postzygotic mosaic mutation in the embryonic precursor cells of melanocytes in the ectoderm.[1,5] This mutation can be found anywhere on the skin and/or the central nervous system (CNS).

Various neurological complications are described ranging from mild or no symptoms to death.[6,7] Neurological symptoms and signs (NS&S) in CMN patients can be caused by an excessive number of melanocytes in the CNS, but infrequently other CNS abnormalities are described as well[1,8,9]. Melanin in the CNS causes a brighter signal detected on T1-weighted MRI, called T1-weighted shortening.[10]

Neurological abnormalities of CMN patients were traditionally termed 'neurocutaneous melanosis'.[1] Suggestions are made to discontinue the use of this term and describe the specific abnormality found.[6,7]

Paediatricians, dermatologists, surgeons and neurologists responsible for the care of CMN patients, struggle with the management strategies regarding neurological involvement in this patient group due to the rarity of this condition. To inform specialists involved in clinical care of CMN patients, we aim to estimate the prevalence of neurological involvement (NS&S and MRI abnormalities) in CMN patients and to summarized what specific NS&S and MRI abnormalities are reported in the medical literature in order to identify what abnormalities should be expected in this patient group. In addition, we summarize and evaluate the recommendations on routine MRI-screening reported in the medical literature.

METHODS

This systematic review was registered in PROSPERO (ID=CRD42020177555) and reported according to the MOOSE checklist[11] and the Joanna Briggs Institute (JBI) guide for prevalence systematic reviews.[12]

Literature search

A systematic search was conducted to find any study that reported CMN and NS&S and/or MRI findings (Supporting Information 1). An information specialist (FE) was consulted to develop the search strategy and perform the search. The search was performed in PubMed, EMBASE and the Cochrane Library in February 2021. References of included studies were searched for potentially eligible studies.

Study selection and data extraction

We included all studies without year limits, in Dutch and English, assessing NS&S and CNS MRI abnormalities in ten or more patients. We included studies with patients of any age with CMN > 1.5 cm. We included systematic reviews, cross-sectional studies, cohort studies and controlled clinical

trials. Case reports, descriptive reviews and letters to the editor were excluded. When more than one study was published concerning the same patient cohort or ccase-series, we only included the most recent article with the most detailed description of that particular cohort.

Study selection and data extraction were performed by two independent reviewers to assess eligibility (ACF,ALW) and disagreement was resolved through discussion with another author (ME). The title and abstract of the studies and subsequently the full text of the selected studies were screened. Authors were contacted when articles were not available.

The following data was extracted: study details, patient and CMN characteristics, follow up time, NS&S, CNS MRI characteristics/abnormalities, location of melanocytosis, death due to neurological disease and recommendations for MRI-screening.

Risk of bias and quality assessment

The risk of bias was assessed by two independent reviewers (ACF, ALW) using the JBI Prevalence Critical Appraisal Tool.[12] Quality assessment was performed with GRADE methodology for quality assessment on the outcome level and the Oxford Centre for Evidence-based Medicine for ratings of individual studies.[13,14] Studies were not excluded based on their methodological quality as we expected that the study quality would be generally low.[15]

Analysis

We provided a narrative overview of the following outcomes: specific NS&S, MRI abnormalities, deceased patients and recommendations on MRI-screening. In addition to the PROSPERO protocol, we performed a meta-analysis of weighted means of proportions to estimate the prevalence of neurological involvement in R studio version 1.2.1335. We used a random-effects model, as this is advised for prevalence analysis.[12] In contrast to the protocol, we did not exclude studies with a high risk of bias as we wanted to provide an estimate of the best available evidence. We did exclude studies with a high risk of selection bias for this analysis. When considerable statistical heterogeneity (I^2 > 70 %) was found, we performed subgroup analysis in groups with similar patient characteristics.[16,17]

RESULTS

Search and selection

Fourteen studies, reporting on 2339 patients, met the inclusion criteria. The study selection flow diagram is presented in figure 1.[7,8,10,18-28]

Data extraction and risk of bias assessment

Study, patient and CMN characteristics are shown in table 1. The mean patient age was 5 years and 6 months and ranged between 1 day and 59 years. The female to male ratio was 1.03:1. The classifications/definitions of different CMN size and number of CMN groups were heterogeneous among studies.

Figure 2 shows the risk of bias assessment and Supporting Information 2 shows the complete risk of bias assessment. High risk of bias was found in all studies, regardless of the number of patients included.

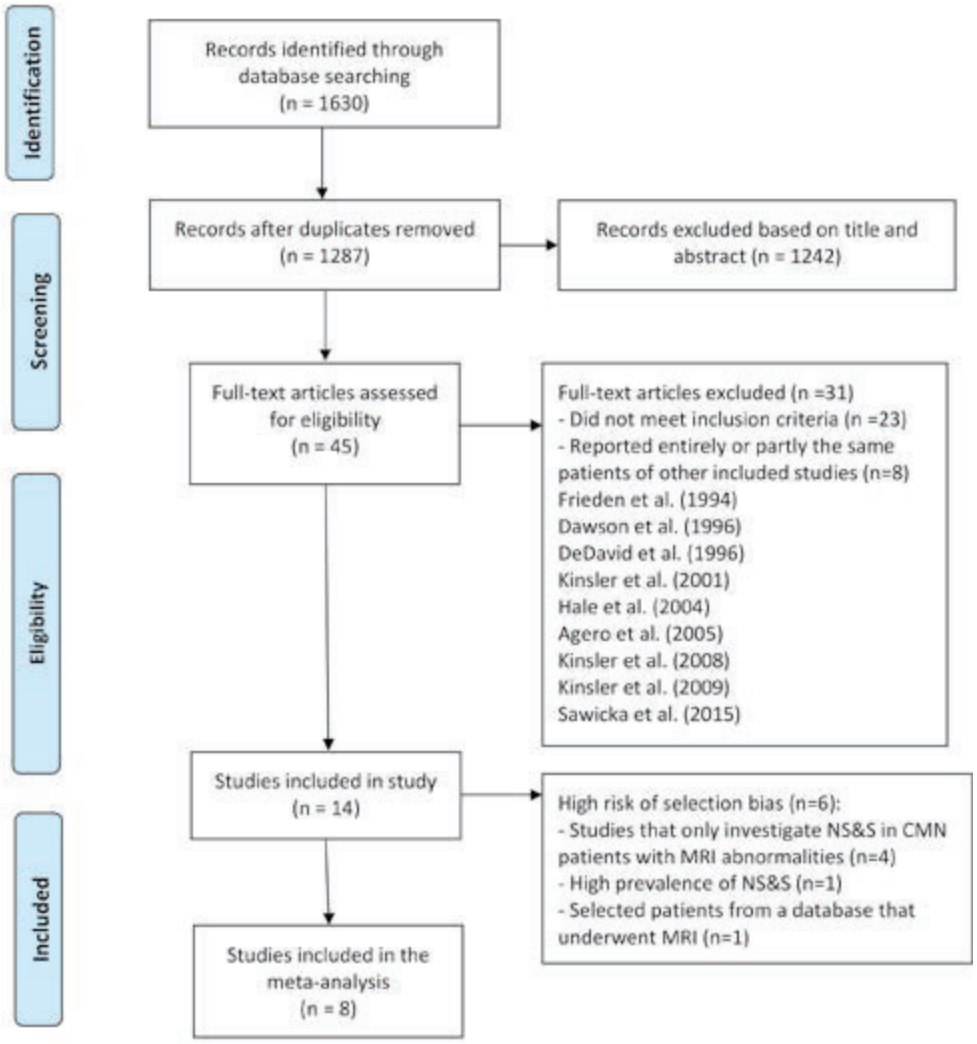

Figure 1. Flow diagram of study selection

Analysis and quality assessment

Descriptive statistics of NS&S, MRI abnormalities and patient death are shown in table 2, 3 and 4. A meta-analysis could only be performed for NS&S prevalence and not for MRI abnormality, due to incomplete data. For the analysis, we excluded four studies from the analysis that only reported on NS&S in patients with MRI abnormalities. Furthermore, we excluded two studies due to (1) much higher prevalence of NS&S (84.5%)[18] and (2) a study design where patients that had undergone MRI imaging were selected from a large database, potentially causing a bias, as it is likely that MRI is performed in individuals in this database considered to be at higher risk of neurological involvement.[27] With our first analysis we found NS&S in 7.04 % (CI 95% 4.47% - 10.93%) in the CMN population, with an I^2 of 71% representing considerable statistical heterogeneity. Therefore, we

Table 1. Study characteristics

Author	Country	Patient number†	Patient age, mean (range; median)	Female : male ratio	CMN location	CMN size and inclusion criteria	Follow-up time mean (range; median)	Level of evidence‡
Ruiz-Maldonado et al. (1997)	Mexico	13	11 yr 7 mo (0.6 -32 yr)	8:5	Whole body	'Giant' CMN involving the head and neck in reportedly asymptomatic patients.	Unreported	4
Bittencourt et al. (2000)	U.S.A.	160	6 yr 6 mo (1-63yr; 1.2 yr)	89:71	Whole body	≥ 20 cm or ≥ 20 cm PAS	66.2 mo SD 64.1 (1- 238 mo; 42 mo)	3
Foster et al. (2001)	U.S.A.	46	5 mo (4 days-8 yr)	22:27	Head, neck, trunk	≥ 9 cm (scalp) or ≥ 6 cm (body) CMN involving the head, neck and dorsal spine	5 yr (2-8 yr) (of 44pt)	3
Bett et al. (2006)	U.S.A.	1072	6 yr 11 mo (1-23 yr)	22:23	Head, neck, trunk (information of extremities CMN available)	≥ 9 cm (scalp), ≥ 6 cm (body) or nevus covering a substantial part of a small body area (face, hand, foot), multiple small/ medium	5.6 yr	3
Chan et al. (2006)	Singapore	39	18 yr 11 mo (1.9-60 yr)	16:23	Whole body	> 10 cm	16.9 y (12 mo-38 y; 15.4 y)	3
Lovett et al. (2009)	Canada	54	1 yr 4 mo (0-14yr)	29:25	Whole body	≥ 9 cm (scalp) or ≥ 6 cm (body) in infants, ≥ 20 cm PAS or at least 3 medium-sized (1.5-19.9 cm diameter) CMN of the head	89 mo (82.5 mo)	3
Ramaswamy et al. (2012)	U.S.A.	14	(1-6 yr; 2.6 yr) (of 8 survivors)	3:11	Unreported	High risk patients, according criteria of Kadonaga and Frieden, ≥ 20 cm PAS or multiple small/medium	Unreported	4
Bekiesinska-Figatowska al. (2014)	Poland	24	(12 days -7 yr)	4:3	Whole body	≥ 9 cm (scalp) or ≥ 6 cm (body), ≥ PAS	(15-62 mo)	4

Table 1. Study characteristics

Author	Country	Patient number†	Patient age, mean (range; median)	Female : male ratio	CMN location	CMN size and inclusion criteria	Follow-up time mean (range; median)	Level of evidence‡
Price et al. (2015)	U.S.A.	45	Unreported	28:17	Whole body	> 10 cm PAS and multiple CMN > 1,5 cm PAS, Krengel classifications	No follow up	4
Waelchi et al. (2015)	U.K.	636	1 yr 6 mo (0.6 yr)	1:2	Whole body	Before 2008: > 2 cm/1% BSA (overlying spine or brain) after 2008: > 1 CMN (regardless the size)	11.0 yr (8.5 yr)	3
Viana et al. (2017)	Brazil	57	8yr 4 mo (2 yr 5 mo)	28:29	Whole body	≥ 20 cm or ≥ 20 cm PAS	5.5 y ± 3.8 SD, (5.2 y)	3
Wramp et al. (2017)	Germany	83	11 yr 4 mo	41:42	Whole body	> 1,5-20 cm PAS, Krengel classification	4.6 yr	3
Jakchairoongruang et al. (2018)	U.S.A.	80	1 yr 10 mo (1 day -22 yr; 6 mo)	Unreported	Unreported	'Large' CMN	(1 mo-11 yr) (of 9pt with brain melanocytosis)	3
Qian et al. (2018)	China	13	36 yr 6 mo (18- 59 yr)	4:9	Whole body	CMN > 20 cm and/or multiple (3 or more) small/medium CMN (neurocutaneous melanocytosis according to Kadonaga and Frieden, included 3 patients without cutaneous CMN)	3 yr	4

CMN: congenital melanocytic naevi, Mo: months, PAS: projected adult size, yr: years

†: CMN patient included in the study

‡: according to the Oxford Centre for Evidence-based Medicine

Figure 2. risk of bias assessment

performed a subgroup analysis of patients with similar patients characteristics: CMN size > 6 cm or >20 cm in adults or multiple medium CMN. In this group we found NS&S in 6.26 % (95%CI: 3.85 - 10 %) with moderate heterogeneity (I^2 = 55%). The forest plots are shown in Supporting Information 3 and 4. The mean age of the patients in the different studies did not correlate with the proportion of patients with NS&S.

It was not possible to perform subgroup analysis in different CMN patient groups based on the age, size, number or locations of CMN groups, due to the lack of uniform definition, clinical heterogeneity or missing data. The quality of evidence regarding the prevalence of NS&S was very low according to the GRADE methodology due to heterogeneity, imprecision of estimates and high risk of bias. The summary of findings table is shown in Supporting Information 5.

Out of 2339 patients included in the study, 576 received an MRI. When excluding the four studies that only reported on NS&S in patients with MRI abnormalities, 511/2107 (24%) patients had an MRI scan. MRI abnormalities were reported in 130 patients (25% of scans). The exact number of patients with MRI abnormalities but no NS&S was unknown, but at least 51 patients in this category were reported. At least 24 patients were reported with NS&S but without MRI abnormalities, but the exact number in this category was unknown as well. The correlation between the amount of CNS melanocytosis and the risk of NS&S or mortality is unclear.[21,22] The patients with diffuse leptomeningeal melanocytosis had poor prognosis.[28] One study reported that isolated intraparenchymal melanocytosis was less associated with need for surgical intervention or mortality, compared with melanocytosis in combination with other MRI abnormalities.[7]

The most frequently reported NS&S were seizures and neurodevelopmental delay, although the exact number is unclear. Melanocytosis, described as T1-weighted shortening, was the most frequently reported MRI abnormality. The most frequently reported location of melanocytosis was in the parenchymatous brain area (table 3). Hydrocephalus/increased intracranial pressure was frequently described as well. Hydrocephalus is a radiological diagnosis that can cause increased intracranial pressure which sometimes causes severe NS&S.

Death was reported for 34 patients (of the total 2339 patients), their details are found in table 4 and Supporting Information 6. Death was due to CNS malignant melanoma (15/34) or proliferating melanocytosis (19/34), a persisting proliferation of melanocytes, with rapid clinical deterioration leading to severe increased intracranial pressure and subsequent death.[29,30] Supporting Information 7 shows the central nervous system melanoma found in the included studies. The majority of deceased patients had multiple cutaneous satellites (Supporting Information 6).

Six studies made recommendations concerning indications for routine MRI-screening[7,8,20-22,26] and one study made recommendations for imaging techniques.[27] Five studies recommended routine MRI-screening in the 'high-risk groups'.[7,8,21,22,26] However, the definition of high-risk group differs between studies (Table 5). Another study argued that screening might not be cost-effective as the absolute risk of neurological involvement in larger CMN appeared to be low in their study.[20]

DISCUSSION

This study provides an overview of NS&S and CNS MRI abnormalities in CMN patients reported in the medical literature. We found an NS&S prevalence of 6.26 % (95%CI: 3.85 - 10 %) in patients with a CMN > 6 cm or multiple medium CMN. A quarter of the performed MRIs (25%) found neurological abnormalities. Due to low quality of evidence, it is not possible to state the prevalence of these outcomes with certainty and to make an association between specific MRI abnormalities and NS&S. The increased risk of clinically relevant neurological abnormalities in CMN patients can therefore not be estimated.

The most frequently reported NS&S were neurodevelopmental delay and seizures. The risk of these NS&S in CMN could not be estimated due to incomplete data or of poor definitions. An estimated 0.5 to 1 percent of the general paediatric population will experience at least one afebrile seizure.[31-34] The prevalence of neurodevelopment delay in CMN patients could not be compared to the general paediatric population as clear definitions of neurodevelopment delay were generally missing in the CMN studies. One study performing routine MRI for all patients, showed seizures or neurodevelopmental delay in CMN patients without MRI abnormalities.[7] However, these NS&S were milder and less frequent than these NS&S in the group with MRI abnormalities, implicating an association between these NS&S and MRI abnormalities.[7]

The most frequently reported MRI abnormalities were melanocytosis (described as T1-weighted shortening) and hydrocephalus. Hydrocephalus and increased intracranial pressure can be caused by obstruction of the ventricular system due to melanocytosis.[30] The severity and nature of the hydrocephalus was not well reported in the different studies.

Other MRI abnormalities besides melanocytosis and hydrocephalus were described as well (table 3). On one hand, these findings may be considered as incidental findings as incidental brain MRI findings are common in the paediatric population.[35,36] On the other hand, these findings might be a part of the "CMN syndrome" i.e. the combination of cutaneous CMN with additional abnormalities.[7,37,38] For instance, Dandy-Walker syndrome was found in eight CMN patients, an association documented in other articles.[39-41] It was difficult to determine what specific MRI abnormalities, besides melanocytosis and hydrocephalus, are associated with CMN.

Table 2. Neurological symptoms and signs in CMN patients

Author	Patient number†	Symptoms signs n (%)	Epilepsy/seizures n (%)	Neurodevelopmental delay n (%)	Symptoms of increased intracranial pressure/ Hydrocephalus‡ n (%)	Other n
Group 1: general CMN group						
Ruiz-Maldonado et al. (1997)	13	11/13 (85%)	1/13 (8%)	5/13 (38%) - Impaired mental status (n=4) - Language retardation and brain immaturity (n=1)	Unreported	Cephalalgia (headache) (n=4) Pyramidal syndrome (n=5) Dysesthesia in nevus (n=4) Soft signs (n=3) Cranial nerves dysfunction (n=2) Hypoacusis (n=1) Motor deficit (n=1) Somniloquy (sleep-talking) (n=1)
Foster et al. (2001)	46	1/46 (2%) 4/49 (8%)§	Possible seizures, number unknown	1/46 (2%) - Developmental delay (most notably in speech development)	Unreported	Generalized hypotonia (n=1)
Bett et al. (2006)	1008 (One patient with a Cafe au lait macula)	43/1008 (4%)	25/1008 (2%)	10/1008 (1%) - Developmental delay (n=7) - Speech delay (n=4)	28/1008 (3%) Hydrocephalus	Depression (n=2) ADHD (n=1) Autism (n=1) Behaviour disorder (n=1) Incontinence (n=1) PTSD (n=1) Right hemimegalencephaly (n=1) Strabismus (n=1) Substance abuse (n=1)
Chan et al. (2006)	39	0/39 (0%)	0/39 (0%)	0/39 (0%)	0/39 (0%)	0
Lovett et al. (2009)	61	5/61 (8%)	3/61 (5%)	1/61 (2%) Learning difficulties	1/61 (2%) Increased intracranial pressure	Behavioural problems (n=1)

Table 2. (continued)

Author	Patient number†	Symptoms signs n (%)	Epilepsy/seizures n (%)	Neurodevelopmental delay n (%)	Symptoms of increased intracranial pressure/ Hydrocephalus‡ n (%)	Other n
Bekiesinska-Figatowska al. (2014)	24	1/24 (4%)	1/24 (4%)	Unreported	Unreported	Unreported
Waelchi et al. (2015)	271	41/271 (15%)	17/263 (6%)	41/271 (15%)	6/18 (33%)¶	Unreported
Viana et al (2017)	57	4/57 (7%)	Seizures (number unknown)	Number unreported - Delay in neuropsychomotor development	Unreported	Unreported
Wramp et al. (2017)	83	9/83 (11%)	1/83 (1%)	3/83 (4%)	2/83 (2%) Increased intracranial pressure	Locomotor impairment (n=2) Deafness in left ear (n=1) Difficulties concentrating (n=1) Central sleep apnoea (n=1) Hearing impairment in both ears (n=1) Visual impairment (n=1)
Jakchairoongruanget al. (2018)	80	17/80 (21%)	Seizures (number unknown)	Unreported	≥ 5 Exact number unreported	Unreported
Group 2: only reporting on NS&S in patients with MRI abnormalities						
Bittencourt et al. (2000)	13	9/13 (69%)	5/13 (38%)	Unreported	4/13 (31%) Hydrocephalus	Dandy-Walker syndrome (n=1) Decreases arm function (n=1) Paraparesis (n=1)
Ramaswamy et al. (2012)	14	14/14 (100%)	7/14 (50%)	6/14 (43%) - Delayed development (n=5) - Mild motor and cognitive delay (n=1)	3/14 (14%) Hydrocephalus 1/14 (7%) Headache due to increased intracranial pressure	West syndrome (n=1)
Price et al. (2015)	12	5/12 (42%)	Unreported	Unreported	Unreported	Unreported

Table 2. (continued)

Author	Patient number†	Symptoms signs n (%)	Epilepsy/seizures n (%)	Neurodevelopmental delay n (%)	Symptoms of increased intracranial pressure/ Hydrocephalus‡ n (%)	Other n
Qian et al. (2018)	13	13/13 (100%)	8/13 (62%)	11/13 (85%) Cognitive impairment	9/13 (69%) Hydrocephalus on MRI 13/13 (100%) Acute or subacute headache and intracranial pressure 4/13 Ventriculoperitoneal shunt	Abduction nerve paralysis, hearing loss, vision loss (n=1)

ADHD: Attention Deficit/Hyperactivity Disorder, CMN: congenital melanocytic naevi, CNS: central nervous system, PTSD: Post-traumatic stress disorder

We identified two study groups. Ten studies reported on a NS&S and MRI imaging in a general CMN population 'general CMN group' (2107 patients) and four studies reported on NS&S only in patients with MRI abnormalities 'only reporting on NS&S in patients with MRI abnormalities'(232 patients).

†: this number represents the group of CMN patients where the proportion of symptoms and signs can be calculated. Patients that were excluded by the individual studies were included in our studies if information about neurological involvement was available about these excluded patients.

‡: hydrocephalus is a radiological diagnosis and not a symptom, but sometimes it was classified as a symptom, however, it was not clear if the diagnosis hydrocephalus was accompanied with symptoms or signs.

§: 3 patients were excluded because they already symptoms before the study a total of 4 patients of 49 had symptoms/signs.

¶: (33%) had hydrocephalus on MRI, of 18 subjects with 'additional pathology' beside melanocytosis and 5/6 were asymptomatic.

Table 3. MRI characteristics/abnormalities and location of melanocytosis

	MRI		Location of MRI abnormalities		
Author	**MRI performed n**	**MRI abnormalities n (%)**	**Leptomeningeal melanocytosis n (%)**	**Parenchymatous melanocytosis n (%)**	**Others Other findings than melanocytosis**
Group 1: general CMN group					
Ruiz-Maldonado et al. (1997)	13/13	7/13 (45%) No CNS melanocytosis	Not applicable	Not applicable	Ventricular system asymmetry (n=4) Calcifications (n=2) Large cisterna magna (n=2) Cortical atrophy, loss of cortico subcortical volume (n=1) Right frontotemporal subgaleal collection (n=1)
Foster et al. (2001)	42/46	14/42 (33%) (10 CNS melanocytosis)	2/10 (20%)	10/10 (100%)	Middle cranial fossa arachnoid cyst (n=1) Chiari type 1 malformation (n=1) Tethered spinal cord secondary to a filum terminal fibrolipoma (n=1) Transient crescentic enhancement over the right parietal convexity (that was not evident on repeated examination seven months later) (n=1)
Bett et al. (2006)	Unreported	Unreported	Unreported	Unreported	Dandy-Walker complex (n=5) Cerebral cortical dysplasia (n=1) Cerebral matrix haemorrhage (n=1) Chiari malformation (n=1) Choroid plexus tumour (n=1) Encephalocraniocutaneous lipomatosis (n=1) Tethered cord (n=1) Unknown tumour (n=1)

Table 3. (continued)

	MRI		Location of MRI abnormalities		
Author	**MRI performed n**	**MRI abnormalities n (%)**	**Leptomeningeal melanocytosis n (%)**	**Parenchymatous melanocytosis n (%)**	**Others Other findings than melanocytosis**
Chan et al. (2006)	7/39 Head (n=5) Spine (n=2)	0/0 (0%)	Not applicable	Not applicable	Not applicable
Lovett et al. (2009)	27/61 (and 1 CT and 1 myelogram)	7/27 (26%) (and 1 CT abnormality)	Unreported	Unreported	- CT scan: 2 hyperdense foci (n=1) - Spinal cord MRI: Mega cisterna magna, increased amount of fluid in post fossa with hydromyelia from C4-T6 (n=1) - Brain MRI: arachnoid cyst (n=1) - One case with ventriculomegaly with haemorrhagic changes, VP shunt, diffuse enhancement of meninges, intraparenchymal hematoma (n=1)
Bekiesinska-Figatowska al. (2014)	24/24	8/24 (33%) (CNS melanocytosis)	4/7 (57%)	7/7 (100%)	Neurofibromatosis type 1 (multiple multilevel roots neurofibromas op MRI) (n=1)

Table 3. (continued)

	MRI		Location of MRI abnormalities		
Author	**MRI performed n**	**MRI abnormalities n (%)**	**Leptomeningeal melanocytosis n (%)**	**Parenchymatous melanocytosis n (%)**	**Others Other findings than melanocytosis**
Waelchi et al. (2015)	271/271	46/271 (17%) (36 (13%) CNS melanocytosis)	3/36 (8%)	35/36 (97%)	Dandy-Walker malformation with hydrocephalus (n=2) Lack of white matter bulk (n=2) Larger ventricles (n=2) Benign intradural tumour (n=1) Choroid plexus papilloma (n=1) Cortical thinning (n=1) Extramedullary dural stranding (n=1) Filum terminal lipoma (n=1) Left frontal lobe meningioma (n=1) Leptomeningeal disease (n=1) Low volume inferior vermis (n=1) Midline posterior fossa arachnoid cyst (n=1) Posterior fossa melanoma (n=1) Right cerebellar astrocytoma (n=1) Small right cerebellar hemisphere (n=1) Spinal cord compression (n=1) Venous angioma left cerebellar hemisphere (n=1)
Viana et al. (2017)	11/57	Unreported	Unreported	Unreported	Unreported
Wramp et al. (2017)	36/83	4/36 (11%) (2 melanoma, 2 CNS melanocytosis)	Unreported	Unreported	Unreported

Table 3. (continued)

	MRI		Location of MRI abnormalities		
Author	**MRI performed n**	**MRI abnormalities n (%)**	**Leptomeningeal melanocytosis n (%)**	**Parenchymatous melanocytosis n (%)**	**Others Other findings than melanocytosis**
Jakchairoongruang et al. (2018)	80/80	35/80 (41%) (33 CNS melanocytosis)	5/33 (15%)	33/33 (100%)	Periventricular grey matter heterotopia (n=3) Dysmorphic cerebellar hemispheres (n=2) Small left-side ventral pons (n=2) Small pons and cerebellum (n=2) Corpus callosum hypogenesis (n=1) Inferior vermian hypoplasia (n=1) Small right cerebellar hemisphere (n=1) Right temporal lobe polymicrogyria (n=1) Vermian hypoplasia (n=1)
Group 2: only reporting on NS&S in patients with MRI abnormalities					
Bittencourt et al. (2000)	38/194	13/38 (34%) (CNS melanocytosis)	Unreported	Unreported	Unreported
Ramaswamy et al. (2012)	14/14	14/14 (100%)	7/14 (54%) Diffuse leptomeningeal deposits	8/14 (62%)	Lower cervical benign spindle cell tumor (n=1) Holocord arachnoid cyst (n=1) Cervical/thoracic cyst (n=1) Dorsal thoracic cyst (n=1)
Price et al. (2015)	Unreported	12 (CNS melanocytosis)	Unreported	Unreported	Unreported
Qian et al. (2018)	13/13	13/13 (100%) (CNS melanocytosis)	13/13 (100%) Diffuse leptomeningeal deposits	Unreported	Leptomeningeal thickening (n=13)

CMN: congenital melanocytic naevi, CNS: central nervous system,

We identified two study groups. Ten studies reported on a NS&S and MRI imaging in a general CMN population 'general CMN group' (2107 patients) and four studies reported on NS&S only in patients with MRI abnormalities 'only reporting on NS&S in patients with MRI abnormalities' (232 patients).

Table 4. Patients with CMN who died due to neurological complications

Total number of patients who died	34 (of a total of 2339 patients), excluding the studies that only reported NS&S in patients with MRI abnormalities: 24 (of a total of 2107 patients)
Age of neurological diagnosis	Mean: 5.86 years, Median: 3 years, Range: birth - 27 years
Age of death	Mean: 7.44 years, Median: 5.15 years, Range: 0.7 - 28 years
Time between diagnosis and death	Mean: 1.43 years, Median: 0.76 years, Range: 0 - 4.4 years
Sex	Female: (n=14), Male: (n=20)
Cause of death	Proliferating melanocytosis of the CNS (n=19), Malignant Melanoma (n=15)
Number of CMN	Multiple (n=27), Single (n=0), Unreported (n=7)
Symptoms/signs	Neurodevelopmental delay (n=9), seizures (n=11), hydrocephalus/ increased intracranial pressure (n= 28)

Table 5. The various definitions for high-risk patients who are suggested to receive routine MRI-screening

Study	Definitions
Bittencourt et al. (2000)	Large CMN on the head, neck or over the dorsal spinal cord
Lovett et al. (2009)	Large CMN on the head, neck or over the dorsal spinal cord or with multiple satellites
Ramaswamy et al. (2012)	CMN on the head, neck or over the dorsal spinal cord
Waelchi et al. (2015)	Children with two or more CMN at birth, independent of projected adult size or site of the largest CMN
Wramp et al. (2017)	CMN of > 40 cm projected adult size or with > 20 satellites

We could not perform a subgroup analysis and estimate the risk of neurological involvement in different subgroups based on CMN locations, sizes, or number. It has been suggested that CMN location on the head, neck or spine should no longer be considered a risk factor for neurological involvement but rather a confounder for large or giant CMN.[5,7]

Studies have shown that the risk increases with size of the largest CMN and the number of satellites.[1,3,5,42,43] We found a positive correlation between increased number of satellites and mortality. However, rare cases are described of individuals with no evident CMN and CNS melanocytosis.[28,44,45] These cases did not meet our inclusion criteria and might be underestimated in this study. Nonetheless, when mutations occur in the ectoderm in an early embryotic stage, mutations could affect both the CNS and large or multiple areas of the skin making larger CMN (>20 cm PAS) or the multiple CMN the 'high risk group' for neurological involvement.[46]

In contrast to the older studies,[1,47,48] recent studies show that the prognosis of symptomatic CMN patients is not necessarily poor.[5,7,22] The proportion of deceased CMN patients reported in these studies may be an overestimation as deceased patients may be better documented compared to asymptomatic patients.

MRI-screening

It is of great importance to detect NS&S at an early stage to provide adequate management.[7,29] Epilepsy in CMN patients can be often effectively treated by antiepileptic drugs, and if resistant, by surgery.[49] Increased intracranial pressure can be treated with ventriculo-peritoneal shunting, and tumours can be resected.[7,28] It is debated whether routine MRI is needed to adequately manage neurological complications in an early stage.[7,20,21,29]

Experts state that clinical management can be substantially adapted by routine MRI-screening.[7,21] Furthermore, it can be used to establish prognosis and prepare families and clinicians for possible severe complications.[21,50] Collecting data by routine MRI-screening may also benefit future understanding of this rare disease.[27] Five of the included studies recommended routine baseline MRI-screening in all high-risk CMN patients. However, the definitions of high-risk were heterogeneous (table 5). The value of repeat MRI-screening in asymptomatic patients is debated.[7,21,22,51] When routine MRI-screening is performed, it is advised to perform screening in the first four months of life as myelinization of the CNS may obscure the melanocytic lesions.[22,23,27]

Others argue that advantages do not outweigh the inconveniences of routine MRI-screening including extra costs, need for anaesthesia, false positives/negatives and uncertainties of the predictive value of routine MRI-screening compared with routine neurological examination.[20,29] It is unclear how many patients benefited from routine MRI and if patients that received MRI only when NS&S appeared had poorer neurological outcomes.

A false negative MRI can lead to false sense of security and misdiagnosis of neurological problems. Four fatal cases from neurological complications in patients with a negative baseline MRI are reported in the literature.[7,19,21,23] This can be explained by a false negative MRI analysis[7,21] or by the fact that new lesions developed after the baseline MRI.[23]

Routine MRI may also cause overdiagnosis of neurological involvement in CMN patients. Incidental MRI findings are common in the general paediatric population[35,36] as well as other aetiologies than melanin can cause T1-weighted shortening.[52,53] Moreover, MRI abnormalities are not necessarily associated with severe neurological complications. The exact proportion is unidentified, but we found at least 51 patients with MRI abnormalities without NS&S. Patients with a positive MRI who never develop complications, could be exposed to unnecessary, possibly invasive, interventions and may live with a fear of severe complications.

The strength of this review is the systematic approach to provide an overview of the evidence gaps of the current literature. The limitation of this study is the clinical heterogeneity and the high risk of bias that hindered accurate statistical data synthesis. The article with the best methodological quality had a higher prevalence of NS&S (15%) than our point-estimate (7.04%).[7] This can be explained by the prospective study design, which implied adequate NS&S reporting. Another possible explanation is that patients with NS&S were more likely to visit that expert centre. From 2008, only patients with multiple CMNs were included, which may have further raised the NS&S prevalence. We did not correct for age. Studies with younger patients are expected to have less cases with NS&S, as young patients can still develop NS&S later in life. However, this was not seen in the results, the mean age of the study groups did not correlate with NS&S prevalence. This may be explained

by the high risk of bias but might also imply that NS&S mainly appear at a younger age. Relevant articles in other languages than English or Dutch could be missed, however, there was a global representation of studies. Large heterogeneity was found between different aspects of the included studies. Firstly, classification of CMN was reported in different ways, this hindered subgroup analysis of different phenotypes. Secondly, the inclusion criteria were different between studies. For instance, the minimum size of CMN differed. Lastly, the reporting of outcomes was heterogeneous. Some studies described a wide variety of outcomes ranging from death to very mild NS&S, while other studies limited their results to a few predefined outcomes.[7] Furthermore, clear definitions for specific NS&S were missing. Especially 'neurodevelopmental delay' could be interpreted in various ways.

The prevalence of outcomes could be an over- or underestimation of the actual risk. Reporting bias could cause an underestimation as some NS&S or MRI abnormalities might not be well reported in the retrospectively reviewed medical records. Publication and selection bias may have caused an overestimation as people with CMNs without neurological complications are less likely to visit specialized medical research centres or be included in registries. The prevalence of MRI abnormalities found in the patients receiving MRI (26%) may be an overestimation, as it is likely that clinicians reserve MRI investigations for individuals they consider to be at high risk, especially in the older studies as MRI was not a commonly used diagnostic tool.[1,47,48]

The rarity of larger CMN (> 20 cm PAS) makes it difficult to conduct research with large sample sizes. To gain high-level evidence regarding CMN, uniformity and standard reporting is needed. We recommend the use of the Krengel classification and the 6B classification[54,55] for homogenous baseline characteristics and the CMN core outcome set for homogenous outcomes, i.e., a consensus-based agreed minimum set of outcomes that should be measured and reported in all clinical research and care of CMN.[15,56,57] NS&S are selected as core outcomes and the next step will be to find a measurement instrument to standardize reporting on NS&S in CMN patients. Our overview can support such a project. Furthermore, our review provides the best available evidence that can be used to inform patients and therefore enables shared decision making.

CONCLUSION

Based on current evidence, it is not possible to make high-level evidence recommendations regarding routine MRI-screening. The risk of severe neurological complications in CMN patients is unclear as well as it is not clear how many patients actually benefited from routine MRI. Standardization in studies and a multi-centre prospective study are needed to improve knowledge on neurological involvement and to evaluate MRI-screening.

For now, every clinical centre should decide on its own policy and weigh the advantages and disadvantages of MRI-screening in high risk CMN. Nonetheless, an MRI is recommended at any age, when an individual develops new NS&S.[7,29]

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SUPPORTING INFORMATION

Online Resource 1. Search strategy

PubMed

("Magnetic Resonance Imaging"[Mesh] OR "Neuroimaging"[Mesh] OR "Neurologic Manifestations"[Mesh] OR "Brain Diseases"[Mesh] OR "Neurodevelopmental Disorders"[Mesh] OR magnetic resonance imaging[tiab] OR MRI[tiab] OR neuroimaging[tiab] OR neurocutaneous melanocytosis[tiab] OR neurocutaneous melanocytosis[tiab] OR neurolog*[tiab] OR fits[tiab] OR epilep*[tiab] OR neuro*[tiab] OR seizure*[tiab] OR hydrocephalus[tiab] OR brain*[tiab] OR neurodevelop*[tiab]) AND ("Nevus"[Mesh] OR nevus[tiab] OR nevi[tiab] OR naevus[tiab] OR naevi[tiab] OR birthmark*[tiab]) AND ("congenital" [Subheading] OR congenital*[tiab] OR bathing trunk*[tiab] OR garment[tiab] OR giant[tiab] OR tierfell*[tiab] OR gigantic[tiab] OR inborn[tiab] OR hereditary[tiab] OR newborn[tiab]) NOT ("Case Reports" [Publication Type] OR case report*[tiab])

EMBASE (Ovid):

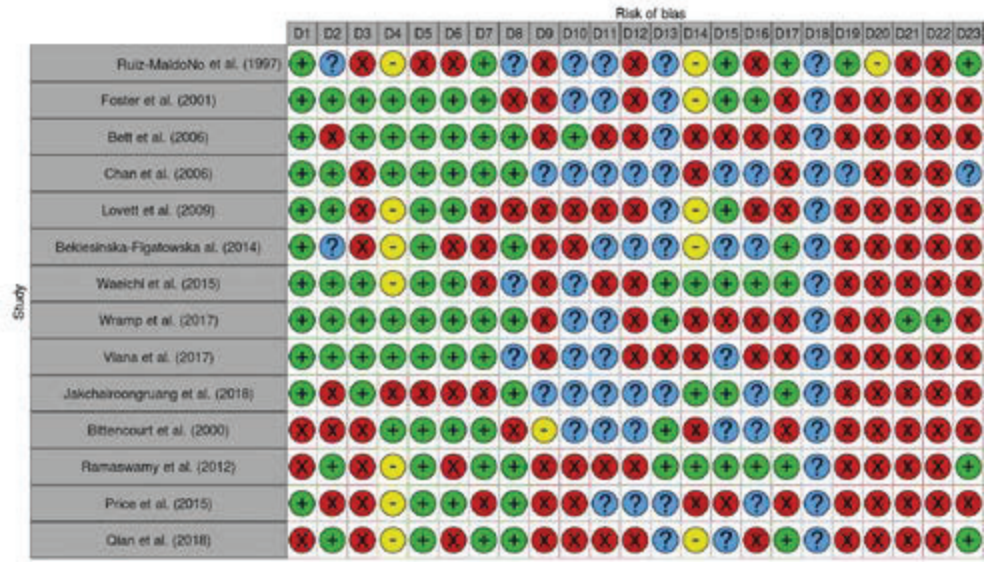
Database(s): **Embase Classic+Embase**

Search Strategy:

#	Searches
1	exp nuclear magnetic resonance imaging/ or exp neuroimaging/ or exp neurologic disease/ or exp brain disease/ or exp mental disease/ or (magnetic resonance imaging or MRI or neuroimaging or neurocutaneous melanocytosis or neurocutaneous melanocytosis or neurolog* or fits or epilep* or neuro* or seizure* or hydrocephalus or brain* or neurodevelop*).ti,ab,kw.
2	exp nevus/ or (nevus or nevi or naevus or naevi or birthmark*).ti,ab,kw.
3	(congenital* or bathing trunk* or garment or giant or tierfell* or gigantic or inborn or hereditary or newborn).ti,ab,kw. or cn.fs.
4	1 and 2 and 3
5	limit 4 to conference abstract status
6	4 not 5
7	case report/ or case report*.ti,ab,kw.
8	6 not 7

Cochrane Library of Systematic Reviews and the Cochrane Central Register of Controlled Trials

ID	Search Hits
#1	(magnetic resonance imaging or MRI or neuroimaging or neurocutaneous melanocytosis or neurocutaneous melanocytosis or neurolog* or fits or epilep* or neuro* or seizure* or hydrocephalus or brain* or neurodevelop*):ti,ab,kw
#2	(nevus or nevi or naevus or naevi or birthmark*):ti,ab,kw
#3	(congenital* or bathing trunk* or garment or giant or tierfell* or gigantic or inborn or hereditary or newborn):ti,ab,kw



Online Resource 2. risk of bias assessment

D1: 1. Was the sample representative of the target population?

D2: 2. Were the study participants recruited in a consecutive way?

D3: 3. Was the sample size adequate (n>40)?

D4: 4. Were the study subjects described in detail?

D5: 4a) Was the CMN size clearly defined?

D6: 4b) Was the number of CMN clearly defined?

D7: 4c) Was the age of subjects clearly defined?

D8: 5. Was the data analysis conducted with sufficient coverage of the identified sample?

D9: 6. Were objective, standard criteria used for the measurement of the condition?

D10: 6a) Was epilepsy clearly defined?

D11: 6b) Was hydrocephalus clearly defined?

D12: 6c) Was neurodevelopmental delay clearly defined?

D13: 6d) Is the melanoma in the central nervous system confirmed?

D14: 7. Was the condition measured reliably?

D15: 7a) Were the symptoms and signs identified by a clinician who is able to perform neurological examination?

D16: 7b) Did the authors describe the measurement instrument used for neurodevelopmental problems?

D17: 7c) Were MRI performed on all investigated subjects?

D18: 8. Was there appropriate statistical analysis?

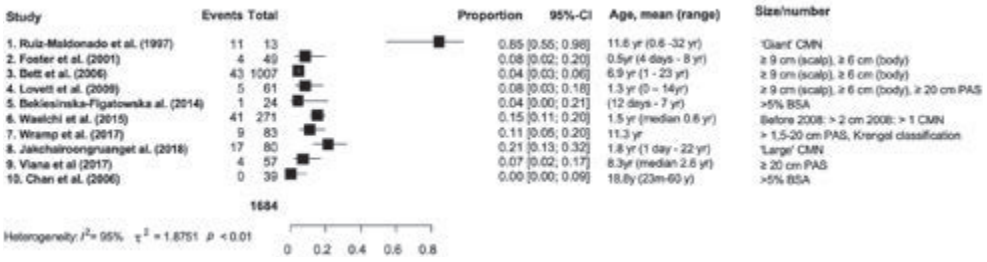
D19: 9. Are important confounding factors for symptoms and signs described?

D20: 10. Were subpopulations identified using objective criteria?

D21: 10b) Was it possible to do a sub-group analysis of different size groups (according to the Krengel classifications)?

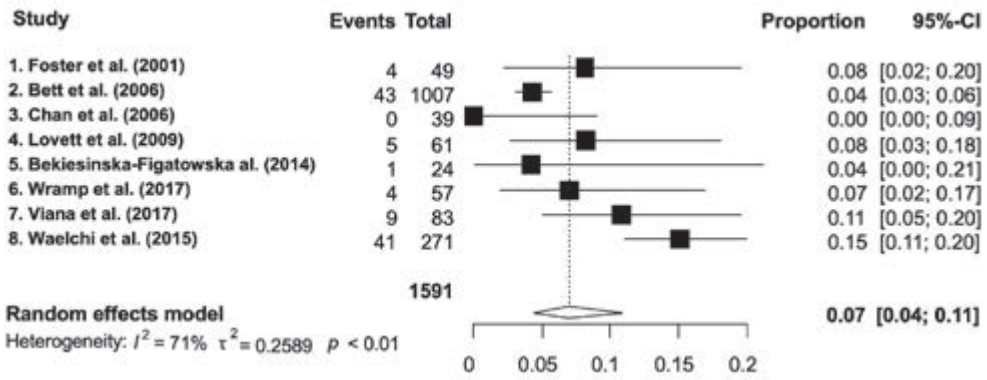
D22: 10d) Was it possible to do a sub-group analysis of different CMN number groups (according to the Krengel classifications)?

D23: 10f) Was it possible to do a sub-group analysis of different age groups?

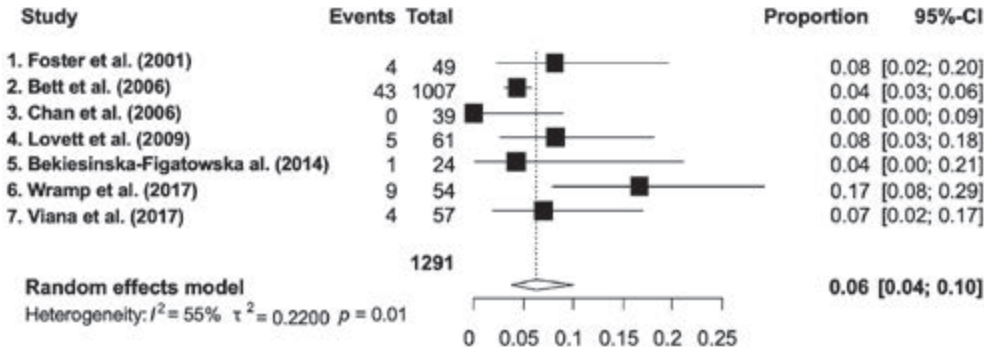


Online Resource 3. Informative forest plot for prevalence of neurological symptoms and signs in a general CMN population. The symptoms and signs of the 'general CMN population' and how the prevalence varies between mean age and CMN size/number.

4a: Studies with all sizes of CMN



4b: Patients with CMN size of at least > 6 cm in children or multiple medium CMN



Online Resource 4. Forest plot: estimation of prevalence of neurological symptoms and signs
These forest plots show the studies used for estimating the prevalence of neurological symptoms and signs

Online Resource 5. CMN patients with melanoma of the central nervous system

Outcome	Result	Subjects (studies)	Quality of evidence (GRADE)
Prevalence of neurological symptoms and signs	7.04 % (CI 95% 4.47% - 10.93%) in the whole group	1591 (9 observational studies)	⨁◯◯◯ VERY LOW[a]
	6.26 % (95%CI: 3.85 - 10 %) patients with similar characteristics: a naevus > 6 cm or multiple medium naevi	1291 (8 observational studies)	
Prevalence of MRI abnormalities	Not possible to estimate due to clinical heterogeneity, selection bias and missing data		⨁◯◯◯ VERY LOW[b]

a: very low quality of evidence due to heterogeneity, imprecision of estimate and high risk of bias.

b: not possible to estimate due to heterogeneity, selection bias and missing data.

Online Resource 6. CMN patients who died due to neurological involvement

Article	Age (age diagnosis neurologic involvement/ age of death)	Sex	Cause of death	CMN location/size/ number of CMN	Signs and symptoms	MRI characteristics
Bittencourt et al. (2000)	78 months † 87 months	Male	Proliferating melanocytosis of the CNS	Lumbosacral/ ≥ 20 cm/number unknown	Dandy-Walker syndrome	Positive for NCM
	11 months (melanoma diagnosis) † 13 months	Male	Cerebral melanoma	Back and trunk/ ≥ 20 cm/number unknown	Hydrocephalus	Positive for NCM
	20 months (melanoma diagnosis) † 21 months	Female	Cerebral melanoma	Lumbosacral/ ≥ 20 cm/number unknown	Decreased function of right arm	Not performed
	36 months † 47 months	Female	Proliferating melanocytosis of the CNS	Trunk/ ≥ 20 cm/number unknown	Seizures, Hydrocephalus	Positive for NCM
Bett et al. (2006)	4 years †4 years	Male	Meningeal melanoma	Bathing trunk nevus/ ≥ 20 cm/with satellites	Unreported	Hydrocephalus
	11 years † 11 years	Male	Meningeal melanoma	Bathing trunk/ ≥ 20 cm/number of satellites unknown	Unreported	Hydrocephalus
	23 years † 23 years	Male	Meningeal melanoma	Back / ≥ 20 cm/ with satellites	Unreported	Hydrocephalus
	27 years † 28 years	Female	Meningeal melanoma	Bathing trunk/ ≥ 20 cm/ with satellites	Unreported	Hydrocephalus (developed at age 27 years)

Online Resource 6. (continued)

Article	Age (age diagnosis neurologic involvement/ age of death)	Sex	Cause of death	CMN location/size/ number of CMN	Signs and symptoms	MRI characteristics
	9 months † 10 months	Male	Proliferating melanocytosis of the CNS	Bathing trunk/ ≥ 20 cm/ with satellites	Unreported	Hydrocephalus Leptomeningeal melanocytosis
	Infancy † 7 years	Male	Proliferating melanocytosis of the CNS	Bathing trunk/ ≥ 20 cm/ satellites number unknown	Seizures, Neurodevelopmental delay	Dandy-Walker complex Hydrocephalus as infant
	3 years † 3 years	Female	Proliferating melanocytosis of the CNS	Bathing trunk/ ≥ 20 cm/ with satellites		Hydrocephalus
	3 years † 4 years	Female	Proliferating melanocytosis of the CNS	Bathing trunk ≥ 20 cm/ with satellites	Seizures	Normal MRI at birth Later: hydrocephalus
	3 years † 9 years	Female	Proliferating melanocytosis of the CNS	Back/ ≥ 20 cm/ with satellites	Seizures (at age 3), Neurodevelopmental delay	Hydrocephalus
	Unknows † 11 years	Male	Proliferating melanocytosis of the CNS	Torso/ ≥ 20 cm/ with satellites	Unreported	Hydrocephalus
	14 months †28 months	Female	Cerebral melanoma	Medium, multiple CMN, 30 satellites	Unreported	Hydrocephalus (only at age 14 months) Positive for NCM (24 months with brain melanoma)
	1 months † 9 months	Female	Proliferating melanocytosis of the CNS	Medium multiple CMN, many satellites	Unreported	Hydrocephalus (at 1 months) Dandy-Walker complex

Online Resource 6. (continued)

Article	Age (age diagnosis neurologic involvement/ age of death)	Sex	Cause of death	CMN location/size/ number of CMN	Signs and symptoms	MRI characteristics
	9 months † 18 months	Female	Proliferating melanocytosis of the CNS	Medium multiple CMN, many satellites	Seizures	Hydrocephalus Dandy-Walker complex
	4 months † 37 months	Male	Proliferating melanocytosis of the CNS	Medium multiple CMN, many satellites	Seizures	Hydrocephalus, Positive for NCM
	2 years † 2 years	Female	Proliferating melanocytosis of the CNS	Medium multiple CMN, many satellites	Unreported	Hydrocephalus, Positive for NCM
	5 years † 8 years	Male	Proliferating melanocytosis of the CNS	Medium multiple CMN, many satellites	Unreported	Hydrocephalus, Positive for NCM
	< 8 years † 8 years	Male	Proliferating melanocytosis of the CNS	Medium multiple CMN, many satellites	Unreported	Hydrocephalus
Lovett et al. (2009)	10 months † 13 months	Female	Proliferating melanocytosis of the CNS Uncontrollable intracranial pressure	Trunk anterior and posterior/ > 20 cm/multiple satellites (>20)	Initially presented with vomiting and signs of increased intra-cranial pressure. Deteriorating mental status Seizures (probably due to haemorrhage caused by V-P shunt) Encephalopathy Ophthalmology: peripapillary pigmentation	Positive for NCM Size of ventricles diffuse enhancement of meninges

Online Resource 6. (continued)

Article	Age (age diagnosis neurologic involvement/ age of death)	Sex	Cause of death	CMN location/size/ number of CMN	Signs and symptoms	MRI characteristics
Waelchi et al. (2015)	Unknown	Male	Cerebral melanoma	Multiple CMN (exact number and size unknown)	Neurodevelopmental delay by time of first MRI	Posterior fossa malignant melanoma
	Unknown	Female	Proliferating melanocytosis of the CNS	Multiple medium CMN/ largest lesion projected adult size < 5 cm/ > 200 nevi	Seizures, Neurodevelopmental delay (moderate global delay) No symptoms at the time of first MRI	Diffuse leptomeningeal melanocytosis and Dandy Walker Malformations with hydrocephalus at 2 weeks. Congenital leptomeningeal disease at 13 days. At 6 months diffuse leptomeningeal melanoma
	Unknown	Female		Location unknown / CMN > 60 projected adult size/ 20-50 satellites	Neurodevelopmental delay (mild) by time of first MRI	Intraparenchymal melanocytosis and subsequent diffuse leptomeningeal melanoma Hydrocephalus
	Unreported	Unreported	Primary CNS melanoma	Unreported	Unreported	Normal initial MRI scan
Wramp et al. (2017)	5.4 years † 5.8 years	Male	Cerebral melanoma (NRAS-Q61R mutation)	Lumbar spine/ 20–30 cm projected adult size/ few satellites (<20)	Symptoms of increased intracranial pressure	Positive for NCM
	9 years † 9 years Died a few weeks after the diagnosis	Female	Metastasized cerebral melanoma	Location unknows/ >60 cm projected adult size/ >50 satellites	Asymptomatic at time of research, developed symptoms shortly before the diagnosis	Positive for NCM

Online Resource 6. (continued)

Article	Age (age diagnosis neurologic involvement/ age of death)	Sex	Cause of death	CMN location/size/ number of CMN	Signs and symptoms	MRI characteristics
Ramaswamy et al. (2012)	15 months † 19 months	Male	No leptomeningeal at 15 months biopsy performed, but spinal lesion benign. CSF negative for malignancy.	Unreported	Epilepsy, focal at 15 months, Neurodevelopmental delay	Diffuse leptomeningeal deposits of the brain and spine, lower cervical benign spindle cell tumour
	13 months † 23 moths	Male	Leptomeningeal melanoma	Unreported	Epilepsy, focal age 13 months, Neurodevelopmental delay	Diffuse leptomeningeal deposits of the brain and spine
	Birth † 4.5 years	Male	Right cerebellar melanoma, skin negative for malignancy	Unreported	Hydrocephalus, Neurodevelopmental delay, Normal development until hydrocephalus developed	Diffuse leptomeningeal deposits of the brain and spine
	9 years † 9 years	Male	CNS and skin negative for malignancy. No leptomeningeal biopsy done	Unreported	Hydrocephalus, Normal development	Diffuse leptomeningeal deposits of the brain and spine
	8 years † 10.5 years	Male	Left gyrus rectus biopsy: leptomeningeal melanoma	Unreported	Epilepsy, focal age 8 years, Neurodevelopmental delay, Normal development until age 8 then progressive decline	Diffuse leptomeningeal deposits of the brain, normal spine MRI

Online Resource 6. (continued)

Article	Age (age diagnosis neurologic involvement/ age of death)	Sex	Cause of death	CMN location/size/ number of CMN	Signs and symptoms	MRI characteristics
	25 years † 28 years	Male	Right frontal melanoma, CSF positive for malignancy	Unreported	Headaches due to increased intracranial pressure, Normal development	Diffuse leptomeningeal deposits, Left temporal and mesial temporal, right frontal melanoma

†: death, CMN: congenital melanocytic naevi, CNS: central nervous system, NCM: neurocutaneous melanocytosis,

Online Resource 7. CMN patients with melanoma of the central nervous system

Author	Melanoma in CNS
Group 1: general CMN group	
Ruiz-Maldonado et al. (1997)	Unreported
Foster et al. (2001)	1/49 (one of the excluded patients)
Bett et al. (2006)	6/1008
Chan et al. (2006)	0/39
Lovett et al. (2009)	0/61
Bekiesinska-Figatowska al. (2014)	1/24 (primary site unknown)
Price et al. (2015)	1/45 (primary site unknown)
Waelchi et al. (2015)	4/271
Viana et al (2017)	1/57 (primary site unknown)
Wramp et al. (2017)	2/83 (primary site unknown (n=1))
Jakchairoongruanget al. (2018)	Unreported
Group 2: only reporting on NS&S in patients with MRI abnormalities	
Bittencourt et al. (2000)	2/194 (primary site unknown n=1)
Ramaswamy et al. (2012)	4/14
Viana et al (2017)	1/57 (primary site unknown)
Qian et al. (2018)	4/13
Total	**22/1937**

Yael Portugheis

Twelve Tribes, Jerusalem

This artwork was chosen by the head of the CMN patient association of Israel. It represents the twelve tribes of Israel, that originated from the descendants of Jacob through his twelve sons. Interestingly, the twin brother of Jacob, Esau, may be the first example in the literature of a person with a giant naevus. It is possible that Esau עֵשָׂו (a word similar to the Hebrew word for "hair" שֵׂעָר) had a giant hairy torso naevus, possibly extending to the extremities, as the Book of Genesis reads: The first came out red, all over like a hairy garment "יֵצֵא הָרִאשׁוֹן אַדְמוֹנִי כֻּלּוֹ כְּאַדֶּרֶת שֵׂעָר" (some references say "cloak" or "mantle") and they called his name Esau. Occasionally giant naevi can look reddish at birth.

Reference: www.nevusnetwork.org

3

SAFETY AND EFFECTIVENESS OF SURGICAL EXCISION OF MEDIUM, LARGE, AND GIANT CONGENITAL MELANOCYTIC NEVI: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Submitted

ABSTRACT

Background

Medium-to-giant congenital melanocytic nevi (CMN) can greatly impact patients' life, due to their abnormal appearance, and association with melanoma and neurological complications. During the last decade, treatment of CMN has shifted from prevention of malignant transformation towards improvement of appearance. Consequently, the risks of excision should be weighed against these benefits. This systematic review aims to elucidate the safety (complications) as primary outcome, and effectiveness (satisfaction and core outcomes) as secondary outcome, of surgical excision of CMN.

Methods

PubMed, EMBASE, and CENTRAL were searched for studies evaluating safety of surgical excision of CMN. Studies were included based on the patients studied: medium-to-giant CMN, and/or lesions requiring serial excision or reconstruction after excision. Pooled outcomes of safety, effectiveness, and all CMN core outcomes, were presented in summary-of-findings tables and meta-analysis of safety per patient was conducted.

Results

1444 articles were found, of which 22 were included, evaluating 643 patients who met the inclusion criteria. The quality of studies was generally low, and reporting of baseline characteristics and outcomes was heterogeneous. Pooled proportions were 9.8% for major wound-related complications, 1.2% for minor wound-related complications, 1.2% for scar-related complications, and 4.3% for anatomical deformations. Cosmetic outcome was rated by patients as excellent in 24.4%, good in 71.0%, and poor/moderate in 4.6% of cases. Core outcomes were scarcely reported.

Conclusions

This literature overview demonstrates that surgical excision of CMN can be safe and effective. We showed that harmonization of baseline characteristics and outcomes is needed in CMN research.

INTRODUCTION

Congenital melanocytic nevi (CMN) are benign proliferations of melanocytes that are present at birth or develop within the very first months of life and can cover large areas of the body.[1-3] CMN are classified by the maximum diameter they are expected to reach by adulthood (projected adult size, PAS)[4], and have an incidence that ranges from 1 in 100 births for small CMN (<1.5 cm PAS), to 1 in 20.000 births for large/giant CMN (>20 cm PAS).[5]

CMN are associated with somatic mutations in NRAS, BRAF, and other genetic alterations[6,7] and patients with large/giant CMN or multiple CMN are at an increased risk of developing melanoma as well as neurological complications.[8,9] Because of these risks and the abnormal appearance, CMN can have a great impact on life.[10,11]

Previously, treatment had primarily been focused on the prevention of malignant transformation at all costs and as early as possible, by removal of the CMN with surgical excision, curettage, or dermabrasion.[12] However, the risk of melanoma development is lower than previously assumed.[13,14] Furthermore, it is not clear whether excision reduces this risk[15], whereas complications of excision may occur.[1] Consequently, during the last decade, treatment indications have shifted from prevention of malignant transformation towards improvement of appearance and psychosocial health, often with less invasive treatment[12,16], although controversy remains.[17,18]

Presently, surgical excision is preferred in general, followed by reconstruction if needed.[1] This need for reconstruction increases with lesion size. Hence, comprehensive information on surgical outcomes is needed to weigh the risks against the benefits, especially since treatment indications have shifted. Two earlier systematic reviews evaluated surgical outcomes in CMN as well. However, one only included studies on small and medium lesions[19], and the other review did not evaluate outcomes of safety.[13] Thus, the risks and benefits of excision remain unclear, especially for CMN that require reconstructive techniques. Therefore, we conducted a systematic review on the safety and effectiveness of surgical excision of medium-to-giant or difficult-to-excise CMN. Safety was our primary outcome, measured by surgical complications. Effectiveness was our secondary outcome, measured by patient and physician satisfaction of cosmetic and functional outcomes, and all core outcomes of the Outcomes for Congenital Melanocytic Nevi (OCOMEN) project[20-23]

METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[25] reporting guidelines. The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), registration no. CRD42021245506.[26]

Literature search

Literature was searched with the assistance of a medical information specialist on April 21, 2021, in PubMed (MEDLINE), Ovid (EMBASE), and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy consisted of keywords on CMN and excisional treatment (Supplemental Digital Content 1). Krengel et al. (2006) demonstrated that the risk of melanoma

is lower than previously considered.[9] Consequently, treatment indications may have changed. Therefore, only articles published since 2006 were included.

Eligibility criteria

This systematic review focuses on CMN that are relatively difficult to excise and/or are particularly noticeable, which may have a greater impact on quality of life (QoL). Therefore, we aimed to included studies on excision of large and giant CMN (>20 cm PAS), as well as CMN located on the head or neck of at least medium size (≥1.5 cm PAS)[4]. When the PAS was not reported, we included studies with CMN that required serial excision or reconstruction after excision, potentially being an indicator of medium-to-giant and/or difficult-to-excise CMN. If studies reported both eligible and non-eligible CMN and/or treatments, only eligible cases and treatments were included.

Full eligibility criteria are listed in Table 1.

Study selection

Study selection, data extraction, and critical appraisal were performed by two independent, blinded reviewers (HAG, ACF). Disagreement between individual judgments was resolved by consensus, or by consulting the final supervisor (CMAMH). After title and abstract screening, studies were selected based on full-text, and reasons for exclusion were collected.

Data extraction and analysis

Data were extracted on study-, patient-, and lesion-characteristics, used classification system for CMN size, and (previous) treatment characteristics. Surgical complications were extracted as the outcomes of safety. Patient and physician satisfaction of cosmetic and functional outcomes were extracted as outcomes of effectiveness. In addition, all outcomes of the Outcomes for

Table 1. Eligibility criteria. cm = centimeter, CMN = congenital melanocytic nevus, PAS = projected adult size

Inclusion	Exclusion
✓ Patients of all ages with CMN, without limitations concerning any previously performed treatment	× No full-text available despite contacting authors
✓ Patients treated with surgical excision	× Non-human
✓ CMN > 20 cm PAS and located on the trunk or extremities, or CMN ≥ 1.5 cm PAS and located on the head or neck, or any CMN requiring reconstruction after excision, or any CMN requiring serial excision.	× Articles in languages other than English, French, or Dutch
✓ Evaluation of complications of surgical excision	× Treatment results not specified for CMN that meet the criteria for size, location, and treatment
✓ Original study (observational study or randomized controlled trial)	
✓ At least 10 patients who meet the criteria for CMN size, location, and treatment	

Congenital Melanocytic Nevi (OCOMEN) project[20-23] were extracted. These included outcomes of QoL, malignancy, neurological symptoms and signs, and skin appearance.

Complications were categorized into wound-related complications, scar-related complications, and anatomical deformations. Wound-related complications were subclassified using the extended Clavien-Dindo classification of surgical complications.[27] This classification distinguishes five grades of severity, of which grade I-II were categorized as minor, and grade III-V as major wound-related complications. Minor wound-related complications typically demand no invasive intervention, whereas major complications do. Complications that were reported with too little detail to objectively classify them as minor or major, were counted as major in the meta-analysis.

Results of patient and/or physician overall satisfaction of treatment outcome were interpreted as satisfaction with cosmetic results. Ordinal measures for cosmetic and functional outcomes were converted into a single scale with three levels: 'poor/moderate', 'good', and 'excellent'. Results were classified as 'poor/moderate' if terms such as poor, moderate, fair, or bad were used, they were classified as 'good' for terms such as good, pleased, satisfactory, or acceptable, and classified as 'excellent' for terms such as excellent, or very/high satisfactory.

Non-quantified results were summarized narratively, whereas inconclusively reported results were excluded from synthesis.

Statistical analysis

Descriptive statistics for patient-, CMN-, and treatment-characteristics were calculated and specified for included CMN that met the eligibility criteria. Complication rates were calculated, defined as complication per patient. Studies that reported incomplete, inconclusive, or narrative results were excluded from meta-analysis. Meta-analysis of complication rates was executed in RStudio (version 1.4.1717).[28] A subgroup analysis of different treatment modalities was performed if there was sufficient clinical homogeneity, treatments were clearly defined, and outcomes were reported per modality. Anticipating heterogeneity, random-effects models were applied, and heterogeneity was expressed by the I^2 statistic.[29]

Critical Appraisal and Quality Assessment

All included studies were assessed with the Joanna Briggs Institute Critical Appraisal Checklist for Case Series[30] (Supplemental Digital Content 2). Results were weighted by study size. Anticipating overall limited study quality, no study was excluded based on risk of bias.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE[31]) approach to rate the quality of the evidence for all individual outcomes and used the GRADEpro GDT[32] format to create summary-of-findings tables.

RESULTS

The search yielded 1444 articles, of which 22 were included.[33-54] These evaluated a total of 691 patients, of which 643 were treated with surgical excision of 700 CMN. A PRISMA flow chart of the study selection is provided in Figure 1.

Patient-, CMN-, and (previous) treatment-characteristics are presented in Table 2. All studies collected data retrospectively and all were performed in university (affiliated) hospital clinics.

Patient and lesion characteristics

The mean number of eligible patients was 29, range 10-136. The youngest patient was three months at first excision[40], the oldest 36 years.[49] Follow-up ranged from 1 month to 20 years. Most patients had giant CMN. However, different definitions for GCMN were used, as shown in Table 3.

Treatment characteristics

Further treatment details are presented per study in Supplemental Digital Content 3. Twenty-one of the 22 included studies quantified treatment modalities, for 599 patients: 316 procedures of excision with tissue expansion, 256 with skin grafts, 103 with non-expanded flaps, and 14 with artificial skin (Integra). No reconstruction was required for 83 patients treated with serial excision, and 35 with a single-stage excision.

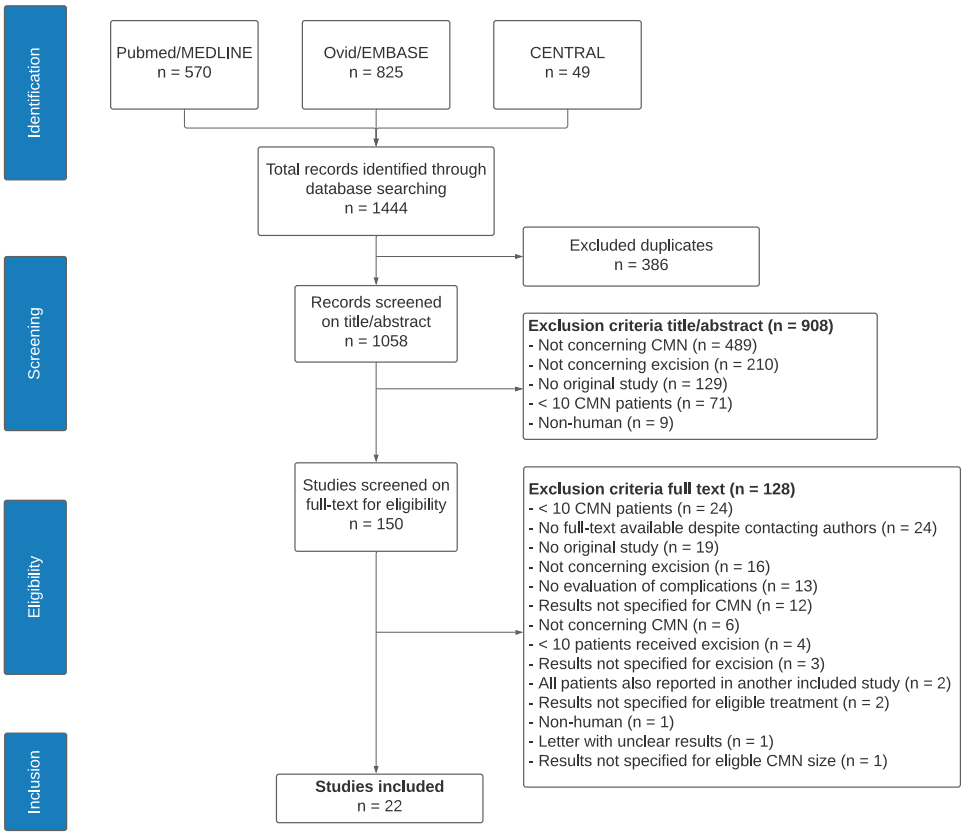

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study screening and selection

Safety of surgical excision

A summary of findings is presented in Table 4. Complications of surgical excision per study are presented in Supplemental Digital Content 3. Details of meta-analyses are provided in Supplemental Digital Content 4.

The rate for major wound-related complications was 9.8% (confidence interval (CI) 4.1 - 21.6%, 127 complications in 622 patients in 21 studies) and for minor wound-related complications 1.2% (CI 0.3 – 5.1%, 16 complications in 622 patients in 21 studies). The rate for scar-related complications was 1.2% (CI 0.2 - 7.1%, 45 complications in 603 patients in 21 studies) and for anatomical deformations 4.3% (CI 1.2 - 14.6%, 100 complications in 610 patients in 20 studies). Statistical heterogeneity (I^2) was "not important" for minor wound-related and scar-related complications and "substantial" for major wound-related complications and anatomical deformations.[29]

Effectiveness of surgical excision

A summary of findings is presented in Table 5. Effectiveness of surgical excision per study is provided in Supplemental Digital Content 5. Functional outcomes were reported by only small numbers of studies. Core outcomes such as scar assessment, outcomes of QoL, neurological symptoms and signs, and skin appearance, were scarcely reported.

Patient satisfaction with cosmetic outcome was pooled for six studies , reporting an excellent outcome in 24.4%, good in 71.0%, and poor/moderate in 4.6% of cases.[43-46,48,53] Physician satisfaction was pooled for ten studies and was good in 70.1%, excellent in 17.3%, and poor/moderate in 11.7% of cases.[35,36,39,41,48,51,53,54].

Twelve studies presented histopathological results of excised lesions from 272 patients, in which no malignancy was detected.[35,37-40,42,44,45,50,52-54] Post-excision malignancy incidence was reported by seven studies, evaluating 339 patients, in which four cases of melanoma occurred.[34,35,39,47,48,52,53]

Seven studies evaluated color changes and reported repigmentation in 15.5% of patients[37,46,48,53] and hyperpigmentation in 12.9% of patients.[34,39,54] For most of these patients, it is unclear whether the lesion had been excised completely. However, Zaal & Van Der Horst reported repigmentation after tissue expansion and complete excision of scalp nevi, although it is not clear whether this complete excision was confirmed by histopathology.[53]

Sub-group analysis

Sub-group analysis of different modalities was not feasible as most studies did not assess different modalities and/or report outcomes separately for each. Furthermore, there was clinical heterogeneity between and within different modalities, including different definitions of treatment, different indications, and different CMN characteristics.

Critical Appraisal

Figure 2 summarizes the results of the critical appraisal. All studies were of limited quality. Results of critical appraisal per study are provided in Supplemental Digital Content 2.

Table 2. Study-, patient-, lesion-, and (previous) treatment-characteristics.

Author (year); country	No. of patients (no. of females)	Age at first excision: mean (range)	CMN size	CMN size classification	CMN location
Multiple modalities; results not specified per modality					
Margulis et al. (2009); USA	44 (NR)	NR (6 mo – 17 yr)*	NR	NR	Head/neck: 44
Multiple modalities; results (partially) specified per modality					
Adler et al. (2009); USA & Israel	14 (6)	4.5 yr (7 mo – 13 yr)	NR	NR	Head/neck: 14
Ceballos-Rodríguez et al. (2021); Spain	136 (83)	34 (SD 61.45) mo	GCMN: 136 - Mean 39.27 (range 20 130) cm PAS	GCMN defined as: > 20 cm PAS	- Head/neck: 38/136 - Trunk: 68/136 - Extremity: 29/136 - Multiple CMN: 1/136
Goil et al. (2018); India	17 (10)	18.6 (14 – 24) yr	GCMN: 17	GCMN defined as: CMN that precludes complete excision and simple primary closure without the need for expansion, skin graft or flap.	Head/neck: 17
Hong et al. (2019); Vietnam	20 (NR)	NR	GCMN: 44 in 20 pts	NR	NR
Li et al. (2021); China	CMN: 12 (5)	5 (3-21) yr*	GCMN: 12	NR	Extremity :12
	Non-CMN: 2 (2)*	NA	NA		NA

CMN skin appearance 1.Color 2.Texture 3.Satellites 4.Hairiness	Excised specimen 1.Histopathology 2.Molecular characteristics	Previous treatment	Treatment modality	Follow-up: mean (range)
NR	NR	NR	"Excision with reconstruction" (including SG, TE, flap): 44 pts	NR (6 mo - 20 yr)
NR	NR	NR	36 procedures in 14 pts - FTSG (n=18) - Non-expanded flap (n=13) - TE (n=5)	1.6 yr (1 mo - 13 yr)
NR	NR	NR	172 procedures in 136 pts - TE (n=81) - SG (n=62) - SE (n=29)	9.2 (6.3 - 19.4) yr
1. NR 2. NR 3. NR 4. Hairy GCMN: 17/17	1. Malignancy: 0/17 2. NR	NR	20 procedures in 17 pts - Free flap (n=3) - TE (n=12) - FTSG (n=4) - STSG (n=1)	16.2 (SD 7.2) mo
NR	NR	NR	44 procedures in 44 CMN in 20 pts - Distant flap (n=1) - Adjacent flap (n=2) - TE (n=6) - SG (n=16) - SE (n=16) - Primary closure (n=3) ‡	6 mo†
NR	NR	SG on hand: 1/12 pts	- TE (with transferred flap): 9 pts - TE (with transferred flap) + STSG: 3 pts NA	NR

Table 2. (continued)

Author (year); country	No. of patients (no. of females)	Age at first excision: mean (range)	CMN size	CMN size classification	CMN location
Mérigou et al. (2009); France	Operated: 65 (NR)	<6 mo: 67% of pts	- Small: 11/65 - Medium: 47/65 - Giant: 7/65	- Small: <1.5 cm - Medium-large: 1.5-20 cm - Giant: ≥20 cm	- Head/neck: 35% - Trunk: 28% - Extremity: 37%
	Non-operated: 43 (NR)		- Small: 16/43 - Medium: 27/43		
Rehal et al. (2011); USA	36 (23)	7 yr (NR)	GCMN: 36 - <10 cm: 23/36 - 11-20 cm: 5/36 - >20 cm: 6/36 - Unknown: 2/36	NR ("International Classification of Diseases 9 code for giant hairy nevus")	36 GCMN in 51 locations (some covered multiple locations) - Head/neck: 33/51 - Trunk: 10/51 - Extremity: 8/51
Warner et al. (2008); USA	40 (25)	5.14 (0.5 - 15) yr	GCMN: 40 - Mean 10 (range 0.5-75) %TBSA	GCMN classified as: ≥20 cm	NR
One combination of different modalities					
Dong et al. (2020); China	21 (9)	10.6 (2 – 30) yr*	GCMN: 21 - Range: 5×6 to 13×15 cm	GCMN defined as: >20 cm^2	Head/neck: 21
Ma et al. (2017); China	11 (6)	6.6 (3 - 21) yr*	GCMN: 11 - Mean 5.5 (range 3-7) %TBSA	GCMN defined as: - In newborns ≥2 %TBSA - In older children and teenagers >20 cm	Extremity: 11

CMN skin appearance 1.Color 2.Texture 3.Satellites 4.Hairiness	Excised specimen 1.Histopathology 2.Molecular characteristics	Previous treatment	Treatment modality	Follow-up: mean (range)
NR	NR	- Attempts with different laser techniques: "some patients" - Curettage: 2/65 pts	- Non-expanded flap: 51 pts - TE: 12 pts - SG: 2 pts - Curettage: 2 pts‡ NA	33 mo (8 mo - 10 yr)
1. NR 2. NR 3. >1 lesion: 4/36 pts 4. Giant hairy nevus: 36/36 pts	1. 66 examined specimen: - Compound: 49/66; Intradermal: 13/66 - Nevus sebaceous: 3/66; Organoid nevus: 1/66‡ 2. NR	NR	50 procedures in 36 pts - TE (n=10) - FTSG (n=12) - STSG (n=5) - SE (n=17) - Integra artificial skin (n=2) - Laser (n=1); Kenalog injection (n=3)‡	NR
NR	1. 38 examined pts: Compound: 16/38; Intradermal: 14/38; Junctional: 3/38; Neurotinization: 2/38; Atypia: 1/38; Dysplasia: 1/38; Severe atypia: 1/38 2. NR	≥1 previous surgical procedure: 13/40 pts	63 procedures in 40 pts - TE (n=10) - FTSG (n=7) - STSG (n=22) - Cultured SG (n=3) - Allograft (temporary) (n=3) - Primary closure (n=18)‡	NR; for three patients with histopathologic cytoatypia: mean 11.25 yr
1. Black CMN: 21/21 2. NR 3. NR 4. NR	NR	NR	TE + SG: 21 pts	3 yr†
NR	1. Melanoma: 0/11 2. NR	NR	TE (with transferred flap) + SG: 11 pts	NR (3 mo - 5 yr)

Table 2. (continued)

Author (year); country	No. of patients (no. of females)	Age at first excision: mean (range)	CMN size	CMN size classification	CMN location
Flap					
Liu et al. (2020); China	17 (7)	15 (1 - 33) yr	17 divided CMN Upper eyelid: - Small: 11/17; Medium: 2/17; Large: 4/17 Lower eyelid: - Small: 12/17; Medium: 3/17; Large: 2/17	- Small: <1.5 cm - Medium: 1.5–2.0 cm - Large: > 2.0 cm	Head/neck: 17
Zhu et al. (2009); China	10 (4)	11.8 (5 - 18) yr	10 divided CMN Upper eyelid: - Small: 6/10; Medium: 1/10; Large: 3/10 Lower eyelid: - Small: 1/10; Medium: 7/10; Large: 2/10	- Small: <1.5 cm - Medium: 1.5–2.0 cm - Large: > 2.0 cm	Head/neck: 10
Tissue Expansion					
Fahmy & Mazy (2010); Egypt	12 (3)	6.8 (2 – 12) yr*	GCMN: 12 - Mean 21.5 (range 17-35); median 22 cm PAS	GCMN defined as: ≥20 cm PAS	Trunk: 12
Kim et al. (2020); Korea	55 (NR)	6.59 (SD 3.88) yr*	88 GCMN in 55 pts	NR	88 CMN in 55 pts: - Head/neck: 26/88 - Trunk: 37/88 - Extremity: 25/88

CMN skin appearance 1.Color 2.Texture 3.Satellites 4.Hairiness	Excised specimen 1.Histopathology 2.Molecular characteristics	Previous treatment	Treatment modality	Follow-up: mean (range)
1. Darkly pigmented lesions: 17/17 2. NR 3. NR 4. "Hair on some lesions"	1. Compound: 12/17; Intradermal: 4/17; Junctional: 1/17 2. NR	NR	Advanced orbicularis oculi myocutaneous (OOMC) flap: 17 pts	32 (10 - 80) mo
1. Darkly pigmented lesions: 10/10 2. NR 3. NR 4. NR	1. Melanocytic: 9/10; Melanocytic with cellular element: 1/10 2. NR	None	18 procedures in 10 pts - Orbicularis oculi muscle (OOM) flap (n=10) - Retroauricular superficial musculoaponeurotic system (SMAS)-pedicled flap (n=3) - Reversal superficial temporal artery (STA) flap (n=3) - Single-stage primary closure for upper eyelid part of the lesion (n=2)[‡]	NR (6-36 mo)
1. NR 2. NR 3. NR 4. Woolly nevus: 2/12	1. "Any melanotic changes": 0/12 2. NR	NR	TE: 12 pts	NR
NR	1. - Compound: 52/88; Intradermal: 27/88 - Nevus sebaceous: 6/88; Blue nevus: 1/88; Lentiginous compound: 2/88[‡] 2. NR	NR	TE for 88 CMN in 55 pts - Single TE (n=64) - Serial TE (=31)	23.74 (SD 14.10) mo

Table 2. (continued)

Author (year); country	No. of patients (no. of females)	Age at first excision: mean (range)	CMN size	CMN size classification	CMN location
Maillet-Declerck et al. (2012); France	CMN: 12 (NR) Non-CMN: 3 (NR)ǂ	15.6 (9 – 23) mo NA	NR	NR	Head/neck: 12 NA
Zaal & Van Der Horst (2009); The Netherlands	17 (11)	9.4 (4 - 36) mo	GCMN: 17 - Mean 3.3 (range 2-5); median 3.5 %TBSA	GCMN defined as: >1 %TBSA in the face/ neck >2 %TBSA elsewhere	Head/neck: 17
Skin Graft					
Dai et al. (2016); China	20 (8)	3.8 yr (6 mo - 9 yr)	Large/giant CMN: 20	Large/giant CMN defined as: - In infants/toddlers >2% TBSA - In adults > 20 cm	- Head/neck: 10/20 - Extremity: 10/20
El-Sabbagh & Hassan (2017); Egypt	16 (12)	8.17 yr (4 mo - 22 yr)*	GCMN: 16 - Head/neck: range 6x7 cm to 15x25 cm) - Trunk: range 14x18 to 30-35 cm) - Extremity: range 6x10 to 18x20 cm)	GCMN defined as: CMN that cannot be closed primarily after excision	- Head/neck: 9/16 - Trunk: 4/16 - Extremity: 3/16
Schiestl et al. (2010); Switzerland	12 (8)	3.8 yr (7 mo - 11 yr)	GCMN: 12 - Mean 4.2 (range 1-12) %TBSA	GCMN defined as >1 %TBSA in the face >2 %TBSA elsewhere	- Head/neck: 3/12 - Trunk: 6/12 - Extremity: 3/12
Primary Closure					
Hassanein et al. (2015); USA	21 (10)	4.3 yr (3 mo - 15 yr)	Mean 2.2 (SD 1.2) %TBSA	Size in %TBSA	- Head/neck: 7/21 - Trunk: 3/21 - Extremity: 11/21
Qiao et al. (2019); China	35 (27)	20.4 (3 - 36) yr	Mean 5.5 (SD 1.6); range 3.5-11 cm PAS	PAS in cm	Head/neck: 35

cm = centimeter, FTSG = full-thickness skin graft, (G)CMN = (giant) congenital melanocytic nevus, mo = month, NA = not applicable, NR = not reported, PAS = projected adult size, pts = patients, SD = standard deviation, SE = serial excision, SG = skin graft, STSG = split-thickness skin graft,

CMN skin appearance 1.Color 2.Texture 3.Satellites 4.Hairiness	Excised specimen 1.Histopathology 2.Molecular characteristics	Previous treatment	Treatment modality	Follow-up: mean (range)
NR	NR	NR	TE: 12 pts NA	3.1 yr (7 mo - 6.1 yr) NA
NR	NR	NR	TE: 17 pts	8.7 (1.5 - 16) yr
NR	1. Melanoma: 0/20 2. NR	NR	- FTSG: 6 pts - FTSG + STSG: 14 pts	1 yr (6 mo – 2 yr)
1. NR 2. Verrucous texture: 16/16; Associated with lumps: "sometimes" 3. NR 4. NR	1. Malignancy: 0/16; "Hamartomatous lesions formed of dermal nests of melanocytes +/- melanin. Spindled melanocytes deep in the dermis. Junctional activity." 2. NR	Operation for GCMN, 2 years before: 1/16 pts	- "Meshed SG": 4 pts - FTSG + STSG: 4 pts - STSG: 8 pts	NR (6 mo - 1 yr)
NR	NR	Incomplete excision after TE: 1/12 pts	Integra Artificial Skin + STSG: 12 pts	2.2 (0.5 - 4) yr
NR	1. Malignancy: 0/21 2. NR	NR	SE: 21 pts	4.1 yr (NR)
NR	NR	Excision with SG: 1/35 pts	Single-stage excision with primary closure: 35 pts	1 yr†

%TBSA = percentage of total body surface area, TE = tissue expansion, yr = year, *age not otherwise specified, †follow-up not otherwise specified, ‡excluded from this systematic review

Table 3. Definitions of giant congenital melanocytic nevus (GCMN) used by studies that included

	Definition of giant congenital melanocytic nevus	No. of studies
1)	CMN not amenable to excision without the need for reconstruction	3
2)	> 1 %TBSA in the head/neck region, > 2 %TBSA elsewhere on the body or extremities	2
3)	≥ 2 %TBSA in newborns, > 20 cm in diameter in older children, teenagers, and adults	2
4)	> or ≥ 20 cm PAS	2
5)	≥ 20 cm	2
6)	> 20 cm^2	1
7)	No definition reported	3

GCMN. cm = centimeter, CMN = congenital melanocytic nevus, PAS = projected adult size, %TBSA = percentage of total body surface area

Table 4. Safety of surgical excision: summary of findings.

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
Major wound-related complications - Defined as Clavien-Dindo Grade III-IV (invasive intervention typically demanded) - Follow-up: range 1 mo - 20 yr	Complication rate: **9.8%**, CI 4.1% - 21.6%, range 0.0% - 85.5% Total of 127 complications: Infection (n=39)‡, exposure/extrusion of tissue expander (n=24), graft loss (n=18)§, hematoma / seroma (n=16), dehiscence (n=15), flap necrosis (n=6), rupture of tissue expander (n=5), failure of tissue expander (n=3), malposition of tissue expander (n=1) 35 of these 127 complications were not reported with sufficient data to objectively classify them as major or minor complications: Dehiscence (n=15), infection (n=10), hematoma / seroma (n=2), graft necrosis (n=8) 1 study reported only narrative results: Dong (n=21) "poor skin grafting"	622 (96.7)	21 (95.5)	⊕◯◯◯ VERY LOW [a, b]
Minor wound-related complications - Defined as Clavien-Dindo Grade I-II (invasive intervention typically not demanded) - Follow-up: range 1 mo - 20 yr	Complication rate: **1.2%**, CI 0.3% - 5.1%, range 0.0% - 25.0% Total of 16 complications: Graft loss (n=4), seroma (n=4), flap necrosis (n=3), dehiscence (n=2), infection (n=1), hematoma (n=1), exposure of tissue expander filling valve (n=1)‖	622 (96.7)	21 (95.5)	⊕◯◯◯ VERY LOW [a, b]

Table 4. (continued)

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
Scar-related complications - Follow-up: range 1 mo - 20 yr	Complication rate: **1.2%**, CI 0.2% - 7.1%, range 0.0% - 75.0% Total of 45 complications: Wide scar (n=29), scar hypertrophy (n=14), scar-related scalp alopecia (n=1), secondary contracture (n=1) 1 study reported only unspecified results: Warner (n=40) "9 patients required additional surgical procedures due to growth-induced scar contractures, hypertrophy, hirsutism, and pigment changes"	603 (93.8)	21 (95.5)	⨁◯◯◯ VERY LOW [a, b]
Anatomical deformations - Follow-up: range 1 mo - 20 yr	Complication rate: **4.3%**, CI 1.2% - 14.6%, range 0.0% - 79.5% Total of 100 complications: Marked asymmetry (n=50), burn-like appearance (n=14), excess flap bulk (n=10), ectropion (n=6), flap irregularity (n=3), contour deformity (n=3), dog ear deformity (n=3), brow elevation (n=3), skull deformation (n=2), brow ptosis (n=2), lipoatrophy (n=2), stenosis of external auditory meatus (n=1), helical rim deformity (n=1) 2 studies reported only narrative results: Dong (n=21) "effects on the shape of the outer auricle"; Li (n=12) "flap debulking may be demanded by patients with thick abdominal flaps"	610 (94.9)	20 (90.9)	⨁◯◯◯ VERY LOW [a, b]

Complication rates were defined as complication per patient. CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation. *No. of patients for which quantified data was reported. †No. of studies in which quantified data was reported. ‡1 infection concerned a necrotizing fasciitis. §4 of 18 cases of graft loss were cases of graft necrosis as a result of infection and were not considered separate complications in the meta-analysis of complication rates. ‖ The external valve was used to complete the injection and no invasive intervention was demanded. a) high risk of bias. b) results varied between studies (inconsistency).

Table 5. Effectiveness of surgical excision: summary of findings.

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
Cosmetic and functional outcomes				
Cosmetic outcome: patient satisfaction Follow-up: range 7 mo - 19.4 yr	**Excellent 24.4%** (32/131), **good 71.0%** (93/131), **poor/moderate 4.6%** (6/131) One study only reported mean results on a continuous scale: Tissue expansion: **3.58**; no tissue expansion (serial excision, skin grafts): **3.21**; skin grafts: **3.46** (-5 to +5; -5= lesion greatly worsened; +5= lesion completely disappeared) reported by Ceballos-Rodríguez (n=136) One study reported only narrative results: Qiao (n=35) "average satisfaction on appearance was high"	267 (41.5)	7 (31.8)	⨁◯◯◯ VERY LOW [a, b]
Cosmetic outcome: physician satisfaction Follow-up: range 3 mo - 20 yr	**Excellent 17.3%** (34/197), **good 70.1%** (138/197), **poor/moderate 11.7%** (23/197)‡ Two studies only reported mean results on a continuous scale: Tissue expansion: **3.52**; skin grafts: **3.22**; no skin grafts (tissue expansion, serial excision): **3.69** (-5 to +5; -5= lesion greatly worsened; +5= lesion completely disappeared); reported by Ceballos-Rodríguez (n=136) **Mean (SD) 8.0 (0.7)**; range 7-10 (scale 0 to 10; 0 = no cosmetic improvement; 10 = best imaginable outcome); reported by Qiao (n=35) in a study of single-stage excision with primary closure. 4 studies reported only narrative results: Margulis (n=44) "good aesthetic results for intermediate-size CMN confined to the eyelid"; El-Sabbagh & Hassan (n=16) "satisfactory appearance was obtained"; Ma (n=11) "good aesthetic results"; Li (n=12) "excellent aesthetic outcomes" <u>"Symmetric facial contour after 1-year follow-up"</u> **100.0%** (35/35); reported by Qiao (n=35)	368§ (55.7)	10 (45.5)	⨁◯◯◯ VERY LOW [a, b]

Table 5. (continued)

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
Functional outcome: patient satisfaction Follow-up: range 10 - 80 mo	**Excellent 0.0%** (0/17), **good 100.0%** (17/17), **poor/ moderate 0.0%** (0/17); reported by Liu (n=17)	17 (2.6)	1 (4.5)	⨁◯◯◯ VERY LOW a, b, c
Functional outcome: physician satisfaction Follow-up: range 6 mo - 20 yr	**Excellent 16.7%** (7/42)**, good 73.8%** (31/42), **poor/ moderate 9.5%** (4/42) 4 studies reported only narrative results: Margulis (n=44) "good functional results for intermediate-size CMN confined to the eyelid"; Liu (n=17) "satisfactory functional outcomes"; Li (n=12) "excellent functional outcomes"; Ma (n=11) in a study of GCMN of the arm "good functional results", "retention of sensibility", "some patients after treatment were stiff with flexion restriction of the elbow joint due to long-time immobilization, although most recovered after 1-month of functional training"	42 (6.5)	3 (13.6)	⨁◯◯◯ VERY LOW a, b, c
Scar assessment by patient Follow-up: range 1.6 - 16 yr	Patient and Observer Scar Assessment Scale (POSAS) (6= best, 60= worst imaginable scar) **Mean 20.7** (range 6-37); median 21.5; reported by Zaal & Van Der Horst (n=17) in a study of tissue expansion on the head Overall scar impression (1= best, 10 = worst imaginable scar) **Mean 4.3** (range 1-8); median 4.5; reported by Zaal & Van Der Horst (n=17) in a study of tissue expansion on the head Patient scar satisfaction **Good: 50.0%** (6/12); **Moderate: 41.7%** (5/12); **Mild: 8.3%** (1/12); reported by Fahmy & Mazy (n=12) in a study of tissue expansion on the trunk	29 (4.5)	2 (9.1)	⨁◯◯◯ VERY LOW [a, c]
Scar assessment by physician Follow-up: range 6 mo - 16 yr	Patient and Observer Scar Assessment Scale (POSAS) (6= best, 60= worst imaginable scar) **Mean 20.7** (range 6-37); median 21.5; reported by Zaal & Van Der Horst (n=17) in a study of tissue expansion on the head	72 (11.2)	3 (13.6)	⨁◯◯◯ VERY LOW [a, c]

Table 5. (continued)

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
	Overall scar impression (1= best, 10 = worst imaginable scar) **Mean 3.7** (range 1-7); median 4; reported by Zaal & Van Der Horst (n=17) in a study of tissue expansion on the head Vancouver Scar Scale (VSS) (0= best, 4= worst scar formation) **Mean (SD) 2.6 (1.0)**; range 0-4; reported by Qiao (n=35) in a study of single-stage excision with primary closure of large facial CMN "Favorable linear scar" **85.0%** (17/20); reported by Dai (n=20) in a study of skin grafting 1 study reported only narrative results: Zhu (n=10) "well healed and concealed scars on both donor and recipient sites"			
Quality of life				
Acceptance of CMN as part of identity Follow-up: range 6.3 - 19.4 yr	Patient's preference for GCMN or scar in terms of cosmetics GCMN: **11.92%**; Scar: **86.75%**; Indifferent/not relevant: **1.33%;** reported by Ceballos-Rodríguez (n=136) Satisfaction of body image Mild: **0.0%** (0/12); Moderate: **41.7%** (5/12); Good **58.3%** (7/12); reported by Fahmy & Mazy (n=12) in a study of tissue expansion on the trunk	148 (23.0)	2 (9.1)	⨁◯◯◯ VERY LOW [a, c]
Satisfaction with treatment choice Follow-up: range 1.5 - 19.4 yr	Would the patient undergo the surgical treatment again if he/she had the chance? Yes: **89.7 %** (122/136); No: **10.3%** (14/136); reported by Ceballos-Rodríguez (n=136) Would the parents recommend the treatment to other parents with children with a GCMN at the scalp? Yes: **100.0%** (17/17); No **0.0%** (0/17); reported by Zaal & Van Der Horst (n=17)	153 (23.8)	2 (9.1)	⨁◯◯◯ VERY LOW [a, c]

Table 5. (continued)

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
Aesthetic issues Follow-up: range 8 mo - 10 yr	<u>Request for surgery due to negative aesthetic impact of the lesion</u> **21.4%** (9/42) of non-operated patients/families whose surgeries were initially postponed until the child could give his/her opinion. Surgeries had only been postponed for CMN that were considered as not having a high risk of malignancy and not causing an aesthetic prejudice; reported by Mérigou	-	1 (4.5)	⨁◯◯◯ VERY LOW [a, c]
Perceived stigmatization Follow-up: range 6.3 - 19.4 yr	Patient's belief of whether GCMN or a scar is more socially accepted GCMN: **0.65%,** Scar: **94.12%;** Indifferent/not relevant: **5.23%;** reported by Ceballos-Rodríguez (n=136)	136 (21.2)	1 (4.5)	⨁◯◯◯ VERY LOW [a, c]
Social relations Follow-up: range 1.5 - 16 yr	<u>Absence from school:</u> **0.0%** (0/17); reported by Zaal & Van Der Horst (n=17) in a study of tissue expansion on the head	17 (2.6)	1 (4.5)	⨁◯◯◯ VERY LOW [a, c]
Emotional/ psychological functioning Follow-up: range 7 mo - 19.4 yr	<u>Suicide attempt</u> **1 case of suicide attempt.** This patient presented with a complex facial nevus and, having suffered from depression for years, ultimately wanted to remove the nevus. During the long treatment period, the patient could not accept the morphological changes, which contributed to the suicide attempt. Explantation was performed, not meeting the treatment goal; reported by Kim (n=55) in a study of tissue expansion. <u>Memories of the reconstruction period by the patient</u> **0.0%** (0/29) unpleasant memories; **3.4%** (1/29) not-unpleasant memories; reported by two studies of tissue expansion in children <u>Impact of surgery on QoL in patients during the week after the intervention</u> Not at all: **0.0%**; A little: **70.4 %**; A lot: **25.9 %**; Very much: **3.7%;** reported by Ceballos-Rodríguez (n=136) <u>Psychological problems of the patient</u> **0.0%** (0/17); reported by Zaal & Van Der Horst (n=17)	220 (34.2)	4 (18.2)	⨁◯◯◯ VERY LOW [a, c]

Table 5. (continued)

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
	1 study reported additional narrative results: Zaal & Van Der Horst (n=17) "some parents remembered the expansion period as a psychological war of attrition"			
Malignancy				
Melanoma in excised specimen	**0.0%** (0/272) melanoma in excised specimens Other concerning histopathological findings: Warner (n=38): atypia: 1/38, dysplasia: 1/38, severe atypia: 1/38. However, no malignant transformation (follow-up: mean 11.2 years)	272 (42.3)	12 (54.5)	⨁◯◯◯ VERY LOW [a]
Melanoma incidence Follow-up: range 6 mo - 20 yr	4 cases of melanoma in 339 patients: 1) Ceballos-Rodríguez (n=136): 8-year-old boy with completely excised GCMN, location NR. Primary, fatal melanoma developed on the spinal chord. 2) Ceballos-Rodríguez (n=136): 25-year-old woman. Fatal melanoma developed in partly excised GCMN on the back. 3 Margulis (n=44): one patient died as a result of extensive metastatic melanoma from an extracutaneous site. Patient age, CMN location, and extent of excision NR. 4) Warner (n=40): male patient with a CMN of 60% TBSA. Location and extent of excision NR. Initial histopathology showed only intradermal nevi and no dysplasia or melanoma. Melanoma development (location NR) and death by cerebral metastases, two years after initial presentation.	339 (52.7)	7 (31.8)	⨁◯◯◯ VERY LOW [a]
Neurological symptoms and signs				
Epilepsy Follow-up: range 1.5 - 16 yr	"Any kind of neurological symptoms" **0.0%** (0/17); reported by Zaal & Van Der Horst (n=17)	17 (2.6)	1 (4.5)	⨁◯◯◯ VERY LOW [a,c]
Magnetic resonance imaging findings Follow-up: range 1.5 - 19.4 yr	Neurocutaneous melanocytosis (NCM) **8.7%** (15/17); However, no study reported a clear definition of NCM.	172 (26.7)	4 (18.2)	⨁◯◯◯ VERY LOW [a,c]
Hydrocephalus	- Not assessed in any study -	-	-	-
Motor development Follow-up: range 7 mo - 6.1 yr	Normal (psycho)motor development **100.0%** (12/12); reported by Maillet-Declerck (n=12)	12 (1.9)	1 (4.5)	⨁◯◯◯ VERY LOW [a,c]

Table 5. (continued)

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
Brain complications due to melanocytosis, melanoma or metastasis Follow-up: NR	Death by cerebrally metastasized melanoma. **1 case.** Male patient with a CMN of 60% of total body surface area. Initial histopathology showed no dysplasia or melanoma. Melanoma development (location NR) and death by cerebral metastases, 2 years after initial presentation; reported by Warner (n=40).	40 (6.2)	1 (4.5)	⨁◯◯◯ VERY LOW [a,c]
Skin appearance				
Color Follow-up: range 3 mo - 19.4 yr	Repigmentation **15.5%** (17/110) Hyperpigmentation **12.9%** (21/163)‖ 1 study reported only unspecified results: Warner (n=40) "9 patients required additional surgical procedures due to growth-induced scar contractures, hypertrophy, hirsutism, and pigment changes" 3 studies reported narrative results concerning color of the surgical site: Ma (n=11) "a close match in terms of tissue color"; Zhu (n=10) "excellent color matching"; Liu (n=12) "excellent color match was typically achieved"	273 (42.5)	7 (31.8)	⨁◯◯◯ VERY LOW [a]
Texture Follow-up: range 3 mo - 5 yr	2 studies reported only narrative results concerning texture of the surgical site: Ma (n=11): "a close match in terms of tissue texture"; Zhu (n=10): "excellent texture matching"	-	-	⨁◯◯◯ VERY LOW [a,c]
Satellites Follow-up: range 8 mo - 10 yr	Development of new satellite nevi **16.7%** (2/12) of patients who received tissue expansion reported by Mérigou (n=65)	65 (10.1)	1 (4.5)	⨁◯◯◯ VERY LOW [a,c]
Hairiness Follow-up: range 1 mo - 16 yr	Hair growth disturbance **5.9%** (1/17) reconstruction-related alopecia (classified as a scar-related complication); **35.3%** (6/17) no hair growth disturbance at all; reported by Zaal & Van Der Horst (n=17) in a study of tissue expansion on the head. **8.3%** (1/12) lower hair density; **91.7%** (11/12) correct hair growth pattern; reported by Maillet-Declerck (n=12) in a study of tissue expansion on the head	60 (9.3)	4 (18.2)	⨁◯◯◯ VERY LOW [a,c]

Table 5. (continued)

Outcome	Impact	Patients* (%)	Studies† (%)	GRADE
	Partial cilia loss **35.3%** (6/17); this loss was a direct result of excision of CMN that involved the palpebral margin or conjunctiva and was therefore not considered a complication. Patients stated that it was acceptable because it made little impact on appearance; reported by Liu (n=17) in a study of divided eyelid nevi	60 (9.3)	4 (18.2)	⨁◯◯◯ VERY LOW [a,c]
	Hairy surgical site (earlobe) requiring treatment **7.1%** (1/14); this patient had been treated with a full-thickness skin graft from the groin and was subsequently referred for additional laser treatment; reported by Adler (n=14) in a study of auricle CMN			
	1 study reported unspecified results: Warner (n=40) "9 patients required additional surgical procedures due to growth-induced scar contractures, hypertrophy, hirsutism, and pigment changes"			

GRADE = Grading of Recommendations Assessment, Development and Evaluation. (G)CMN = (giant) congenital melanocytic nevus, mo = month, NR = not reported, yr = year. *No. of patients for which quantified data was reported. †No. of studies in which quantified data was reported. ǂresults of 38 lesions in 20 patients were only reported per lesion and were therefore recorded as separate cases. §No. of lesions for which quantified data was reported. ‖ Goil (n=17) reported 2 additional cases of post-surgical hyperpigmentation that improved over 3 weeks. These cases were therefore excluded. a) high risk of bias. b) different measures were converted to a single ordinal scale (indirectness). c) results varied between studies (inconsistency). c) small sample size (imprecision).

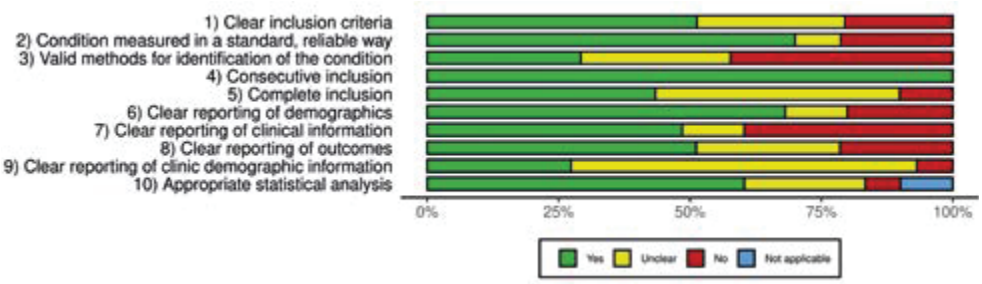

Figure 2. Critical appraisal of included studies with the Joanna Briggs Institute Checklist for Case Series. Results were weighted by study size.

DISCUSSION

A good or excellent cosmetic outcome of their surgical excision was reported by 95.4% of patients. However, complications can occur, with complication rates of 9.8% for major wound-related complications, 1.2% for minor wound-related complications, 1.2%, for scar-related complications, and 4.3% for anatomical deformations. The quality of the studies was generally low, and reporting of baseline characteristics and outcomes was heterogeneous. Core outcomes were scarcely reported.

We decided to choose the side of overreporting, classifying wound-related complications as major when insufficient data was available (35 of 143 complications). If we would have classified these as minor, the rate of major wound-related complications would have been 4.0% (CI 1.1-13.2%) and the rate for minor 6.1% (CI 3.3-11.0%).

Due to incomplete and heterogeneous reporting, it was difficult to uncover outcome-predicting factors and to evaluate the results of different surgical modalities. The largest included study (n = 136), assessing tissue expansion, skin grafts, and serial excision, reported that excision of head lesions (when compared to the extremities), was significantly associated with higher patient satisfaction with surgical results. However, not with satisfaction of the surgeon.

No study included a true control group, i.e. comparable patients not receiving surgical excision. Furthermore, follow-up was limited. Therefore, outcome results such as melanoma incidence (four cases[34,47,52] in 339 assessed patients, follow-up range 6 months - 20 years) should be interpreted with caution. However, the assumed preventative role of excision was not supported by the observation that two of these patients developed melanoma at an extracutaneous site, of which at least one had received complete excision of the nevus. Neither seemed initial histopathology indicative, as one patient who exhibited no cellular atypia in the excised nevus, still developed melanoma, whereas all three other patients who did display atypia, did not develop any malignancy.[52]

We used satisfaction with cosmetic and functional results as the main outcomes of effectiveness. However, QoL is an important outcome as well, as the abnormal appearance of CMN can have a negative impact on patients' life[10,55], which may be improved by excision. Yet, few studies reported outcomes concerning QoL. Interestingly, a cross-sectional study of 235 patients found that QoL was not predicted by CMN size or whether the CMN had been (partially) removed.[55] QoL can even be impeded by treatment, as 33.3% had post-traumatic stress disorder four months post-surgery in a study of thirty children (mean age 4.23 years).[56] However, in two included studies concerning children treated with tissue expansion before the age of three, only 1 of 29 patients had any memories of their treatment (tissue expansion), and none had any unpleasant ones.[46,53] However, some parents recalled the tissue expansion period as "a psychological war of attrition". Still, all 17 families of this study would recommend tissue expansion to other parents with children with a giant CMN.[53] Furthermore, the largest included study reported that 89.7% percent of patients and their families would undergo the surgical treatment again if they had the chance[34], indicating a positive balance between the burden of treatment and satisfaction with the results.

Fourteen of fifteen studies that discussed the desirable age for treatment, advocated for early treatment, although most did not indicate a specific age.[34,35,37,39,40,43-47,50,52-54] Reasons for (early)

treatment were (assumed) prevention of malignant transformation, and providing a solution of the aesthetic, functional, physically discomforting, and psychosocial impact of CMN.

Early treatment is sometimes considered to yield better cosmetic outcomes. However, consistent evidence for this is lacking. Interestingly, the largest included study reported that early treatment predicted only higher surgeon satisfaction of surgical results, but not patient satisfaction.[34] Neither was the age at first surgery related to the complication rate, as was also found by another included study of twelve children treated with tissue expansion.[38] However, the second-largest study (n= 65), assessing tissue expansion, grafts, and flaps, remarked that all excellent results, rated by both patients and physicians, were of patients operated before the age of thirty months, and the worst marks were given for patients operated after the age of eight. However, surgeries for large/giant scalp nevi were postponed, as those seemed to show regression over time.[48] Kinsler et al. too, reported spontaneous lightening of the majority of CMN.[15] Furthermore, postponing surgery also provides patients the opportunity to partake in the decision-making or to accept the lesion over time.[57] On the other hand, early treatment might mitigate psychosocial impact, by limiting school absence, and by preventing social stigmatization in case of conspicuous lesions.[11]

Deciding on the proper surgical technique depends on many factors, including shape, size, location of the CMN, experience of surgeon, and the wishes of the patient or parents. Several treatment algorithms have been presented[1,58-63]. These strategies differ, but there seems to be a preference for primary closure if this is possible within three or fewer excisions. Otherwise, tissue expansion may be preferable, or a non-expanded flap or full-thickness graft for locations where tissue expansion may not be possible or desirable. Many included studies also mentioned tissue expansion as a preferable technique, as favorable results can be yielded by achieving an optimal match in terms of tissue color, texture, skin appendages, and sensation.[34,39,41-43,45,46,48,52] Furthermore, the largest included study reported that tissue expansion was significantly associated with higher patient satisfaction of surgical results, although not with satisfaction of the surgeon.[34] However, tissue expansion may not always be a feasible option, such as in the case of lesions involving the eyelids. Furthermore, tissue expanders on the distal extremities are associated with complications due to the mobility of these sites and limited available space. However, two included studies transferred expanded flaps from the trunk to the upper extremities.[43,45] A limitation of this technique is the large scar on the trunk. For these locations, excision and closure with artificial skin and a split-thickness skin graft may be a good option.[64]

However, skin grafting, especially split-thickness, can result in unsightly scarring and poor aesthetic and/or functional outcomes, as reported by two included studies.[37,39] However, the largest included study remarked that the use of skin grafts was significantly associated with lower satisfaction of the surgeon, but not of the patient.

New insights for reconstructive treatment continue to be developed. For instance, one included study demonstrated that single-stage excision with primary closure of medium to even large lesions on the cheek can yield pleasing results.[49] Another one successfully treated divided eyelid nevi with island flaps.[54]

Value of the work

To the best of our knowledge, this systematic review is the first to provide pooled evidence on safety and effectiveness of surgical excision in patients with medium-to-giant and/or difficult-to-excise CMN. Although our review used the best available data, the results may only give an indication of the true effect sizes, as all included studies were of limited quality and were prone to selection bias. Therefore, the level of evidence of all synthesized outcomes was rated as "very low". Furthermore, we showed heterogeneity in baseline characteristics and outcomes used in research of CMN.

CONCLUSIONS

The treatment paradigm of CMN has shifted from prevention of malignant transformation towards improvement of appearance and psychosocial health. Consequently, these potential benefits should weigh against the risks and burden of treatment. Overall, we conclude that surgical excision has a high satisfaction rate, but complications can occur. This overview may support clinicians to make weighted decisions regarding the need for surgical excision and may enable shared decision-making with patients. Due to incomplete and heterogeneous reporting, it is difficult to uncover outcome-predicting factors. Therefore, we believe that future research should report more extensively on patient-, lesion-, and treatment-characteristics. Furthermore, results should be reported separately per clinically distinct group, using standardized patient-reported outcome measures. As larger CMN are rare, international collaboration is needed to create large cohorts for the research of long-term outcomes of different treatments. This can be facilitated by developing a core outcome set of CMN to increase uniformity in care and research.[20-23]

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SUPPORTING INFORMATION

Supplemental Digital Content 1. Full search strategies
Pubmed (MEDLINE)

	Medical Subject Headings		Title, abstract		Other
Nevus	"Nevus"[Mesh]	OR	nevus[tiab] OR nevi[tiab] OR naevus[tiab] OR naevi[tiab] OR nævus[tiab] OR birthmark*[tiab] OR mole[tiab] OR moles[tiab])		
AND					
Congenital	"congenital" [Subheading]	OR	congenital*[tiab] OR bathing trunk*[tiab] OR garment[tiab] OR garment-like[tiab] OR giant[tiab] OR gigantic[tiab] OR newborn[tiab] OR pilosus[tiab] OR inborn[tiab] OR non-acquired[tiab] OR kissing[tiab] OR panda[tiab] OR divided[tiab]		
AND					
Excision	"surgery" [Subheading] OR "Surgical Procedures, Operative"[Mesh] OR "Skin Transplantation"[Mesh] OR "Skin, Artificial"[Mesh] OR "Free Tissue Flaps"[Mesh] OR "Surgical Flaps"[Mesh] OR "Tissue Expansion"[Mesh]	OR	surgery[tiab] OR surgical*[tiab] OR reconstruct*[tiab] OR dermatoplast*[tiab] OR dermatosurg* OR resection[tiab] OR excision[tiab] OR transplant*[tiab] OR graft*[tiab] OR autograft*[tiab] OR allograft*[tiab] OR composite graft*[tiab] OR artificial skin*[tiab] OR flap[tiab] OR flaps[tiab] OR expander*[tiab] OR expansion*[tiab] OR treat*[tiab] OR procedur*[tiab] OR modality[tiab] OR modalities[tiab] OR management[tiab]		
NOT					
Study design			case report*[ti]	OR	"Case Reports" [Publication Type]
AND					
Publication date					"2006/07/01"[PDAT] : "3000/12/31"[PDAT]

EMBASE (OVID)

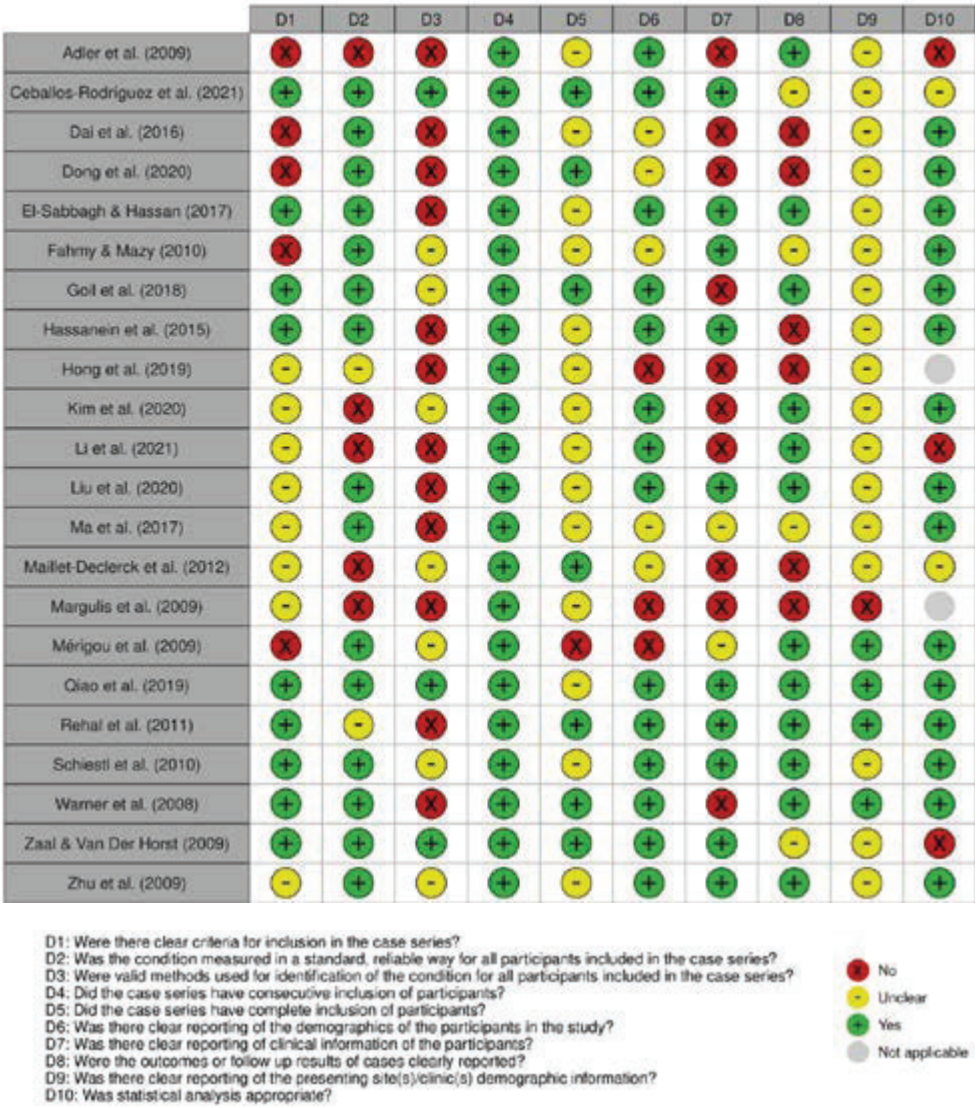
Database(s): Embase Classic+Embase 1947 to 2021 April 20

#	Searches	Results
1	exp nevus/ or (nevus or nevi or naevus or naevi or birthmark* or mole or moles).ti,ab,kw.	62927
2	(congenital* or bathing trunk* or garment or garment-like or giant or gigantic or inborn or newborn or pilosus or non-acquired or kissing or panda or divided).ti,ab,kw. or cn.fs.	1495445
3	surgery/ or reconstructive surgery/ or surgical technique/ or excision/ or surgery.fs. or exp skin transplantation/ or artificial skin/ or exp surgical flaps/ or tissue expansion/ or (surgery or surgical* or reconstruct* or dermatoplast* or dermatosurg* or resection or excision or transplant* or graft* or autograft* or allograft* or composite graft* or artificial skin* or flap or flaps or expander* or expansion* or treat* or procedur* or modality or modalities or management).ti,ab,kw.	13436099
4	1 and 2 and 3	3607
5	case report/ or case report.ti.	2764156
6	4 not 5	2188
7	limit 6 to conference abstract status	371
8	6 not 7	1817
9	limit 8 to yr="2006 -Current"	825

Cochrane Central Register of Controlled Trials (CENTRAL)

Issue 7 of 12, April 2021

#	Searches	Results
1	(nevus or nevi or naevus or naevi or birthmark* or mole or moles):ti,ab,kw	596
2	(congenital* or bathing trunk* or garment or garment-like or giant or gigantic or inborn or newborn or pilosus or non-acquired or kissing or panda or divided):ti,ab,kw	117470
3	(surgery or surgical* or reconstruct* or dermatoplast* or dermatosurg* or resection or excision or transplant* or graft* or autograft* or allograft* or composite graft* or artificial skin* or flap or flaps or expander* or expansion* or treat* or procedur* or modality or modalities or management):ti,ab,kw	1117556
4	#1 and #2 and #3 with Cochrane Library publication date Between Jul 2006 and Dec 2021	49



Supplemental Digital Content 2. Critical appraisal of included studies with the Joanna Briggs Institute Critical Appraisal Checklist for Case Series

Supplemental Digital Content 3. Treatment and safety per study.

Author (year); location	Age at first excision: mean (range)	Treatment modality	1. No. of surgeries 2. No. of excisions	Extent of excision
Multiple modalities; results not specified per modality				
Margulis et al. (2009); USA	NR (6 mo – 17 yr)*	"Excision with reconstruction" (including SG, TE, flap): 44 pts	NR	NR
Multiple modalities; results (partially) specified per modality				
Adler et al. (2009); USA & Israel	4.5 yr (7 mo – 13 yr)	Overall: 36 procedures in 14 pts FTSG (n=18) Non-expanded flap (n=13) TE (n=5)	NR	NR
Ceballos-Rodríguez et al. (2021); Spain	34 (SD 61.45) mo	Overall: 172 procedures in 136 pts (36 pts received TE + SG) TE (n=81) SG (n=62) SE (n=29)	1. mean 5.53 (SD 3.69) 2. NR	Complete excision: 56/136 pts
Goil et al. (2018); India	18.6 (14 – 24) yr	Overall: 20 procedures in 17 pts Free flap (n=3) TE (n=12) FTSG (n=4)	NR	NR

	Major wound-related complications	Non-graded wound-related complications	Minor wound-related complications	Scar-related complications	Anatomical deformations
	None	None	None	None	- Asymptomatic lateral ectropion: 3/44 pts - Residual brow elevation: 1/44 pts - Asymmetry of palpebral aperture: 31/44 pts
	None	None	None	None	Complications per no. of procedures: - Helical rim deformity (caused by FTSG at early age of 16 m): 1/18 - Stenosis of external auditory meatus: 1/18 None
	Complications per no. of patients: Infection of the surgical wound: 7/81 None Complications per no. of procedures: None Seroma, hematoma: 1/12 None	Complications per no. of patients: Suture dehiscence: 8/81 Infection of the surgical wound: 5/62 None Complications per no. of procedures: None None Seroma, hematoma: 1/4	None	Complications per no. of procedures: Wide (and hyperpigmented) scar: 19/81 None Complications per no. of procedures: None Hypertrophic scarring: 3/12 Hypertrophic scarring: 1/4	Overall: - Marked asymmetry: 19/136 pts None Burn-like appearance: 14/62 procedures None Complications per no. of procedures: - Flap irregularity: 3/3 - Bulky upper eyelid: 1/3 - Contour deformity: 3/3 - Ectropion: 1/12 - Dog ear deformity: 1/12 Ectropion: 1/4

Supplemental Digital Content 3. (continued)

Author (year); location	Age at first excision: mean (range)	Treatment modality	1. No. of surgeries 2. No. of excisions	Extent of excision
		STSG (n=1)		
Hong et al. (2019); Vietnam	NR	Overall: 44 procedures in 44 CMN in 20 pts	NR	NR
		Distant flap (n=1) Adjacent flap (n=2) TE (n=6)		
		SG (n=16)		
		SE (n=16) Primary closure (n=3)†		
Li et al. (2021); China	For CMN: 5 (3-21) yr*	TE (with transferred flap): 9/12 pts	NR	Range 18 x 16 cm – 30 x 22 cm
		TE (with transferred flap) + STSG: 3/12 pts	NR	Range 18 x 14 cm – 30 x 17 cm
	For non-CMN: NA	NA	NA	NA
Mérigou et al. (2009); France	<6 mo: 67% of patients	Non-expanded flap: 51 pts	NR	NR
		TE: 12 pts		
		SG: 2 pts Curettage: 2 pts (both received additional excision)† No surgery: 43 pts†		
Rehal et al. (2011); USA	7 yr (NR)	Overall: 50 procedures for 51 CMN in 36 pts (5/36 pts received TE + SG)	1. mean 3.4 (range 1-"5 or more") 2. NR	NR

Major wound-related complications	Non-graded wound-related complications	Minor wound-related complications	Scar-related complications	Anatomical deformations
Partial graft loss (that required secondary grafting): 1/1	None	None	- Hypertrophic scarring: 1/1 - Secondary contracture (after partial STSG loss and secondary grafting): 1/1	Ectropion: 1/1
Complications per no. of procedures: None	Complications per no. of procedures: None	None	None	None
Partial necrosis: 1/6 None	None Infection and resulting partial graft necrosis: 4/16 None			
None	None	Seroma (treated with aspiration): 1/9 pts	None	Thick abdominal flap requiring debulking: unspecified number[#]
Infection of STSG (requiring debridement and regrafting): 1/3 pts		None		
NA None	NA None	NA None	NA None	NA None
	Dehiscence: 3/12 pts None			Lipoatrophy: 2/12 pts None None None
None	Overall: - Wound dehiscence: 2/36 pts - Wound infection: 1/36 pts	None	None	None

Supplemental Digital Content 3. (continued)

Author (year); location	Age at first excision: mean (range)	Treatment modality	1. No. of surgeries 2. No. of excisions	Extent of excision
		TE (n=10) FTSG (n=12) STSG (n=5) Integra artificial skin (n=2) SE (n=17) Laser (n=1); Kenalog injection (n=3)†		
Warner et al. (2008); USA	5.14 (0.5 - 15) yr	Overall: 63 procedures in 40 pts	1. mean 1.58 (> 1 surgery: 22/40 pts) 2. NR	NR
		TE (n=10) FTSG (n=7) STSG (n=22) Cultured SG (n=3) Allograft (temporary) (n=3) Primary closure (n=18)†		
One combination of different modalities				
Dong et al. (2020); China	10.6 (2 – 30) yr*	TE + SG: 21 pts	1. NR 2. 2	Complete excision: 21/21 pts

Major wound-related complications	Non-graded wound-related complications	Minor wound-related complications	Scar-related complications	Anatomical deformations
Extrusion of TE: 1/10 pts Graft failure that required regrafting: 1/17 pts	None			
None				
			Requirement for additional surgery due to contractures/ hypertrophy/ hirsutism/pigment changes: 9/40 pts‡	None
- Infection (including 1 necrotizing fasciitis) : 4/25 expanders - Expander malposition: 1/25 expanders - Advancement flap necrosis: 1/25 expanders - Exposed port: 1/25 expanders	None	None		
Graft loss that required regrafting: 2/28 pts		Graft loss that did not require regrafting: 1/28 pts		
Graft loss that required regrafting: 2/4 pts		None		
None				
None	Poor skin grafting: unspecified number‡	None	Severe scar hyperplasia: 1/21 pts	"Effects on the shape of the outer auricle": unspecified number‡

Supplemental Digital Content 3. (continued)

Author (year); location	Age at first excision: mean (range)	Treatment modality	1. No. of surgeries 2. No. of excisions	Extent of excision
Ma et al. (2017); China	6.6 (3 - 21) yr*	TE (with transferred flap) + SG: 11 pts - Total of 13 expanders - Number of expanders per pt: mean 1.2	1. NR 2. 2	NR
Flap				
Liu et al. (2020); China	15 (1 - 33) yr	Advanced orbicularis oculi myocutaneous (OOMC) flap: 17 pts	1. NR 2. 1	Complete excision: 17/17 pts
Zhu et al. (2009); China	11.8 (5 - 18) yr	Overall: 18 procedures in 10 pts Orbicularis oculi muscle (OOM) flap (n=10) Retroauricular superficial musculoaponeurotic system (SMAS)-pedicled flap (n=3) Reversal superficial temporal artery (STA) flap (n=3) Single-stage primary closure for upper eyelid part of the lesion (n=2)†	NR	- Complete excision: 8/10 pts - Subtotal excision: 2/10 pts

	Major wound-related complications	Non-graded wound-related complications	Minor wound-related complications	Scar-related complications	Anatomical deformations
	Hematoma due to active bleeding in pocket (incision made to prevent further bleeding): 1/13 expanders	None	- Filling valve exposure (external valve was used to complete the injection): 1/13 expanders - Distal tip necrosis of transferred flap (treated with debridement and dressing): 1/11 pts	Significant scarring in the thoracic wall (treated with expanded flap on the back): 1/11 pts	Surgical limb thicker than contralateral limb due to greater thickness of flap: 1/11 pts
	None	None	None	None	Excess bulk upper eyelid (slightly bloated flap as a result of perioperative flap thinning): 4/17 pts
	None	None	Complications per no. of procedures:	None	Complications per no. of procedures:
			None		Slight trapdoor deformation (flap bulk): 1/10
			Partial epidermal necrosis (without the need for surgical revision): 1/3		Slight trapdoor deformation (flap bulk): 2/3
			Partial epidermal necrosis (without the need for surgical revision): 1/3		Slight trapdoor deformation (flap bulk): 1/3
			None		None

Supplemental Digital Content 3. (continued)

Author (year); location	Age at first excision: mean (range)	Treatment modality	1. No. of surgeries 2. No. of excisions	Extent of excision
Tissue Expansion				
Fahmy & Mazy (2010); Egypt	6.8 (2 – 12) yr*	TE: 12 pts - Total of 37 expanders - Number of expanders per pt: mean 3.1 (range 2-5); median 3	1. mean 7.2 (range 4-14); median 7 2. NR	NR
Kim et al. (2020); Korea	6.59 (SD 3.88) yr*	Overall: TE for 88 CMN in 55 pts	1. NR 2. NR	NR
		Single TE (n=64) - No. of expanders per case: mean 1.14 (SD 0.32)	No. of inflations: 6.77 (SD 1.17)	
		Serial TE (=31) - No. of expanders per case: mean 3.26 (SD 1.00)	No. of inflations: 7.70 (SD 1.29)	
Maillet-Declerck et al. (2012); France	For CMN: 15.6 (9 – 23) mo	TE: 12 pts - Total of 22 expanders - Number of expanders per pt: mean 1.8 (range 1-2)	NR	Complete excision: 10/12 pts
	For non-CMN: NA	TE for other indications than CMN: 3 pts†	NA	NA

	Major wound-related complications	Non-graded wound-related complications	Minor wound-related complications	Scar-related complications	Anatomical deformations
	(All were major complications, according to authors:) - TE exposure (which necessitated reimplantation): 1/37 expanders - TE infection: 3/37 expanders - TE failure: 3/37 expanders (of which 1 port failure)	Partial suture dehiscence (managed by sutures): 2/37 expanders	(All were minor complications and conservatively treated, according to authors:) - Hematoma: 1/37 expanders - Seroma around TE: 2/37 expanders	Hypertrophied (not keloid) scars: 2/12 pts	None
	Complications per no. of cases: - Explantation: 5/64 - Port exposure: 4/64 - Skin necrosis: 3/64 - Hematoma / seroma: 9/64 - Rupture: 2/64 - Infection: 4/64 - Explantation: 6/31 - Port exposure: 2/31 - Skin necrosis: 1/31 - Hematoma / seroma: 3/31 - Rupture: 1/31 - Infection: 7/31	None	None	None	None
	Infection (requiring TE removal): 1/22 expanders	None	None	Widening of the scar: 9/12 pts (one can be explained as a result of infection and disunion)	Skull deformation (slight flattening, not visible, only noticeable when touching the scalp): 2/12 pts
	NA		NA	NA	NA

Supplemental Digital Content 3. (continued)

Author (year); location	Age at first excision: mean (range)	Treatment modality	1. No. of surgeries 2. No. of excisions	Extent of excision
Zaal & Van Der Horst (2009); The Netherlands	9.4 (4 - 36) mo	TE: 17 pts - Total of 38 expanders - Number of expanders per pt: mean 2.2	1. mean 3.2 2. NR	Complete excision: 17/17 pts
Skin Graft				
Dai et al. (2016); China	NOS: 3.8 y (6 m - 9 y)	FTSG: 6 pts	1. NR 2. 1	Complete excision: 20/20 pts - Size of excision: range 4x7 cm - 8x19 cm
		FTSG + STSG: 14 pts	1. NR 2. 2	
El-Sabbagh & Hassan (2017); Egypt	8.17 yr (4 mo - 22 yr)*	"Meshed SG": 4 pts	1. mean 1.06 (range 1-2) 2. mean 1.06 (range 1-2)	Size of excision: mean 225.5 (range 42–1050) cm^2
		FTSG + STSG: 4 pts STSG: 8 pts		
Schiestl et al. (2010); Switzerland	3.8 yr (7 mo - 11 yr)	Integra Artificial Skin + STSG: 12 pts	1. mean 2.3 (range 2-3) 2. 1	Complete excision: 12/12 pts

	Major wound-related complications	Non-graded wound-related complications	Minor wound-related complications	Scar-related complications	Anatomical deformations
	- Exposure: 4/17 pts - Wound infection: 2/17 pts - Implant leakage: 2/17 pts	None	None	- Scar widened: 1/17 pts - Scar-related scalp alopecia: 1/17 pts	- Brow elevation: 2/17 pts - Brow ptosis: 2/17 pts
	None	Graft loss (approx. 3-10%), "little graft loss"): 4/20 pts)	None	- Hypertrophic scarring at edges of graft: 3/20 pts - Hypertrophic scarring at donor site: 2/20 pts	None
	None	None	Marginal loss of skin graft (treated conservatively by frequent dressing): 1/4 pts None Marginal loss of skin graft (treated conservatively by frequent dressing): 1/8 pts	None	None
	- Infection (requiring removal of Integra): 3/12 pts - Non-integration of Integra (requiring removal of Integra): 1/12 pts	None	None	None	None

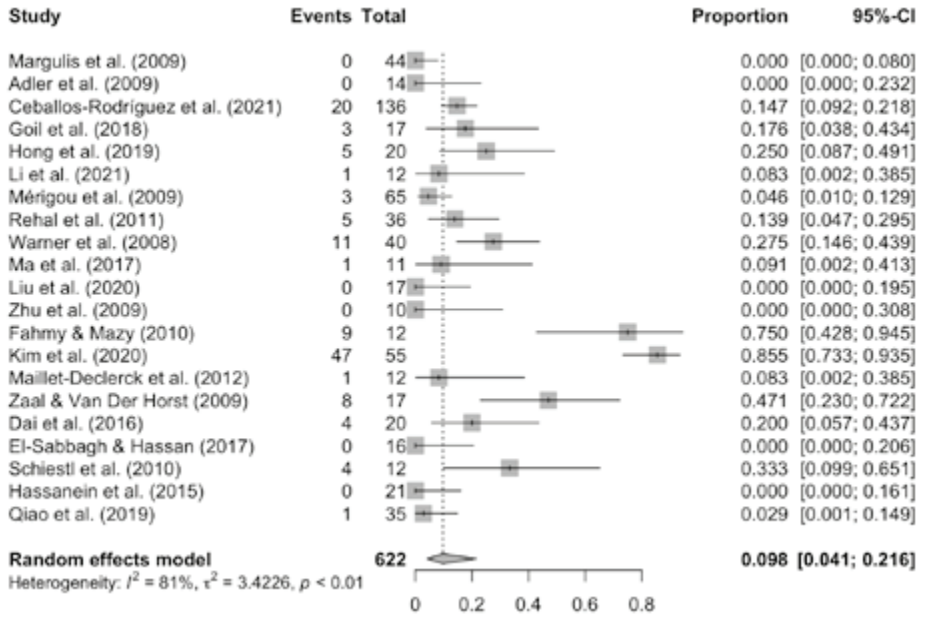
Supplemental Digital Content 3. (continued)

Author (year); location	Age at first excision: mean (range)	Treatment modality	1. No. of surgeries 2. No. of excisions	Extent of excision
Primary Closure				
Hassanein et al. (2015); USA	4.3 yr (3 mo - 15 yr)	SE: 21 pts - Total of 72 staged excisions	1. mean (SD): 3.5 (0.7); range 3-5 2. mean (SD): 3.5 (0.7); range 3-5	NR
Qiao et al. (2019); China	20.4 (3 - 36) yr	Single-stage excision with primary closure: 35 pts	1. mean 1.1 (range 1-2) 2. 1	Complete excision: 35/35 pts

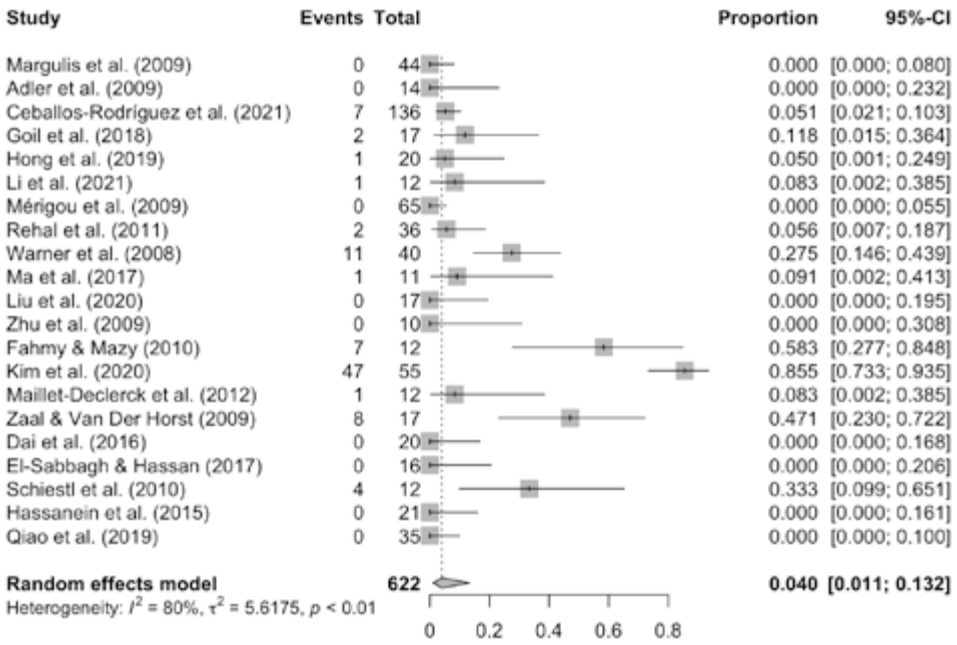
*Age not otherwise specified, †excluded from this systematic review, ‡excluded from meta-analysis, CMN = congenital melanocytic nevus, cm = centimeter, FTSG = full-thickness skin graft, mo = month, NA = not applicable, NR = not reported, pts = patients, SD = standard deviation, SE = serial excision, SG = skin graft, STSG = split-thickness skin graft, TE = tissue expansion, yr = yea

	Major wound-related complications	Non-graded wound-related complications	Minor wound-related complications	Scar-related complications	Anatomical deformations
	None	None	- Wound dehiscence (allowed to heal secondarily): 2/72 excisions - Seroma (which required drainage): 1/72 excisions	None	None
	None	Postoperative, self-limiting hematoma (Immediate management performed to stop the bleeding): 1/35 pts	None	None	Dog ear: 2/35 pts

Major wound-related complications: pooled proportion. 35 of 143 wound-related complications were reported with too little detail to objectively classify them as major or minor. These were classified as major.

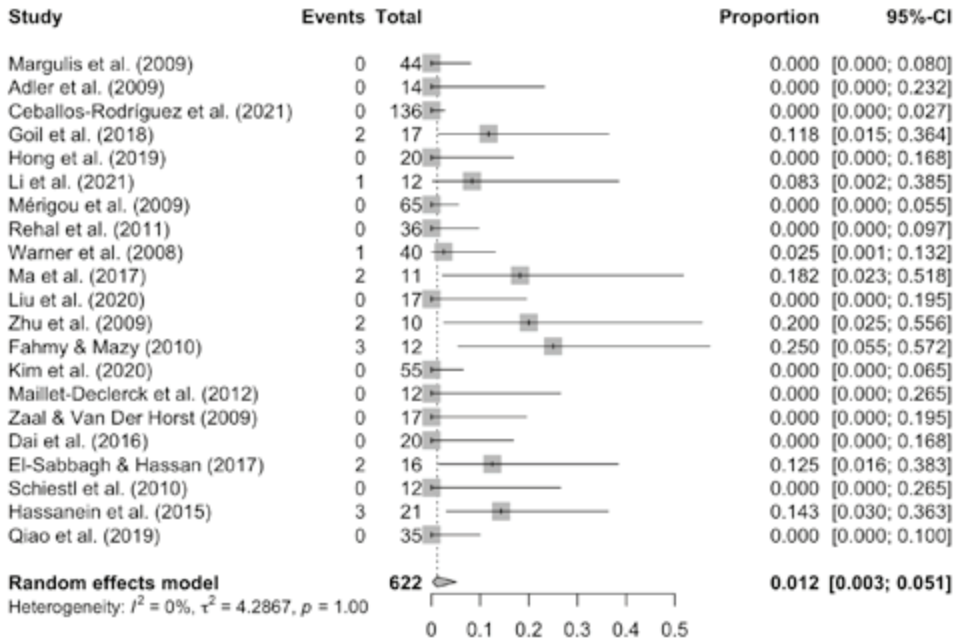


Major wound-related complications: pooled proportion. 35 of 143 wound-related complications were reported with too little detail to objectively classify them as major or minor. These were classified as minor.

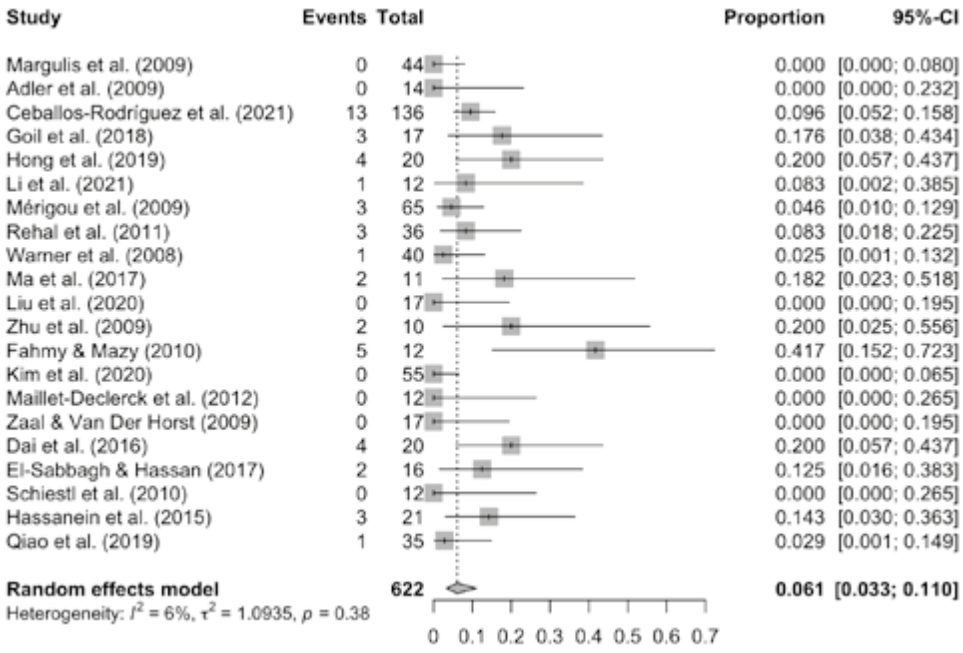


Supplemental Digital Content 4. Results of meta-analysis for all complication categories

Minor wound-related complications: pooled proportion. 35 of 143 wound-related complications were reported with too little detail to objectively classify them as major or minor. These were classified as major.

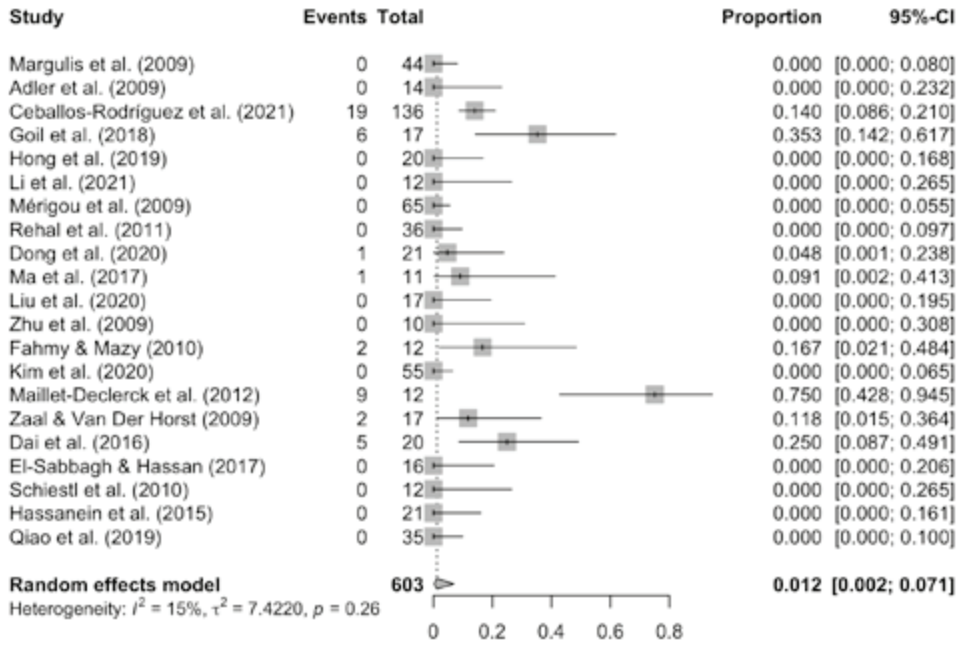


Minor wound-related complications: pooled proportion. 35 of 143 wound-related complications were reported with too little detail to objectively classify them as major or minor. These were classified as minor.



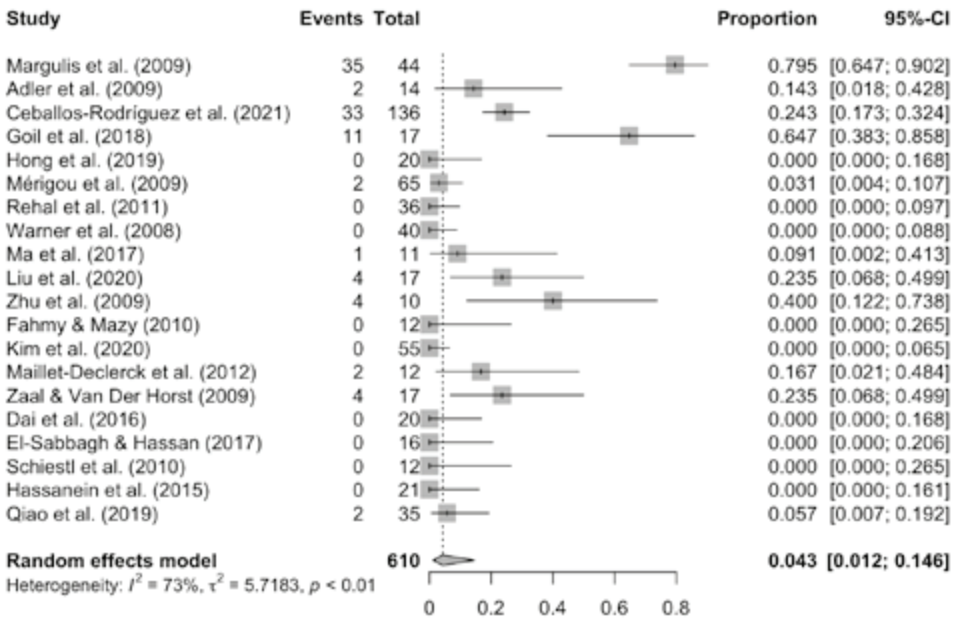
Supplemental Digital Content 4. (continued)

Scar-related complications: pooled proportion.



Supplemental Digital Content 4. (continued)

Anatomical deformations: pooled proportion.



Supplemental Digital Content 4. (continued)

Supplemental Digital Content 5. Treatment and effectiveness per study

Author (year); location	**Treatment modality**	**Cosmetic outcome** 1. patient satisfaction 2. physician satisfaction	**Functional outcome** 1. patient satisfaction 2. physician satisfaction	**Scar assessment** 1. by patient 2. by physician
Multiple modalities; results not specified per modality				
Margulis et al. (2009); USA	"Excision with reconstruction" including SG, TE, flap: 44 pts	1. NR 2. For intermediate-size CMN confined to the eyelid (n=NR): "Good aesthetic results"[‡]	1. NR 2. For intermediate-size CMN confined to the eyelid (n=NR): "Good functional results"[‡]	NR
Multiple modalities; results (partially) specified per modality				
Adler et al. (2009); USA & Israel	Overall: 36 procedures in 14 pts FTSG (n=18) Non-expanded flap (n=13) TE (n=5)	NR	NR	NR

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
NR	1. NR 2. n=1; range 6 mo – 20 yr; pt died as a result of extensive metastatic melanoma from an extracutaneous site. Patient age, CMN location, and extent of excision NR.	NR	NR
NR	NR	NR	Overall: 1. NR 2. NR 3. NR 4. Hairy earlobe (referred for laser treatment): 1/18 4. Hairy earlobe (referred for laser treatment): 0/13 4. Hairy earlobe (referred for laser treatment): 0/5

Supplemental Digital Content 5. (continued)

Author (year); location	Treatment modality	Cosmetic outcome 1. patient satisfaction 2. physician satisfaction	Functional outcome 1. patient satisfaction 2. physician satisfaction	Scar assessment 1. by patient 2. by physician
Ceballos-Rodríguez et al. (2021); Spain	Overall: 172 procedures in 136 pts (36 pts received TE + SG)	Scale −5 to + 5 -5: lesion greatly worsened +5: lesion completely disappeared 1. TE: mean 3.58; no TE: mean 3.21; SG: mean 3.46; no SG: NR 2. TE: 3.52; no TE: NR; SG: mean 3.22; no SG: mean 3.69	NR	NR
	TE (n=81)			
	SG (n=62)			
	SE (n=29)			
Goil et al. (2018); India	Overall: 20 procedures in 17 pts	1. NR 2. Good: 13/17, Poor/ moderate: 4/17	NR	NR
	Free flap (n=3) TE (n=12) FTSG (n=4)			
	STSG (n=1)			

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
1. Patients' preference for GCMN or scar in terms of cosmetics: GCMN: 11.92%; Scar: 86.75%; Indifferent / not relevant: 1.33% 2. Would you under undergo the surgical treatment again if you had the chance? Yes: 89.71%; No: 10.29% 3. NR 4. Patient's belief of whether GCMN or a scar is more socially accepted: GCMN: 0.65%; Scar: 94.12%; Indifferent / not relevant: 5.23% 5. NR 6. Impact of surgery on QoL in pts during the week after the intervention: Not at all: 0.0%; A little: 70.4 %; A lot: 25.9 %; Very much: 3.7%	1. NR 2. n=2; mean 9.2 (range 6.3 - 19.4) yr; - 8-year-old boy with completely excised GCMN, location NR. Primary, fatal melanoma developed on the spinal cord. - 25-year-old woman. Fatal melanoma developed in partly excised GCMN on the back.	1. NR 2. Neurocutaneous melanocytosis: 15/136 pts 3. NR 4. NR 5. NR	Overall: 2. NR 3. NR 4. NR
			1. Hyperpigmented scar: 19/81 1. Hyperpigmented scar: 0/62 1. Hyperpigmented scar: 0/29
NR	1. n=0 2. n=0; mean (SD): 16.2 mo	NR	Overall: 2. NR 3. NR 4. NR 1. NR 1. NR 1. Gradual improvement of hyperpigmentation over 3 weeks: 2/4 1. Hyperpigmentation after partial graft loss and secondary grafting: 1/1

Supplemental Digital Content 5. (continued)

Author (year); location	Treatment modality	Cosmetic outcome 1. patient satisfaction 2. physician satisfaction	Functional outcome 1. patient satisfaction 2. physician satisfaction	Scar assessment 1. by patient 2. by physician
Hong et al. (2019); Vietnam	Overall: - 44 procedures in 44 CMN in 20 pts	Overall (38/44 CMN assessed): 1. NR 2. Good: 34/38; Poor/moderate: 4/38	NR	NR
	Distant flap (n=1)	2. NR		
	Adjacent flap (n=2)	2. NR		
	TE (n=6)	2. Good: 5/6; Poor/moderate: 1/6		
	SG (n=16)	2. Good: 13/16; Poor/moderate: 3/16		
	SE (n=16)	2. Good: 16/16		
	Primary closure (n=3)*	2. NR		
Li et al. (2021); China	TE (with transferred flap): 9 pts	1. Good: 12/12 2. "Excellent aesthetic outcomes"‡	1. NR 2. "Excellent functional outcomes"‡	NR
	TE (with transferred flap) + STSG: 3 pts Treatment for non-CMN: 2 pts*	NA	NA	
Mérigou et al. (2009); France	Non-expanded flap: 51 pts	1. Excellent: 32/62; Good: 24/62; Poor/moderate: 6/62 yr) 2. Excellent: 29/62; Good: 28/62; Poor/moderate: 5/62	NR	NR

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
NR	NR	NR	NR
NR	NR	NR	1. "Excellent colour match was typically achieved"[‡] 2. NR 3. NR 4. NR
			NA
NR	1. NR 2. n=0; mean 33 m (range 8 mo - 10 yr)	NR	1. Pigment resurgence on scar: 5/51 2. NR 3. NR 4. NR

Supplemental Digital Content 5. (continued)

Author (year); location	Treatment modality	Cosmetic outcome 1. patient satisfaction 2. physician satisfaction	Functional outcome 1. patient satisfaction 2. physician satisfaction	Scar assessment 1. by patient 2. by physician
	TE: 12 pts			
	SG: 2 pts			
	Curettage: 2 pts (both received additional excision)*	1. NR 2. Poor/moderate: 2/2 (repigmentation requiring additional excision)		
	No surgery: 43 pts*	NR		
Rehal et al. (2011); USA	Overall: 51 procedures for 51 CMN in 36 pts (5/36 pts received TE + SG) TE (n=10) FTSG (n=12) STSG (n=5) Integra artificial skin (n=2) SE (n=17)	NR	NR	NR
	Laser (n=1); Kenalog injection (n=3)*	NA	NA	NA

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
			1. Pigment resurgence on scar: 4/12 2. NR 3. Eruption of new satellites after surgery: 2/12 4. NR
			1. Homogeneous repigmentation: 2/2 2. NR 3. NR 4. NR
			1. Repigmentation: 2/2 2. NR 3. NR 4. NR
6. Request for surgery due to negative aesthetic impact: 9/42 of assessed, non-operated patients/ families whose surgeries were initially postponed			NR
NR	1. n=0 2. NR	NR	NR

Supplemental Digital Content 5. (continued)

Author (year); location	**Treatment modality**	**Cosmetic outcome** 1. patient satisfaction 2. physician satisfaction	**Functional outcome** 1. patient satisfaction 2. physician satisfaction	**Scar assessment** 1. by patient 2. by physician
Warner et al. (2008); USA	Overall: 63 surgical procedures in 40 pts	NR	NR	NR
	TE (n=10) FTSG (n=7) STSG (n=22) Cultured SG (n=3) Allograft (temporary) (n=3) Primary closure (n=18)*			
One combination of different modalities				
Dong et al. (2020); China	TE + SG: 21 pts	1. NR 2. Good: 21/21	NR	NR
Ma et al. (2017); China	TE (with transferred flap) + SG: 11 pts - Total of 13 expanders - Number of expanders per pt: mean 1.2	1. Good: 11/11 2. "Good aesthetic results"‡	1. NR 2. "Good functional results"; "Retention of sensibility"; Elbow stiffness and flexion restriction: "some pts". (Due to long-time immobilization. Most pts recovered after 1-month of functional training.)‡	NR

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
NR	1. n=0. 2. n=1; mean 11.25 yr; This case concerned CMN of 60% TBSA; Initial histopathology showed only intradermal nevi and no dysplasia or melanoma	1. NR 2. NR 3. NR 4. NR 5. Death by cerebrally metastasized melanoma, 2 years after initial presentation: 1/40 pts	1, 4. Requirement for additional surgery due to contractures/ hypertrophy/ hirsutism/pigment changes: 9/40 pts† 2. NR 3. NR
NR	NR	1. NR 2. Neurocutaneous melanocytosis: 0/21 3. NR 4. NR 5. NR	NR
NR	1. n=0 2. NR	NR	1,2. “a close match in terms of tissue colour, texture” 3. NR 4. NR

Supplemental Digital Content 5. (continued)

Author (year); location	**Treatment modality**	**Cosmetic outcome** 1. patient satisfaction 2. physician satisfaction	**Functional outcome** 1. patient satisfaction 2. physician satisfaction	**Scar assessment** 1. by patient 2. by physician
Flap				
Liu et al. (2020); China	Advanced orbicularis oculi myocutaneous (OOMC) flap: 17 pts	1. Good: 17/17 2. NR	1. Good: 17/17 2. "Satisfactory"‡	NR
Zhu et al. (2009); China	Overall: - 16 non-expanded flaps and 2 single-stage excisions with primary closure in 10 pts	1. NR 2. Good: 8/10; Poor/ moderate: 2/10	1. NR 2. Good: 8/10; Poor/ moderate: 2/10	1. NR 2. "Well healed and concealed scars on both donor and recipient sites"‡
	Orbicularis oculi muscle (OOM) flap (n=10) Retroauricular superficial musculoaponeurotic system (SMAS)-pedicled flap (n=3) Reversal superficial temporal artery (STA) flap (n=3) Single-stage primary closure for upper eyelid part of the lesion (n=2)*			

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
NR	1. n=0 2. NR	NR	1. NR 2. NR 3. NR 4. Partial cilia loss: 6/17 (These CMN involved the palpebral margin or conjunctiva. Patients stated that it was acceptable because it made little impact on appearance.)
NR	1. n=0 2. NR	NR	1. Slight hyperpigmentation after epidermal necrosis: 1/10 1, 2. "excellent color and texture matching" 3. NR 4. NR

Supplemental Digital Content 5. (continued)

Author (year); location	**Treatment modality**	**Cosmetic outcome** 1. patient satisfaction 2. physician satisfaction	**Functional outcome** 1. patient satisfaction 2. physician satisfaction	**Scar assessment** 1. by patient 2. by physician
Tissue Expansion				
Fahmy & Mazy (2010); Egypt	TE: 12 pts - Total of 37 expanders - Number of expanders per pt: mean 3.1 (range 2-5); median 3	NR	NR	1. Good: 6/12; Moderate: 5/12; Mild: 1/12 2. NR
Kim et al. (2020); Korea	Overall: TE for 88 CMN in 55 pts Single TE (n=64) - No. of expanders per case: mean 1.14 (SD 0.32) Serial TE (=31) - No. of expanders per case: mean 3.26 (SD 1.00)	NR	NR	NR

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
1. Satisfaction of body image: Mild: 0/12; Moderate: 5/12; Good 7/12 2. NR 3. NR 4. NR 5. NR 6. NR	1. n=0 2. NR	1. NR 2. Neurological involvement by melanocytic tissue / neurocutaneous melanosis: 0/12 pts 3. NR 4. NR 5. NR	NR
1. NR 2. NR 3. NR 4. NR 5. NR 6. "One pt attempted suicide. This pt presented with a complex facial nevus and, having suffered from depression for years, ultimately wanted to remove the nevus. During the long treatment period, the pt could not accept the morphological changes, which contributed to the suicide attempt. Explantation was performed, not meeting the treatment goal."	1. n=0 2. NR	NR	NR

Supplemental Digital Content 5. (continued)

Author (year); location	**Treatment modality**	**Cosmetic outcome** 1. patient satisfaction 2. physician satisfaction	**Functional outcome** 1. patient satisfaction 2. physician satisfaction	**Scar assessment** 1. by patient 2. by physician
Maillet-Declerck et al. (2012); France	TE: 12 pts - Total of 22 expanders - Number of expanders per pt: range 1-2	1. Good: 12/12 2. NR	NR	NR
	TE for other indications than CMN: 3 pts*	NA		
Zaal & Van Der Horst (2009); The Netherlands	TE: 17 pts - Total of 38 expanders - Number of expanders per pt: mean 2.2	1. Good: 17/17 2. Good: 11/17; Poor/ moderate: 6/17	NR	- Patient and Observer Scar Assessment Scale (POSAS, 6 = best, 60 = worst imaginable scar.) - Overall scar impression: 10-step scale (1= best, 10 = worst imaginable scar) 1. POSAS: mean 20.7 (range 6-37); median 21.5; Overall scar impression: mean 4.3 (range 1-8); median 4.5 (interpretable as "moderate" (4-6)) 2. POSAS: mean 15.7 (range 7-25); median 16 ; Overall scar impression: mean 3.7 (range 1-7); median 4

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
1. NR 2. NR 3. NR 4. NR 5. NR 6. (Any) memories of TE protocol: 1/12 pts; Unpleasant) memories of TE protocol: 0/1 pts	NR	1. NR 2. NR 3. NR 4. Normal psychomotor development: 12/12 5. NR	1. Residual nevus due to regrowth of nevus around the scar: 1/12 2. NR 3. NR 4. Correct hairline implantation / hair growth pattern: 11/12; Hair thinner, less density: 1/12
NA		NA	NA
1. NR 2. Families who would recommend the treatment to other parents with children with a GCMN at the scalp: 17/17 3. NR 4. NR 5. Absence at school: 0/17 pts 6. Psychological problems of the patient: 0/17 pts; Expansion period remembered as a psychological war of attrition: some parents; (Any) memories of the reconstruction period: 0/17 pts	1. n=0 2. n=0; mean 8.7 (range 1.5-16) yr	1. "Any kind of neurological symptoms": 0/17 (FU mean 8.7 y (range 1.5-16 y)) 2. Neurocutaneous melanosis: 0/3 of pts who received MRI 3. NR 4. NR 5. NR	(10-step scale in which 1-4 is mild re-pigmentation, 5-7 moderate, 8-10 severe re-pigmentation) 1. Mild repigmentation: 3/17; No repigmentation: 14/17 2. NR 3. NR 4. For occipital and parietal GCMN (n=6): "no disturbance of hair growth at all" (around surgical site); Reconstruction-related alopecia: 1/17 p (registered as scar-related complication)

Supplemental Digital Content 5. (continued)

Author (year); location	Treatment modality	Cosmetic outcome 1. patient satisfaction 2. physician satisfaction	Functional outcome 1. patient satisfaction 2. physician satisfaction	Scar assessment 1. by patient 2. by physician
Skin Graft				
Dai et al. (2016); China	FTSG: 6 pts	1. NR 2. Good: 20/20 pts	1. NR 2. Good: 20/20 pts	1. NR 2. Favorable linear scar: 17/20 pts
El-Sabbagh & Hassan (2017); Egypt	FTSG + STSG: 14 pts "Meshed SG": 4 pts	1. NR 2. "Satisfactory appearance was obtained"‡	NR	NR
Schiestl et al. (2010); Switzerland	FTSG + STSG: 4 pts STSG: 8 pts Integra Artificial Skin + STSG: 12 pts	1. NR 2. Excellent: 7/12; Good: 3/12; Poor/moderate: 2/12	1. NR 2. Excellent: 7/12; Good: 3/12; Poor/moderate: 2/12	NR
Primary Closure				
Hassanein et al. (2015); USA	SE: 21 pts - Total of 72 staged excisions	NR	NR	NR

	Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
	NR	1. n=0 2. n=0; mean 1 yr (range 6 mo – 2 yr)	NR	NR
	NR	1. n=0 2. NR	NR	1. Recurrence: 0/16 2. NR 3. NR 4. NR
	NR	NR	NR	NR
	NR	1. n=0 2. NR	NR	NR

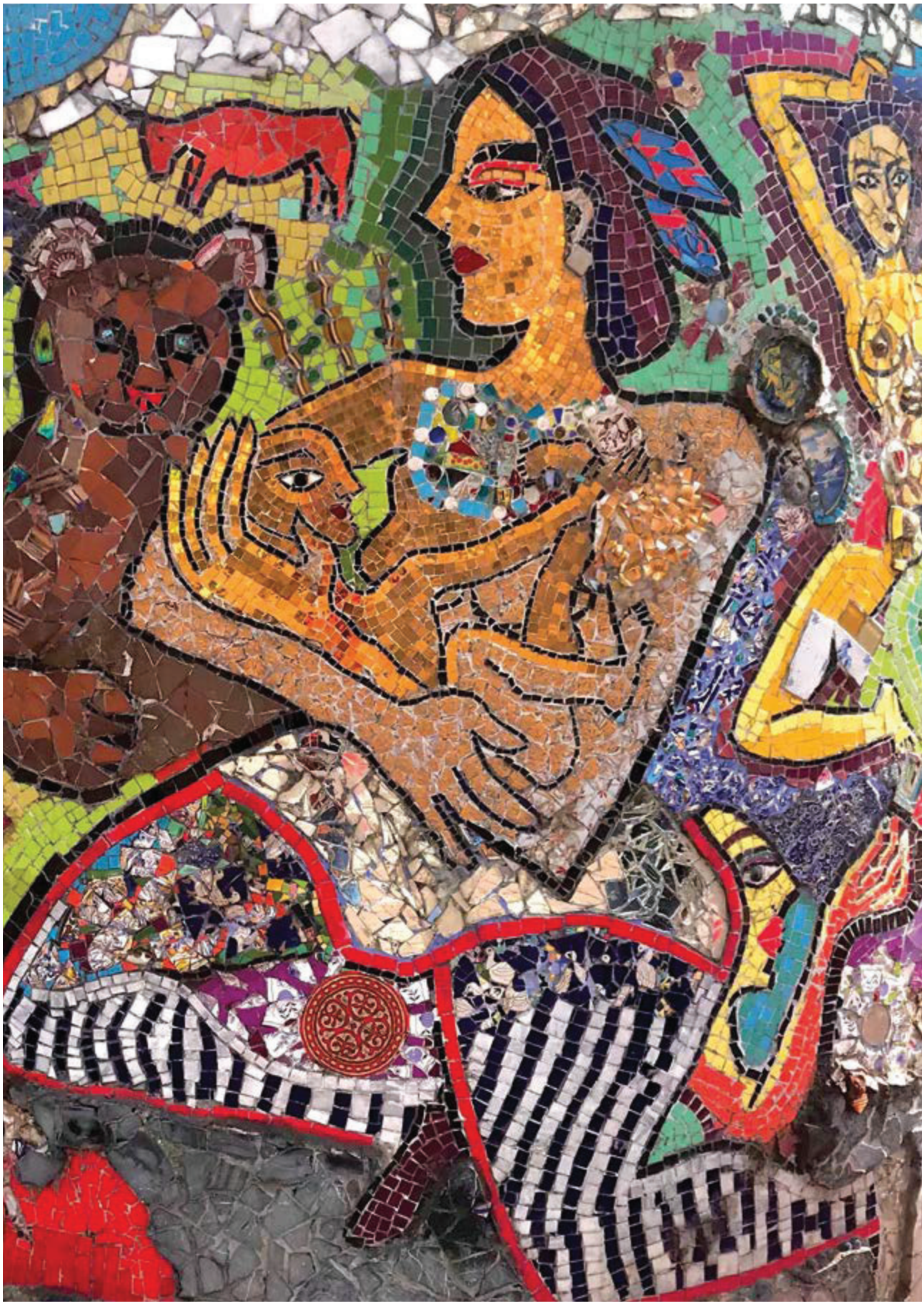
Supplemental Digital Content 5. (continued)

Author (year); location	Treatment modality	Cosmetic outcome 1. patient satisfaction 2. physician satisfaction	Functional outcome 1. patient satisfaction 2. physician satisfaction	Scar assessment 1. by patient 2. by physician
Qiao et al. (2019); China	Single-stage excision with primary closure: 35 pts	Visual Analog Scale (VAS): 0 points indicate no cosmetic improvement, 10 indicates the best imaginable outcome. 1. "Average satisfaction on appearance was high"‡ 2. VAS score: mean (SD) 8.0 (0.7); range 7-10 (indicating a high satisfactory outcome); Symmetric facial contour after 1-year follow-up: 35/35	NR	Vancouver Scar Scale (VSS): assesses pigmentation, height/thickness, pliability, and vascularity, with 4 points indicating the worst scar formation and 0 suggesting the best outcome, resemblance to normal skin. 1. NR 2. VSS score: mean (SD) 2.6 (1.0); range 0-4

FTSG = full-thickness skin graft, FU = follow-up, (G)CMN = (giant) congenital melanocytic nevus, mo = month, NA = not applicable, NR = not reported, pts = patients, SD = standard deviation, SE = serial excision, SG = skin graft, STSG = split-thickness skin graft, TE = tissue expansion, yr = year. * Excluded from this systematic review, †excluded from quantitative synthesis, ‡(only) narrative results were reported

Quality of life 1. Acceptance of CMN as part of identity 2. Satisfaction with treatment choice 3. Aesthetic issues 4. Perceived stigmatization 5. Social relations 6. Emotional/psychological functioning	**Melanoma** 1. no. in excised specimen 2. no. at end of FU; FU; case description	**Neurological symptoms and signs** 1. Epilepsy 2. Magnetic resonance image findings 3. Hydrocephalus 4. Motor development 5. Brain complications due to melanocytosis, melanoma, or metastasis	**Skin appearance** (of surgical site, end-FU)**:** 1. Color 2. Texture 3. Satellites 4. Hairiness
NR	NR	NR	NR

UNIFORMITY IN DOMAINS, OUTCOMES, AND INSTRUMENTS



Fabrice Hünd

Het Kompas (The Compass), Amsterdam

2006

'Het Kompas' represents different continents all over the world. This work of art is located on a street called *Ferdinand Bolstraat* in Amsterdam. I met Fabrice when I took this picture, as he was restoring this work after it was heavily damaged by cars and bikes running in to it. He told me that he had been offered shards of ceramic, plastic, marble and beads by local residents to create this mosaic.

4

PROTOCOL FOR THE DEVELOPMENT OF CORE SET OF DOMAINS OF THE CORE OUTCOME SET FOR PATIENTS WITH CONGENITAL MELANOCYTIC NEVI (OCOMEN PROJECT)

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ABSTRACT

Background

Having large congenital melanocytic nevi (CMN) is associated with a psychosocial burden on patients and their parents because of its remarkable appearance and the extra care it may require. Large CMN also pose an increased risk of malignant melanoma or neurocutaneous melanosis. There is a lack of international consensus on what important outcome domains to measure in relation to treatment. This makes it difficult to compare options, to properly inform patients and their parents, and to set up treatment policy for CMN. Therefore, we aim to develop a core outcome set (COS), i.e. the minimum set of outcomes that are recommended to be measured and reported in all clinical trials of a specific health condition. This COS can be used in the follow-up of CMN patients with or without treatment, in clinical research and practice.

Methods

In the Outcomes in Congenital Melanocytic Nevi (OCOMEN) projects we follow the recommendations from the Core Outcome Measures in Effectiveness Trials (COMET) initiative and the Cochrane Skin Core Outcomes Set Initiative (CS-COUSIN). This project entails: (1) A systematic review to identify previous reported outcomes in literature; (2) Focus groups with national and international patients and parents to identify patient-important outcomes; (3) Classification of outcomes into outcome domains; (4) e-Delphi surveys in which stakeholders (patients/parents and professionals) can rate the importance of domains and outcomes; (5) An online consensus meeting to finalize the core outcome domains of the COS.

Result

The results will be disseminated by means of publication in a leading journal and presentations in international meetings or conferences. We engage international experts in CMN, both patients and professionals, to ensure the international utility and applicability of the COS.

Keywords: Core outcome set, core domains, congenital nevi, clinical research, clinical practice

INTRODUCTION

Scientific background and relevance

Congenital melanocytic nevi (CMN) are birthmarks that sometimes cover large areas of the body.[1-4] They are present at birth or appear within three months after birth. An estimated 1% of infants worldwide are born with CMN. However, large (> 20 cm projected adult size (PAS)) and giant (>40 cm PAS) are rare, with an estimated incidence of 1: 20.000 and 1: 50.000 infants, respectively.[5] CMN may be associated with a psychosocial burden on patients and their families due to their remarkable appearance and the extra care.[6] Large CMN also pose an increased risk of malignant melanoma, soft-tissue tumors or neurocutaneous melanosis.[7] Adequate treatment and monitoring the impact of CMN on patients' lives are therefore crucial. Different interventions for CMN such as laser, curettage and excision are available,[7] but conservative management such as watchful waiting is also possible. Patients with large CMN may undergo several surgeries, which do not always yield satisfactory cosmetic and functional results. It is also not clear whether these surgeries reduce the risk of melanoma.[7] Moreover, guidance on how to perform and the frequency of watchful waiting is not available. Scientific evidence on the best treatment policy in CMN is unfortunately still lacking.

To date, multiple articles describe the impact of having CMN or the effects of treatment on the lives of patients. However, a wide heterogeneity in outcomes used in these articles makes it difficult to combine, compare or contrast the results. Development of a 'Core outcome set' (COS), i.e., the minimum set of outcomes that should be measured and reported in all clinical trials for a specific health condition, is an effective method to reduce heterogeneity and reporting bias in future CMN research.[8] In a strict sense, a COS consists of 'what' (outcome domains) and 'how' (outcome measurement instruments) to measure.[9] This project, the Outcomes for Congenital Melanocytic Nevi (OCOMEN), focuses first on the development of the core outcome domains, and what specific outcomes these domains need to cover. We define a domain as an aspect of disease that should be measured such as cognitive functioning,[10] whereas an outcome describes a sub granular concept/construct of a domain such as learning difficulties or memory lapse.[11] We aim to reach consensus on the core domains of the COS, and initiate the selection of the outcomes of the domains, that can be used in the follow-up of the CMN patients without, during and after treatment. We focus on patients with medium and larger sizes of CMN.[12]

Key objectives

- The key objectives of the Outcomes in COngenital MElanocytic Nevi (OCOMEN) projects are:
- to identify a list of outcomes as previously reported in literature and proposed by patients/parents in focus groups
- to try to reach consensus on the domains and outcomes from the perspective of professionals and patients/parents
- to compare those domains and outcomes from the perspectives of the professionals with that of the patients/parents
- and to integrate the domains and outcomes important to professionals and patients/parents into a combined set of core outcome domains for clinical research and for practice

Scope definition and applicability of the COS

Population: patients with medium size or larger CMN (Figure 1).[12] This includes those patients with M1 (1.5-10 cm PAS) on the face or M2 (>10-20 cm PAS) elsewhere, either single or multiple. We chose this subgroup of patients with CMN because we expect that having medium size of CMN or larger may have a 'considerable' impact on patients' lives.
Intervention: surgical (laser/curettage/excision) and conservative (watchful waiting)
Setting: clinical research and practice
Geographical: International.

METHODS

The research team

The research team consists of the 'Study Management Group' (SMG) and the 'Study Advisory Group' (SAG). The SMG is responsible for the day-to-day management of the study. It consists of: two CMN experts, three methodological experts, four researchers, including 2 plastic surgeons and 3 dermatologists, and one patient representative. The SAG consists of international CMN experts who provide their input at critical points of the study such as: protocol development, stakeholder recruitment and the consensus meeting. The SMG and SAG both participated in the consensus process.

Study design

The OCOMEN project is registered at the Core Outcome Measures in Effectiveness Trials (COMET) website (http://www.comet-initiative.org/studies/details/1124) and the Cochrane Skin-Core Outcomes Set Initiative (CS-COUSIN) website (http://cs-cousin.org/cos-project-groups). We used the guidelines of the (COMET) initiative and the CS-COUSIN.[9,13,14]

The study is done in two phases

Phase one: Identification of potential outcomes and domains important in clinical research and practice by means of:

1. A systematic review and review of clinical guidelines
2. Focus group with patients and parents to include patient-important outcomes
3. Classification of outcomes into domains

Phase two: A consensus process where relevant stakeholders (patients/parents and professionals) can rate the importance of the identified list of outcomes and domains to reach consensus on the domains of the COS. This is done by means of a:

1. Three rounds of e-Delphi survey
2. Consensus Meeting

Figure 1. Preliminary list of outcome domains presented in five core areas for the e-Delphi rounds

Phase 1: Identification of potential outcomes and domains

Phase 1.1: Systematic review

The systematic review was registered in PROSPERO number CRD42018095235. We included all research that focuses on patients with CMN, regardless of age or sizes and locations of CMN. We looked at all types of CMN treatment: interventional (laser, curettage, and excision) and conservative (watchful waiting). We did not perform quality assessment of methodological quality of the studies because we aim to include all outcomes regardless of the methodological quality of the studies.

We searched in PubMed, EMBASE (Ovid) and the Cochrane Library for relevant studies published between 2006 and 2018. We chose the year 2006 because Krengel et al published an article that year about the risk of melanoma being lower than previously thought.[12] From then on, the focus of CMN treatment may have shifted to favor cosmetic results rather than prevention of melanoma. We engaged a clinical librarian to help with the search terms. Keywords, MeSH terms, and synonyms of 'Nevi', 'Congenital', or 'Giant' were used.

All English, Dutch, Italian or French human studies with 10 or more CMN patients that completed the investigated intervention were included. Original articles and systematic reviews are included, whereas letters to the editor, case reports, conference reports, books, descriptive reviews are excluded. Evidence of CMN diagnosis by means of histology or dermatoscopy is lacking. Therefore we excluded studies that diagnosed CMN solely by histology or dermatoscopy.

Two reviewers selected articles and extracted the data independently. Disagreement was resolved by discussion and by consulting a third review author if necessary. The following data were extracted from the articles: authors, year of publication, study design, intervention, objectives,

number of patients, age and gender of patients, location of CMN, size CMN, size classification system used, outcomes reported in the methods or results, including patient reported outcomes and outcome measurement instruments. Information about outcome measurement instruments can later be used in a follow up study on defining the core set of outcome measurement instruments for the domains identified in the current study.

We assessed the following: what outcomes and outcome measurement instrument are used, consistency in outcomes, number of times an outcome was used, number of patient-reported outcomes, consistency in size classification used, correlation between reported outcomes and size of CMN (when there is consistency in classification tools of the size of CMN), correlation between outcomes and visibility of CMN (when descriptions of visible CMN are available).

To exhaust all potentially relevant outcomes for CMN, we also looked at existing guidelines. We found one guideline developed for clinical care of CMN patients.[7]

Phase 1.2: Focus groups

The SMG worked together in recruiting patients and parents for the national focus groups. We also involved patients and parents from Europe and the US through collaboration with the SAG and the international patient support groups. A topic list, which contains open questions in lay language, was prepared. Questions ranged from the impact of having CMN on patients' lives to experiences with treatment. Experienced researchers in focus group discussions facilitated the sessions. Participants signed an informed consent prior to each session. Participation is treated confidentially and semi-anonymously. Participants in a focus group knew who were participating in the same group but they did not know other participants in the other focus groups.

We conducted 3 focus groups at the Erasmus MC, 2 at the Amsterdam UMC, the Netherlands, 1 in Paris, France, and 1 online by means of GoToMeeting application. The focus groups in the Netherlands were conducted in Dutch. Table 1 summarizes the stakeholders' background of the focus groups.

The process was audio-recorded, transcribed, and analyzed for content. Full data analysis was not done in this study as the purpose of this qualitative data was for outcome identification. In the analysis, themes were picked up and grouped (Box 1). The themes from the Dutch focus groups were translated into English by two of our researchers.

Phase 1.3: Classification of outcomes into domains

Outcomes identified in the review and focus groups were classified into domains by following the taxonomies published by the COMET initiative website.[10,15] Since CMN is a specific skin condition, we also consulted the WHO website for a more detailed classification of the skin anatomy and functions (http://apps.who.int/classifications/icfbrowser/).

Two researchers did this grouping independently. Differences were discussed and solved by the SMG. The preliminary list of outcome domains are included in the consensus process (Figure 2).

Phase 2: Consensus Process

Phase 2.1: Delphi study

Relevant stakeholders were presented with the identified list of domains and outcomes. They were asked to rate the importance of these domains and outcomes in three rounds of e-Delphi surveys. Stakeholders consist of two groups: patients/parents and professionals. We approached the stakeholders with the aid of international patient support organizations, among others patient networks from the UK, Germany, Belgium, and the Netherlands. A detailed description of stakeholders' recruitment and methods used to approach them is presented in Table 2. Patients/parents who showed interest in participating were formally invited through e-mail. There is no guideline to optimal sample size for the Delphi method.[16,17] In general, having more participants will increase the reliability of groups' judgment.[18] Nevertheless, a small sample size of experts in the field of interest can provide reliable knowledge.[17] We aimed at having 100 participants in total (patients/parents and professionals). Variable response rates in Delphi studies have been reported.[17,19] We anticipated a response rate around 30% to the invitation for participation. Therefore, we invited around 300 stakeholders in equal proportion to participate in the study.

We prepared the list of domains and outcomes in lay language. A patient/parent representative and a native English speaker reviewed the test version of the survey to ensure clarity and ease of use. We informed participants that agreeing to participation implies that participants give consent to retaining their background information and their rating anonymously. Participants were given

Table 1. Summary of the focus group discussions

No	Date	Location	Parents/family	Patients
1	5 July 2018	Erasmus MC, the Netherlands	4 Dutch parents of giant CMN patients. All patients were treated.	-
2	6 July 2018	Erasmus MC	5 Dutch parents	3 Dutch patients (2 teenagers and 1 child). All patients were treated
3	31 July 2018	Erasmus MC	3 Dutch parents. All patients were treated	-
4	12 September 2018	Paris, France	7 multinational parents	3 patients from European countries, all were treated
5	19 September 2018:	Amsterdam UMC, the Netherlands	2 Dutch parents	4 Dutch patients (1 not treated)
6	20 September 2018	Online	-	4 patients in the US and Canada (3 not treated)
7	24 September 2018	Amsterdam UMC	1 Dutch family member	4 Dutch patients. All were treated

- Lack of information on the condition
- Frightening when first time see the CMN
- Try to cover the nevi vs not bothered by visibility of nevi
- Very self-conscious about the nevi
- Try to find others with the same condition
- Satisfied with treatment choice
- Scare of bullying
- Understanding/knowing about the condition helps with coping
- Acceptance of having the CMN
- Support from a therapist or psychologist is well-appreciated
- Negative body image
- (Dark) color of the nevi
- Hairiness of the nevi
- Satisfied with life
- Scars
- Comfortable with having scars
- Skin graft
- Support from patient network
- The risk of having cancer
- Work on the body image
- Would not recommend having surgeries
- Having CMN has made a patient tough (affects the personality)
- Rejection (hard making friends) because of CMN
- Missed (3 years of) school due to surgeries
- Support from school
- Parents' behavior influences the way a patient sees the CMN
- Itch
- Asymmetrical size of body parts due to the nevi
- Accept CMN as a natural tattoo (in a cool way)
- Very emotional period around the first-time diagnosis and surgeries
- Addiction to morphine
- Neurological complications
- Feeling guilty because of having a CMN child

Box 1. Themes abstracted from the transcripts of the focus groups.

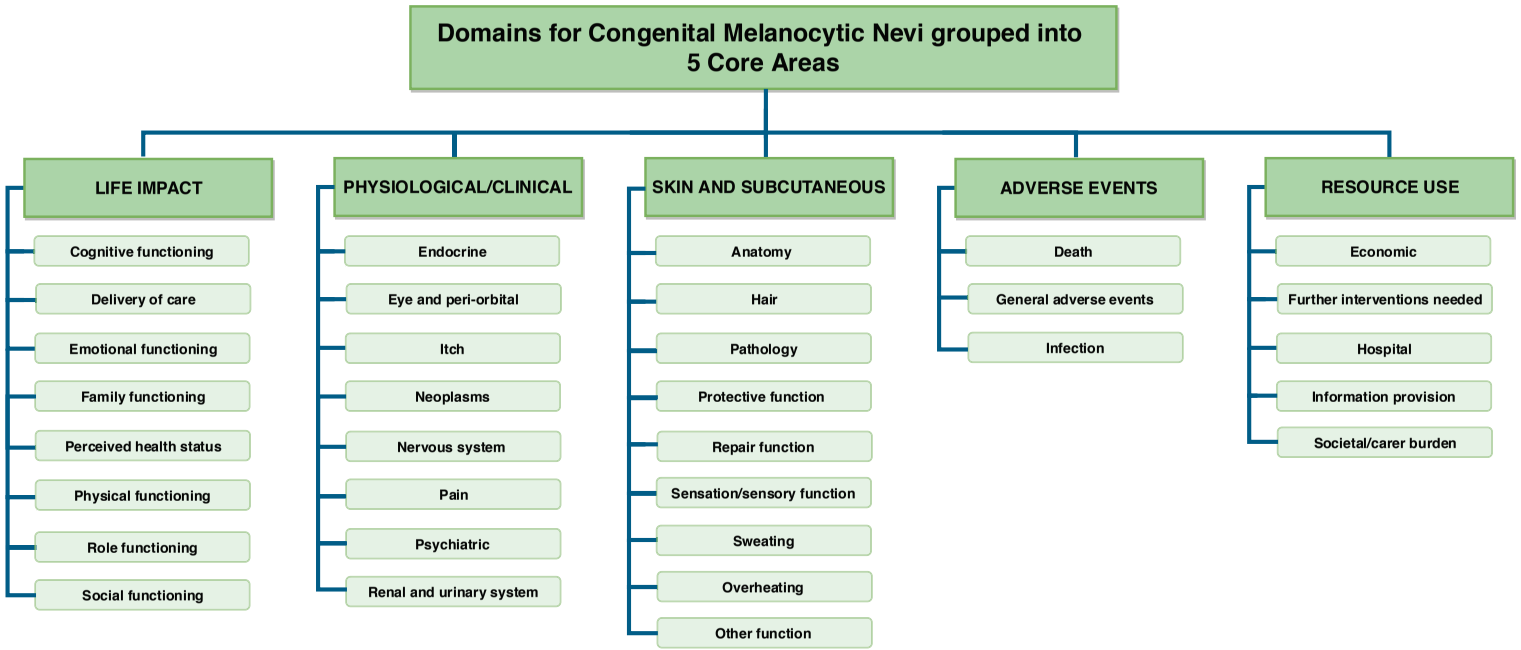

Figure 2. Congenital melanocytic nevi of a patient with medium size nevi on the face and of a patient with giant nevi on the lower back trunk

Table 2. Stakeholders groups and methods of approaching potential participants

Details	Methods of approach
Patients Parents/caregivers*	Identification via the Erasmus MC and Amsterdam UMC database. Invitation to participate is done via email.
Family members	Call for participation, in collaboration with patient advocates, on the **websites and social media of international patient support organizations such as Naevus Network Netherlands, Naevus Global, Nävus Netzwerk Deutschland, Nevus Outreach, Caring Matters Now and Naevus International.**
Dermatologists Plastic surgeons Pediatricians Pathologists Neurologists Psychologists Researchers	Identification of names from the literature, attendance of meetings/ conferences in pediatric dermatology/plastic surgery and trough personal network of the SMG. Invitation to participate is done by email.
	Snowball-sampling method: Ask professionals to suggest names of other professionals who may be interested to participate. We approached those names by email and invited them to participate.
	Call for participants on the Naevus International website and their first meeting in Paris, France (12 September 2018)

1-2 weeks to fill out the survey, reminders were sent frequently. If the response rate is <70% an extra week is given to accomplish the task. Only participants who completed a round will be invited for the subsequent round.

Table 3 presents the geographical distribution of the stakeholders who completed the first round of the Delphi study.

Definition of consensus

For the domains we used the 9-point Likert scoring system where 1-3 signifies a domain of limited importance, 4-6 somehow important but not critical, and 7-9 critical. Domains will be defined as 'important' when scored 7-9 by at least 70% of participants in each stakeholder groups in the previous round, 'unimportant' when scored 1-3 by 70% of participants and 'undecided' when not in any of those two groups.

For the outcomes, we define consensus to have been reached if the outcomes are suggested to be included in a particular domain by at least 70% of participants from each stakeholder group. Outcomes are only scored during the third Delphi round.

First round

In the first round, a list of domains was presented to the participants together with information on the aim and structure of the survey. For each domain a list of outcomes was presented for illustration purposes. Participants needed to indicate how important they find a domain is for the clinical research setting and how important they find it is for the practice. They could also provide comments to elaborate why they deemed a certain domain important. Participants could

Table 3. Country of residence of participants of the Delphi study

Countries	Number of participants (%)
Argentina	2 (1%)
Armenia	1 (1%)
Australia	1 (1%)
Belgium	4 (3%)
Brazil	1 (1%)
Canada	4 (3%)
Czech Republic	3 (2%)
Denmark	2 (1%)
Finland	1 (1%)
France	8 (6%)
Germany	5 (3%)
Greece	1 (1%)
India	1 (1%)
Ireland	1 (1%)
Israel	1 (1%)
Italy	5 (5%)
South Korea	2 (1%)
Netherlands	43 (30%)
Norway	3 (2%)
Poland	1 (1%)
Romania	1 (1%)
Slovakia	1 (1%)
South Africa	1 (1%)
Spain	4 (3%)
Switzerland	4 (3%)
UK	17 (12%)
USA	26 (18%)

suggest additional domains, which will be included in the next round only if they are suggested by at least two participants from either stakeholder groups.

Second round

In the second round, we aimed to reach convergence on the domains. We asked the participants to rate the domains in a similar fashion, but based on the first round the domains are highlighted in the following categories: 'important', 'unimportant' and 'undecided'. They had the opportunity to change their ratings. Additional domains suggested in the previous round were also rated.

Third round

In the third round, participants are asked to only rate the domains that are in the 'undecided' category. Domains in the ' important' category will be highlighted but cannot be re-rated. Domains that were scored as 'unimportant' in the second round will not be retained in the third round. 'Important'

and 'unimportant' domains can only be re-scored in this round if at least 2 participants from either stakeholder groups propose to do so. Stakeholders will also be asked to rate the importance of the outcomes for each domain in the 'important' or 'undecided' category.

Feedback

Between rounds, the rating of domains in the previous round are aggregated across stakeholder groups and summary statistics are presented. We looked at the rating for the clinical research and for practice separately. Domains are summarized in the 'important', 'unimportant', and 'undecided' categories. Domains that are considered to be 'important' after the second round will be directly included in the COS while domains in the 'unimportant' category will be excluded and not be retained in the third round.

The abovementioned rules to reach consensus are often used but there are also other rules being used in other COS development studies.[20]

Phase 2.2: Determine the core set of domains of the COS during the consensus meeting

To reach consensus and finalize the core set of domains of the COS we will organize an online consensus meeting. We will involve the SAG and representatives of stakeholders who completed the 3-round surveys. We will include equal proportion of patients/parents and professionals in this consensus meeting. The stakeholder representatives will be randomly selected from those Delphi completers who noted that they are interested in participating. Participants will be sent a reminder of their personal Delphi scoring prior to the meeting. We have the following criteria for inclusion of domains and outcomes into the COS:

Selection of domains

Domains for which consensus definition has been reached during the Delphi will be included in the core set of domains of the COS.

Domains that are still considered 'undecided' after the third Delphi round will be evaluated during the consensus meeting. During this meeting we will discuss and vote whether or not a domain should be included in the final COS. A domain that reaches at least 70% positive vote from the meeting participants will be included, otherwise not.

Selection of outcomes in the selected domains

Once the domains for the core set of domains of the COS have been selected, we will select the outcomes to be included in those domains. Outcomes that are selected by at least 70% of participants in the third Delphi round will be automatically included in the COS. Outcomes for which consensus definition during the Delphi has not been reached, will be voted here. An outcome for which at least 70% positive votes have been reached during the meeting will be included in the COS.

ETHICS AND CONSENT

We have applied for ethical approval prior to the implementation of this project from the METC board at the Erasmus Medical Center and Amsterdam University Medical Center. In this project, we collected information from patients on their health status and experiences with treatments. Informed consent for each participating patient is sought prior to participation. We will treat all information confidentially and partially anonymously. The data will be treated anonymously in the analysis but the email addresses of each participant are encoded in the data as an identifier. However, participants cannot know who the other participants are and what information they provide.

RESULTS

We will report the results separately for the systematic review, and the focus groups with the consensus process. We will present the selected core set of domains of the COS separately for clinical research and practice.

Dissemination and publication

The protocol and the actual development process will be reported transparently using the COS-STAR guidance.[21] The results will also be disseminated by means of publication in leading journals and presentation in international meetings/conferences. We will engage international experts in CMN, patients and professionals to ensure an international dissemination, utility and applicability of the research outcomes.

Future research plan

The scope of this research is limited to the core outcome domains. Future research would be to define the core set of outcome measurement instruments of the COS.

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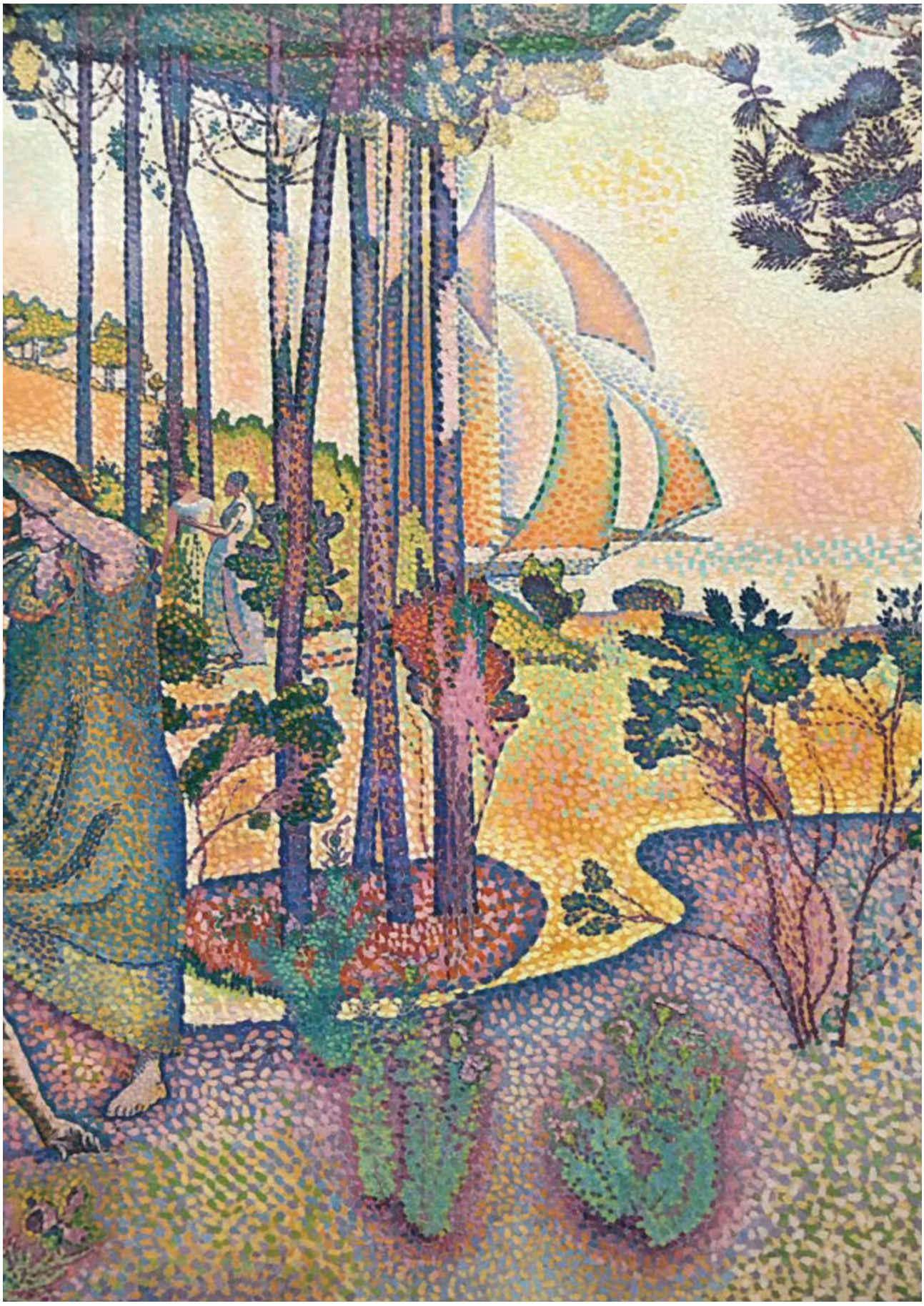

Henri-Edmond Cross

L'Air du Soir (The Evening Air), Musee d'Orsay, Paris

1893

This work was created to celebrate the coast of southern France. Being a Neo-Impressionist, Cross transformed the technique of drawing small dots (pointillism) into drawing larger rectangles, resembling mosaic artwork.

Reference: Musee d'Orsay

5

OUTCOMES AND MEASUREMENT INSTRUMENTS USED IN CONGENITAL MELANOCYTIC NAEVI RESEARCH; A SYSTEMATIC REVIEW

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ABSTRACT

Background

Congenital melanocytic naevi can have a great impact on patients' life due to remarkable appearance and the risk of developing melanoma and neurocutaneous melanosis. Comparison of treatment efficacy is currently hindered by the lack of standard and uniform outcome reporting. This impedes guidance on optimal management policy. To address this, we aim to perform the first step in developing a core outcome set. With this systematic review, we identified a list of domains, outcomes (including patient-reported outcomes), and outcome measurement instruments used in research on congenital melanocytic naevi.

Methods

The review was registered in PROSPERO, registration number CRD42018095235. A search was conducted in EMBASE (Ovid), PubMed, and the Cochrane Library from 2006 to January 2019. Studies with 10 or more patients, with all sizes of congenital melanocytic naevi and reporting outcomes on interventional and conservative management, were included.

Results

A total of 1,285 individual studies was found; 63 studies were included. We extracted 57 different outcomes and 34 outcome measurement instruments showing large heterogeneity. Patient-reported outcomes were included in 38% of studies. Few outcome measurement instruments were described. Moreover, none of the studies reported that the used instruments were ever validated in a congenital melanocytic naevi population.

Conclusion

Heterogeneity exists in outcomes and instruments used in research on congenital melanocytic naevi. The development of a core outcome set may reduce this heterogeneity in future research, thereby enabling treatment comparison and eventually facilitating guidance on management. Furthermore, this overview demonstrates a need for the use and validation of (patient-reported) outcome measurement instruments for congenital melanocytic naevi.

Keywords: Congenital Melanocytic Naevi, Core Outcome Set, Measurement instruments, Neurocutaneous Melanosis, Melanoma, Patient-Reported Outcomes

INTRODUCTION

Congenital melanocytic naevi (CMN) are melanocytic lesions present at birth or soon after birth and may cover large areas of the body.[1] CMN are relatively common, with an incidence of in 1:100 of all infants. However, large or giant CMN are rare, with an estimated incidence of 1:20.000 and 1:500.000.[2] The size of CMN can be classified in different ways. Consensus was reached on a classification system developed by Krengel et al.[3] According to this classification, size is classified as small (<1.5 cm); medium (M1: 1.5-10 cm, M2: >10-20 cm); large (L1: >20-30 cm, L2: >30-40 cm); and giant (G1: >40-60 cm, G2: >60 cm), according to the Projected Adult Size (PAS).

Having a large, giant or visible CMN may have a great impact on life due to the remarkable appearance, the extra care it may require and the risk of developing melanoma or neurocutaneous melanosis. Patients with large and giant CMN have an estimated 2-3% chance of developing melanoma.[1,4,5] Furthermore, CMN patients can develop neurocutaneous melanosis, a rare neurological syndrome with occasionally a poor prognosis.[5] Some patients, primarily those with large or giant CMN or CMN on facial regions are at greater risk of developing psychosocial problems due to remarkable appearance, possible invasive treatment, and fear of melanoma or neurocutaneous melanosis.[6]

Full-thickness (excision) and partial-thickness (laser, curettage, dermabrasion) treatments are reported to be effective in treating CMN.[7] When CMN are excised, the wound can be primarily closed, closed by a skin graft or closed by a transposition flap after skin expansion.

Excision used to be the first choice of treatment in order to prevent the development of melanoma. However, the risk of developing melanoma has now been shown to be lower than assumed before.[4] Moreover, it is unclear if excision can entirely prevent melanoma development. Therefore, there is uncertainty if prophylactic excision is necessary, or that watchful waiting may be sufficient to detect melanoma at an early stage. In other words, patients can choose partial thickness or conservative treatment with watchful waiting instead of full-thickness surgery. Thus, interventional treatment may henceforth be more indicated for "cosmetic" reasons.[8]

Because of the wide diversity of treatment options, evidence-based clinical guidelines are needed to inform patients and specialists about suitable treatment strategies. Development of these guidelines may be hampered by reporting bias, heterogeneity in outcomes used and reported, and lack of outcomes important to patients in clinical research.[1]

Development of a Core Outcome Set (COS) for CMN management can help address these problems.[9] A COS is a consensus-derived minimum set of outcomes important for stakeholders (patients and professionals) that should be measured and reported in all clinical trials of a certain health condition. A COS should ideally represent *what* should be measured (domains and outcomes) and *how* these domains and outcomes should be measured (measurement instruments). In this study, we define a domain as an aspect of a disease that could be measured, such as 'Cognitive functioning', whereas an outcome describes a subgranular concept/construct of a domain, such as 'School performance'.[10]

A systematic review is recommended as the first step of the COS development.[9,11-13] It is important to be aware of what outcomes and outcome measurement instruments are reported

in previously published studies. Furthermore, COS developers should evaluate if heterogeneity indeed exists in research of their studied condition. This study aims to systematically review the literature and describe a list of outcomes, classified into domains, and outcome measurement instruments reported in CMN studies and evaluate potential heterogeneity. We further set out to outline the number of studies that include patient-reported outcomes and which patient-reported outcome measurement instruments are used.

METHODS

The systematic review was registered in PROSPERO, registry number CRD42018095235, and reported according to the PRISMA checklist.[14] The design of the systematic review was based on the guidelines of Core Outcome Measures in Effectiveness Trials (COMET) initiative[9] and the Cochrane Skin Group Core Outcomes Set Initiative (CS-COUSIN).

Scope

Patients: CMN patients at all ages with all sizes and localizations of CMN.

Intervention: All types of management of CMN: interventional (full-thickness: excision, partial-thickness: laser, curettage, and dermabrasion) and conservative (watchful waiting including histology).

Outcomes: all outcomes and outcome measurement instruments reported in the methods and results section of included studies.

Literature Search

The search strategy was developed with the help of an information specialist and was performed in EMBASE (Ovid), PubMed, and the Cochrane Library. The search strategy consisted of controlled terms and words in the title, abstract and other fields for the concepts of CMN. The search was conducted in March 2018 with an update in January 2019. The complete search can be found in appendix 1. Studies published since August 2006 were included. This time point was chosen because a systematic review was published that demonstrated that the melanoma risk in CMN was lower than thought before.[4] We assumed that the finding of this systematic review changed the outcomes measured in the past decades because treatments may be more indicated for "cosmetic" indication instead of melanoma prophylaxis.

Inclusion criteria

Title and abstract were independently screened for eligibility by two reviewers (ACF, CJJF). Full texts of the selected studies were critically reviewed to assess eligibility. Where disagreement was encountered, a third reviewer (SJHB) provided the deciding vote. We included all studies with ten or more patients, written in English, Dutch or French. Study designs eligible for inclusion were: systematic reviews with or without meta-analyses, randomized controlled trials, case-controlled trials, case series, prospective cohorts and, retrospective cohorts. We excluded letters to the editor, case reports, conference reports, and books. We excluded descriptive reviews but included

systematic reviews because a systematic review is a study where researchers define their own outcomes beforehand. When studies included both CMN patients and patients with a diagnosis other than CMN, they were only included when outcomes could be linked to CMN patients.

Data extraction and analysis

A template for data extraction included: study characteristics (author, year, country, study design, level of evidence, intervention), patient characteristics (age, gender), CMN characteristics (CMN size, size classification system used, CMN location), outcomes reported in the method or result section (patient-reported outcomes, investigator reported outcomes) and outcome measurement instruments. For the included systematic reviews, we performed data extraction of full texts of the articles that met our inclusion criteria. On top of that, we included all outcomes and outcome measurement instruments reported in the method or result section of the systematic reviews. In this way, we included outcomes that are considered to be important by the researchers of these systematic reviews. When diagnosis other than CMN were included in the systematic reviews, only data from CMN studies were extracted. Data extraction was conducted independently by two reviewers (ACF, CJJF). Disagreements were solved by discussion or a third reviewer was consulted (SJHB, CMAMH).

We classified the outcomes extracted from the studies into different domains and these domains into core areas, according to the taxonomy of COMET and world health organization (WHO) classification for skin[15] (http://apps.who.int/classifications/icfbrowser/). Domains were classified into four core areas: 'Life impact', 'Pathological/clinical', 'Mortality/survival' and 'Resource use'. Furthermore, we classified the outcomes into Patient or Parent Reported Outcomes (PRO) and Investigator Reported Outcomes (IRO).

Quality assessment of the included studies was performed independently by two researchers (ACF, CJJF) according to the Oxford Centre for Evidence-based Medicine level of evidence guidelines.[16] Disagreement regarding the level of evidence of studies was resolved by discussion. We aimed to include all studies and outcomes used in research on CMN regardless of their methodological quality of the studies. Therefore, we did not exclude articles based on their methodological quality.

Data synthesis was performed by using descriptive statistics. For every domain and every core area, we calculated the percentage of included studies that reported that particular domain or core area.

RESULTS

Search and selection

Once duplicates were removed, 1,285 studies were found. A total of 63 studies met the inclusion criteria including 57 original studies with 3,721 patients and five systematic reviews. Appendix 2 shows the details of the systematic reviews. See figure 1 for the study selection flowchart.

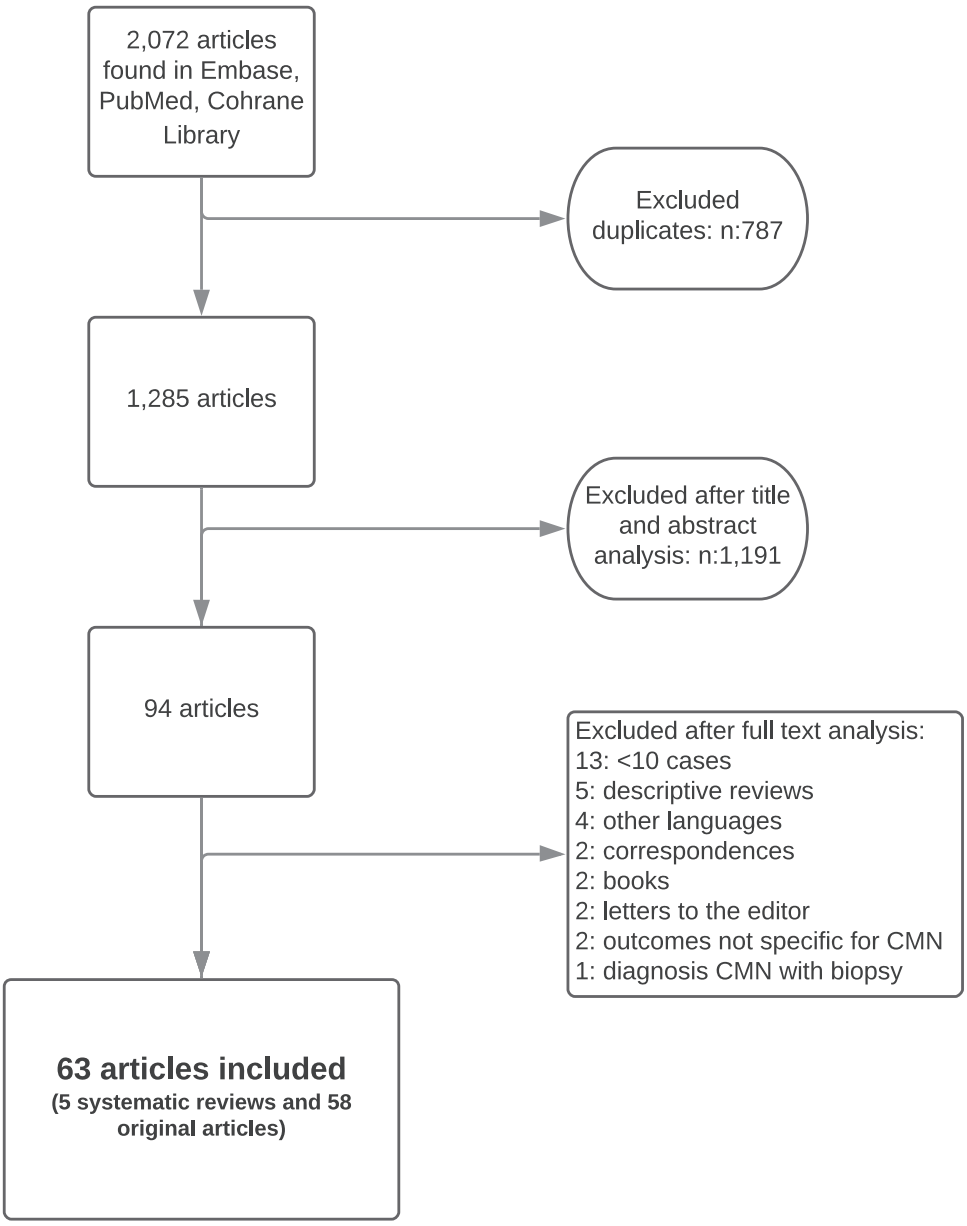

Figure 1. Flow diagram of systematic literature search and study selection, according to PRISMA

Data-extraction

Study, patient and CMN characteristics of these studies are listed in Appendix 3. The majority of studies was conducted in Europe (48%), followed by Asia (21%) and USA/Canada (19%). Six studies were conducted in the Middle East and two in Brazil. We included 33 interventional management studies, 25 conservative management studies and five studies with combinations of conservative

and interventional management. Twelve studies had a prospective study design (19%) and one of those studies was a case-control study. A total of 45 studies were retrospective (71%). Study design was not mentioned in one study (2%). Five systematic reviews (8%) were detected with a total of 215 studies. Only eight of these 215 studies, met our inclusion criteria. These eight studies were already included in our systematic review.

The quality of the studies included in our systematic review was generally low. The majority of studies (65%) were rated as level 4 evidence (very low evidence). All other studies (32%) were rated as level 3 (low evidence). The Oxford Centre for Evidence-based Medicine level of evidence guidelines could not be used to rate the level of evidence of two studies (3%). These studies investigated a new classification system[17] and the comparison of CMN monitoring frequency in different clinics.[18] The level of evidence was mainly low due to small patients' groups, absence of control groups and retrospective study designs.

The number of included patients ranged from 10 to 349 CMN patients. The male:female ratio was 1:1.16. The mean patient age was 5.4 years (0-84 years) mentioned in 39 out of 63 studies. The size was defined in the following ways: the diameter of the nevi in centimetres (17 studies), the diameter in centimetres in projected adult size (PAS) (9 studies) and the percentage of the body surface area (BSA) (7 studies). Combinations were described in 2 studies. One study defined giant CMN as all CMN that could not be closed primarily after excision.[19] Some studies applied standard classifications to define size. For instance, the standard classification of Kopf et al. was frequently used (11 studies), which defines size in diameter in centimetres as follows: small: <1.5 cm, medium: 1.5-19.9 cm, large and giant: >20 cm. The classification of Krengel et al.,[3] which was published in 2013, defines size with the PAS. Only 19 % (five of 26) of the included studies reported after 2013 used this classification system.

Regarding the location of the CMN, separate methods were used to classify specific areas of the body. Most of the studies reported the particular part of the body on which the CMN was located. However, body parts were sometimes classified together, such as the head and neck. This heterogeneity in classification hinders the comparison of outcomes between different size and location categories of CMN.

Identifications of outcomes

Various outcomes were reported in the 63 included studies, showing large heterogeneity among studies, even amongst studies reviewing the same intervention. To create a clear overview, the research team shortened the list of outcomes by merging similar outcomes. For instance: hyperpigmentation, dyspigmentation and hypopigmentation were defined in the outcome 'Skin colour'. This resulted in 57 different outcomes. We classified these 57 outcomes into 25 domains according to the COMET taxonomy[15] and the WHO classifications for skin. These domains were classified into four core areas: 'Life impact', 'Pathological/clinical', 'Mortality/survival' and 'Resource use' (figure 2). Because a large number of outcomes were classified into the domain 'Skin' according to the COMET classification, we defined this domain in greater detail and divided it into five different domains according to the WHO skin classification.

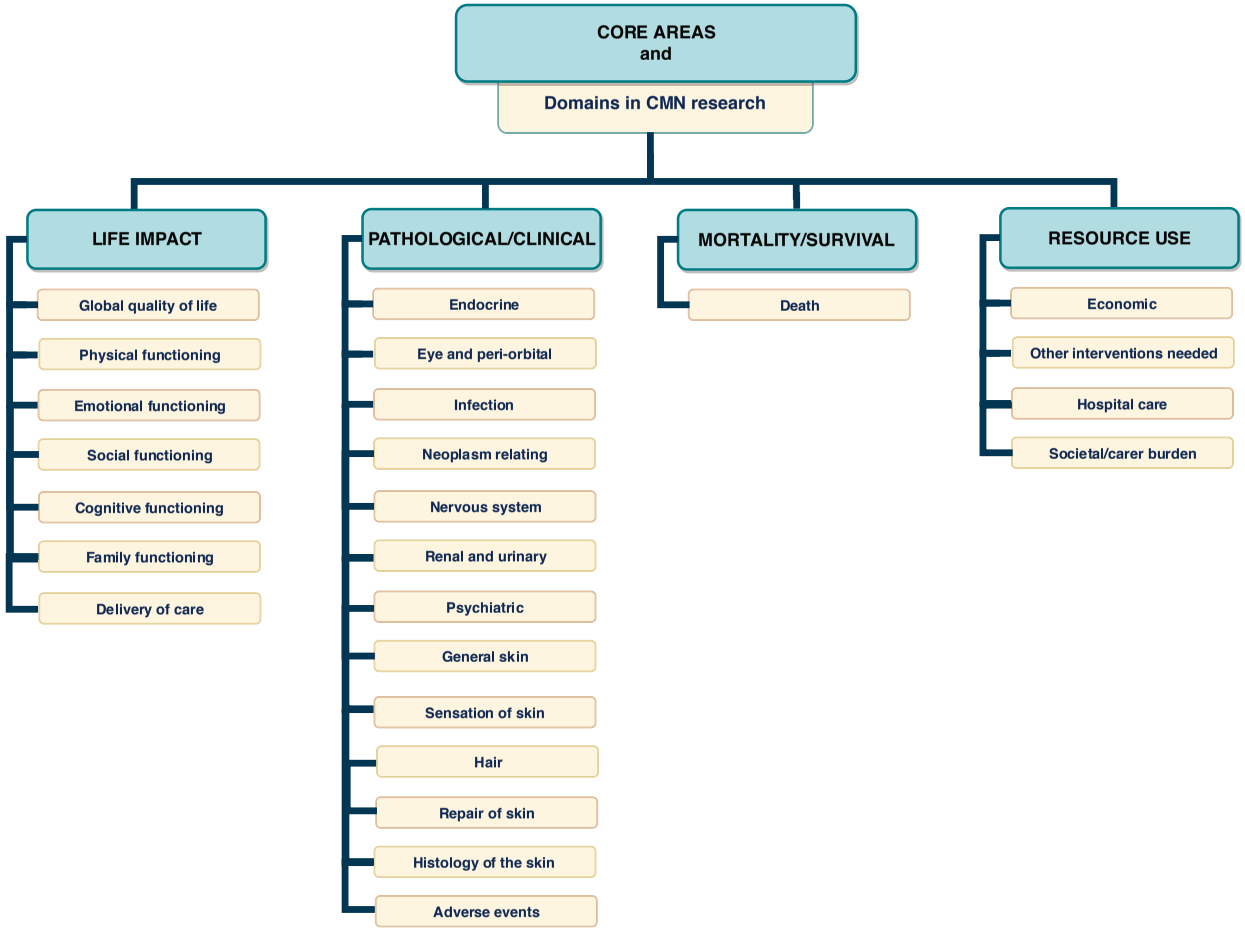

Figure 2. Core areas and domains

Table 1 shows the four core areas mentioned above, 25 domains, 57 outcomes, the number of studies and the percentage of studies that report a specific outcome and whether an outcome is either a PRO or an IRO. The percentages shown in this paper are the percentages of included studies that reported a particular core area or a particular domain.

Domains and outcomes in the core area 'Life impact' were mentioned in 29 studies (46%), with 'Delivery of care' as the most frequently reported domain (20 studies, 32%) and 'Satisfaction (aesthetic and functional) of treatment rated by patients as the most frequently reported outcome (15 studies, 24%). In general, definition of satisfaction (of patient or clinician) was poorly described. A description of the underlying factors that determined the reported 'satisfaction' was frequently missing and the majority of studies did not distinguish between aesthetic and functional satisfaction. Zhu et al. provided a description of what 'satisfied', 'moderately satisfied' and 'dissatisfied' exactly meant.[20]

Table 1. Outcomes and measurement instruments

DOMAIN (% of studies reporting the domain)	OUTCOMES (number of studies reporting the outcome)		PRO or IRO
LIFE IMPACT (46%)			
Global quality of life (3%)	Global quality of life[33, 34]	(2)	PRO
Physical functioning (9%)	General physical health[30, 35]	(2)	PRO
	Mobility of the affected body part[33, 36]	(2)	PRO
	Influence on physical daily activities[21, 23, 35]	(3)	PRO
Emotional functioning (14%)	Emotional problems [23]	(1)	PRO
	Body image[23, 35, 37-39]	(5)	PRO
	Psychological issues[23, 24, 35, 37, 40]	(5)	PRO
	Unpleasant reaction by others[35, 41]	(2)	PRO
	Perceived stigmatisation[33, 38]	(2)	PRO
Social functioning (8%)	Influence on social daily activities[21, 23, 35]	(3)	PRO
	Psychosocial issue[23, 40]	(2)	PRO
	Social well-being[21, 23, 33]	(3)	PRO
Cognitive function (9%)	School performance[21, 23, 26, 35, 42]	(5)	PRO
	Cognitive impairment [43]	(1)	Not specified
Family functioning (6%)	Impact of disease on parents[23, 33, 35, 38]	(4)	PRO
Delivery of care (32%)	Can it be operated with local anashesia[28]	(1)	IRO
	Satisfaction (aesthetic and functional) of treatment rated by physician[19, 20, 28, 34, 44-48]	(9)	IRO
	Satisfaction (aesthetic and functional) of treatment rated by patients[24, 25, 28, 30, 33, 35, 37, 39, 44, 48-53]	(15)	PRO

Table 1. (continued)

DOMAIN (% of studies reporting the domain)	OUTCOMES (number of studies reporting the outcome)		PRO or IRO
PATHOLOGICAL/CLINICAL (97%)			
Endocrine (2%)	Hormone level [54]	(1)	IRO
Eye and peri orbital (3%)	Eye manifestations[42, 55]	(2)	IRO
Infection (27%)	Wound infection[19, 24, 25, 29, 35, 37, 40, 46, 48, 51, 53, 56-61]	(17)	IRO
Neoplasms relating (43%)	Melanoma [18, 23, 24, 26, 30, 34, 40, 42, 45-47, 52, 59, 60, 62-68]	(21)	IRO
	Malignancy (not further specified) [19, 28, 34, 35, 41, 55, 63, 69, 70]	(9)	IRO
	Other malignancy than melanoma [26, 65]	(2)	IRO
Nervous system (19%)	Neurocutaneuos melanosis[33, 39, 42, 43, 46, 62, 67, 71]	(8)	IRO
	Radiological characteristics of the nervous system [33, 39, 42, 46, 62, 67, 71]	(7)	IRO
	Cerebrospinal fluid characteristics[43]	(1)	IRO
	Leptomeningeal histological characteristics[43]	(1)	IRO
	Neurological symptoms/sings[26, 37, 42, 43, 46, 51, 52, 62, 67, 68, 71]	(11)	IRO
Renal and urinary (3%)	Cathacholamins in urine[66]	(1)	IRO
Psychiatric (5%)	Psychiatric problems[42]	(1)	IRO
	Behavioural problems[23, 34]	(2)	IRO/PRO
General skin (60%)	Skin colour[17, 19, 20, 23, 24, 26-30, 33, 34, 37, 44-50, 52, 56, 58, 68, 72-77]	(31)	IRO/PRO
	Skin texture[17, 19, 23, 24, 26-30, 35, 37, 39, 45, 50, 52, 58, 60, 63, 73, 75, 77]	(21)	IRO/PRO
	(Proliferative) noduli [17, 28, 46, 68-70]	(6)	IRO
	Number of satellite naevi [17, 23, 26, 28, 42, 48, 52, 63, 68, 78]	(10)	IRO
	Co morbid skin disease [42, 47, 68, 74, 75]	(5)	IRO
Sensation of skin (9%)	Itching[24, 48]	(2)	PRO
	Pain[24, 28, 29, 40, 53]	(5)	PRO
Hair (22%)	Hypertrichosis [17, 23, 24, 26, 28-30, 46, 49, 51, 52, 73, 79]	(13)	IRO
	Colour of hypertrichosis[26, 68]	(2)	IRO
Repair of skin (21%)	Covering skin defect [37, 40, 45]	(3)	IRO
	Scarring[19, 24, 27, 29, 30, 33, 58, 76]	(8)	IRO
	Erythema[27]	(1)	IRO
	Scar appearance[19, 24, 25, 28]	(4)	PRO/IRO
Histology of the skin (25%)	Histological characteristics of CMN [28, 30, 48, 56, 57, 62, 63, 66, 68, 69, 80]	(11)	IRO
	Dermatoscopic characteristics of CMN[65, 73, 75, 78, 81]	(5)	IRO
Adverse events (52%)	Anatomic deformation [19, 20, 24, 28, 36, 41, 47, 55, 59]	(9)	IRO
	Tissue expander complication [24, 35, 36, 45, 61]	(5)	IRO
	Wound healing problems [19, 20, 24, 25, 27-30, 35-37, 39-41, 45-51, 53, 55-58, 60, 61, 63, 64, 76, 79]	(32)	IRO
MORTALITY/SURVIVAL (14%)			
Death (14%)	Death [23, 26, 33, 42, 43, 52, 61, 63, 68]	(9)	IRO

Table 1. (continued)

DOMAIN (% of studies reporting the domain)	OUTCOMES (number of studies reporting the outcome)		PRO or IRO
RESOURCE USE (33%)			
Economic (3%)	Costs[22, 60]	(2)	IRO
Other intervention needed (3%)	Other treatment needed[19, 46, 47, 49, 55]	(5)	IRO
Hospital care (19%)	Hospital stay after treatment [40]	(1)	IRO
	Frequency of monitoring CMN[18]	(1)	IRO
	Number of treatments needed[27, 30, 35, 44, 47, 48, 50, 57, 59, 64]	(10)	IRO
Societal/carer burden (5%)	School or work missing by patients or family[24, 35, 37]	(3)	PRO

PRO: patient/parent reported outcomes, IRO: investigator reported outcomes

Apart from two studies,[21,22] all studies reported domains and outcomes included in the core area 'Pathological/clinical' (97%). Both 'Skin colour' (31 studies, 49%) and 'Skin texture' (21 studies, 33%) were frequently measured outcomes in both interventional management and conservative management studies. Outcomes in the domain 'Neoplasm' included the presence of the outcomes 'Melanoma' (21 studies, 33%), 'Malignancy' (nine studies, 14%), which lacked a specification of the type of malignancy and 'Other malignancies then melanoma' (two studies, 3%). Most of these studies reported an absence of neoplasm in the investigated patient population. In contrast to the outcome 'Melanoma' (21 studies, 33%), 'Neurocutaneous melanosis' was only reported in eight studies (13%). Outcomes in the domain 'Adverse events' were only described by interventional management studies. 'Wound healing problems' was the most frequently mentioned outcome in 'Adverse events' (32 studies, 51%). According to the COMET taxonomy, the domain 'Adverse events' did not include outcomes related to infection, neoplasm, neurological manifestations and death. The core area 'Mortality/survival' was reported in 9 studies (14%), where most studies stated that none of their subjects passed away. Within the core area 'Resource use' (33% of studies), the outcome: 'Number of treatments needed' was the most frequently reported (10 studies, 16%).

Twenty-four (38%) studies measured outcomes reported by patients or parents (PRO). The outcome 'Emotional problems' and 'Behaviour problems' were rated by the teacher in one article.[23] We classified this as PRO. Most of the PRO were part of the core area 'Life impact', where they were used to measure satisfaction after treatment or aspects of patient and family functioning. In the core area 'Pathological/Clinical' the following outcomes were patient-reported: 'Skin colour', 'Skin texture', 'Pain' and 'Itching'. The PRO 'Missing work or school' was described for the core area 'Resource use'.

Outcome measurement instruments

Thirty-four different outcome measurement instruments were described in the included studies. For most outcomes, descriptions of how it was measured were missing. Both existing and self-made measurement instruments were used, including rating systems, questionnaires, estimations by patient, parents or clinicians, radiological imaging, lumbar puncture, gene expression, laboratory analysis, histology, and dermatoscopy. Estimations by parents or investigators were occasionally described yet explanation on how they estimated the outcomes were missing. See table 2 for an overview of the outcome measurement instruments used in the 63 included studies. Measurement instruments were only described in the core areas 'Life impact' and 'Pathological/Clinical'.

There was no consistency in outcome measurement instruments used. None of the described rating systems or questionnaires were described by more than two studies. None of the included articles described that the existing outcome measurement instruments were ever tested for validity and reliability in patients with CMN or their families. Moreover, studies that used self-made CMN specific outcome measurement instruments did not describe validation of these instruments.

Nineteen different measurement instruments were described for the core area 'Life impact'. Fourteen of the measurement instruments were PRO measurement instruments. Most of the instruments measured 'Satisfaction (aesthetic or functional) after treatment' rated by both patients and physicians (11 instruments). All other instruments in the core area 'Life impact' measured outcomes that measure the impact on patient or family (8 instruments), and was generally measured by existing questionnaires. These questionnaires were developed and validated for a generic population, and were not CMN specific. 'Satisfaction (aesthetic or functional) after treatment' was measured by self-made rating systems or questionnaires. The rating systems were made for clinicians or patients/parents and they could rate between 'good', 'excellent' or 'satisfied' at the one side of the scale and 'poor', 'dissatisfied' or 'fair' on the other side. Questionnaires to measure the satisfaction of patients were developed by three studies, ranging from four to ten questions.

Fourteen outcome measurement instruments were described in the core area Pathological/Clinical. The patient and observer scar assessment scale (POSAS) was used twice and measured specific aspects of the scar.[24,25] It was the only measurement instrument in the core area 'Pathological/Clinical' that measured PRO. Two self-made rating systems were used to measure 'Skin Colour' and one for 'Colour of hypertrichosis'.[24,26] One existing rating system developed for lighting of tattoos after laser therapy was used to measure lightning of 'Skin colour' after laser.[27] The visual analogue scale was used once to measure pain.[28]

Table 2. Outcome measurement instruments

Outcome measurement instrument	Outcomes	Times reported
LIFE IMPACT		
Impact on patient and family functioning		
Dermatology Life Quality Index [33]	Global quality of life Quality of life	1
Perceived stigmatization questionnaire [33, 38]	Perceived stigmatization	2
Social comfort questionnaire [33]	Social well-being	1
Child behaviour checklist for ages 4-10 [21, 23]	Influence on daily activities Social well-being School performance	2
Teacher Report Form [23]	Behaviour problems Emotional problems	1
Parental adjustment to congenital disorder checklist [23]	Impact of disease on parents	1
Mental health symptoms Checklist-27 [38]	Impact of disease on parents	1
Estimation by parents (not formally measured) [34]	Global quality of life	1
SATISFACTION AFTER TREATMENT		
Self-made 10-point scale (9-10 excellent, 6-8 good, 0-5 poor) by Merigou et al. [28]	Satisfaction of treatment by patients/parent and dermatologist	1
Self-made 3-point scale (excellent, good, fair) by Schiesl et al. [60]	Satisfaction (aesthetic and functional) of treatment by clinician	1
Self-made 3-point scale (satisfied, moderate satisfied and dissatisfied) by Zhu et al. [20]	Satisfaction (aesthetic and functional) of treatment by clinician	1
Self-made questionnaire (4 questions) by Romo-Munoz et al. [37]	Satisfaction of treatment by parents Social functioning Body image	1
Self-made questionnaire (5 questions) including a 10-point scale for satisfaction (10 is most satisfied) by August et al. [50]	Satisfaction of treatment by patient Adverse events	1
Self-made questionnaire (10 aspects of treatment) with 4-poit rating for every aspect by Fahmy et al.[39]	Satisfaction of treatment by parents and patients	1
Self-made 4-point scale (excellent, good, fair and poor) by Lim (2009) et al. [58]	Satisfactory of treatment by patient and clinician	1
Self-made 7-point scale (1 = worsened, 7 = total improvement) by Lim (2018) et al. [44]	Satisfaction of treatment by clinician	1
Self-made 5-point scale (0 = No change, 4 = Near or total improvement) by lim (2018) et al.[44]	Satisfaction of treatment by patient	1
Self-made 3-point scale (good, moderate, poor) by Goil et al. [19]	Satisfaction of treatment by senior consultant (not involved in study)	1
Evaluation consultant plastic surgeons [19, 48]	Satisfaction of treatment	2
PATHOLOGICAL/CLINICAL		
The Patient and Observer Scar Assessment Scale (POSAS) [24, 25]	Scar characteristics rated by patient and clinician	2
5-point scale lightning of skin made by Kimler et al. [27]	Skin colour	1

Table 2. (continued)

Outcome measurement instrument	Outcomes	Times reported
Self-made 10-point rating by Zaal et al. [24]	Skin colour	1
Self-made rating system by Kinsler et al. [52]	Skin colour	1
	Colour of hypertrichosis compared with head hair	
Estimation by specialist [49, 58, 75, 81]	Skin colour	4
	Wound infection	
	Wound healing	
	Dermatoscopic characteristics	
Evaluation by specialist blinded to study [27, 49, 73]	Adverse events	3
	Skin colour	
Visual Analogue Scale score [28]	Pain	1
Laboratory analysis [54, 60, 66]	Hormone level	3
	Infection	
	Cathacholamines in urine	
Physical examination by clinician [66]	Neurological sings	1
Lumbar puncture [43]	Cerebrospinal fluid characteristics	1
CT [42, 43]	Radiological characteristics of the nervous system	2
MRI [62 63, 67 33, 39, 42, 43, 66, 68, 71]	Neurocuteneous melanosis	10
	Radiological characteristics of the nervous system	
Gene expression [54, 67, 70]	Melanoma	3
	Benign or proliferative noduli	
Biopsy/histological analysis [27-30, 34, 43, 48, 56, 57, 62, 63, 66, 68, 69, 80]	Histological characteristics	16
	Malignancy	
	Melanoma	
	Leptomeningeal melanocytes manifestations	
Dermatoscopy[65, 73, 75, 78, 81]	Dermatoscopic characteristics	5

DISCUSSION

There is wide heterogeneity in outcomes measured in studies concerning management of CMN. We identified a total of 57 outcomes and 34 measurement instruments in 63 studies. The quality of the evidence was generally low. A few studies described outcome measurement instruments and few instruments were used in more than one study. PRO were measured in 38% of the included studies. Fifteen PRO measurement instruments were described. None of these instruments were described in more than two studies.

Besides outcome heterogeneity, we found inconsistency in outcome classification used for CMN size and location. Consensus was reached about a new classification system of Krengel et al.[3] However, only 19% of the included studies published after the publication of Krengel et al. used this classification system. Uniform use of the classification of the size and location of CMN is important to obtain homogenous patient populations in order to compare these.

Given that we included a wide variety of studies describing different treatments, interventions, and objectives, heterogeneity in outcomes was expected. However, we demonstrated that

heterogeneity exists even in studies evaluating similar interventions or objectives. These findings are similar to previously conducted systematic reviews concerning laser therapy in CMN.[29,30] Moreover, heterogeneity was further caused by missing definitions of outcomes, leading to ambiguity in their interpretation. As mentioned before 'Satisfaction (aesthetic or functional) after treatment' lacked a definition in most studies, while 'satisfaction' can have many underlying factors.

Furthermore, outcome heterogeneity can be caused by differences in outcome measurement instruments used. The usage of separate measurement instruments for the same outcome leads to incomparable results. Descriptions on how outcomes were measured were mostly lacking, and when they were described, different outcome measurement instruments were used in studies measuring the same domains/outcomes.

Although the COMET taxonomy is a useful tool, we found difficulties in classifying some of the outcomes into suitable domains. Especially the outcomes that have a broad impact were difficult to classify. For instance, 'Unpleasant reaction by others' can affect both 'Social functioning' and 'Emotional functioning'. This demonstrates overlap in specific outcomes within the different domains. We chose to classify it into the domain 'Emotional functioning' because 'Unpleasant reaction by others' would not always have a consequence for social behaviour.

The frequency of an outcome used and reported in studies does not indicate the importance of an outcome. For instance, the outcome 'Melanoma' is more frequently reported than 'Neurocutaneous melanosis' (21 and eight studies). Remarkably, the risk of melanoma is now estimated to be approximately the same as the risk of developing neurocutaneous melanosis (an estimated 2–3% and 2%[1,4,5] in patients with CMN size of >20cm PAS). This shows that the emphasis of researchers lies on melanoma.

Only 38% of the studies reported PRO. PRO became an important aspect of clinical research over the past couple of years. Patients are a significant source of information for assessing symptom experiences, quality of life or satisfaction after treatment.[31] Especially in plastic and reconstructive surgical treatment, PRO are essential to measure treatment efficiency.[12] Furthermore, previous research has shown that perception of outcomes can differ significantly between professionals and parents regarding the treatment of their child.[32] Although some outcomes require clinical expertise, investigators should avoid assumptions about patients' experiences and opinions.

We showed a relative low number of PRO reported in research on CMN, what implies a limited number of patients' involvement in research on CMN. To ensure that outcomes important to patients are incorporated in research on CMN, patients should be involved in the decision on what outcomes should be measured in research on CMN.

None of the studies mentioned that the measurement instruments used were ever validated in a CMN population. A questionnaire or rating system should be tested on reliability, responsiveness, and validity for the study population.[11,12] Questionnaires that were used to measure the impact of the disease on patients and family, were tested for validity and reliability. However, these measurement instruments are developed and tested for general population groups. None of the studies mentioned a validation of outcome measurement instruments in CMN patients. It is therefore unclear if these questionnaires measure (changes in) life impact accurately in CMN patients.

Strengths and limitations

The strengths of our study are that we included a broad range of studies on CMN, not only outcomes of treatment but also on watchful waiting. There is also a wide geographical spread in the included publications. Furthermore, we are the first to systematically review register the used measurement instruments, which is helpful in future research and in developing the COS.

A limitation could be that we started our inclusion in 2006, after Krengel et al. showed a lower associated risk of melanoma in CMN patients and a shift towards a more cosmetic indication for treatment was expected, instead of melanoma prevention.[4] Therefore, relevant studies could have been missed. However, we included 5 systematic reviews, which described the outcomes and outcome measurement instruments of relevant older studies published before 2006.[6] Because of the heterogeneity in CMN size and location classifications we could not describe differences between outcomes reported for different CMN size or location (visible/non-visible) categories.

Future perspectives

As mentioned in the introduction, this systematic review is the first step of the development of a COS for CMN management research. The identified list of domains and outcomes will be used in the next step of COS development: rating the importance of domains and outcomes. Patients and specialists will rate a list of domains and outcomes based on the list shown in table 1. This rating will be done in an online survey and consensus meetings. Next, suitable outcome measurement instruments should be chosen, validated and/or developed for these specific outcomes. The Amsterdam University Medical Centre and the Erasmus Medical Centre of Rotterdam have set up a project to develop a COS for research and clinical setting, referred to as the Outcomes in Congenital Melanocytic Naevi (OCOMEN) project. This will be done with the global aid of CMN patients and medical experts from all over the world.

CONCLUSION

This systematic review shows that heterogeneity exists in research on CMN. Moreover, it shows that the quality of evidence of CMN studies is generally low. It further demonstrates a need for the use of CMN specific reliable and valid (patient-reported) outcome measurement instruments. To improve the quality of evidence, consistency in research on CMN is needed. We provided an insight into outcomes and outcome measurement instruments reported in CMN studies, which is an essential step in the CMN COS development.

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Supporting information

Appendix 1. The search strategies
Pubmed

	Medical Subject Headings		Title, abstract / all fields		Other
Nevus	"Nevus"[Mesh]	**OR**	nevus OR nevi OR naevus OR naevi OR birthmark*		
AND					
Congenital	"congenital" [Subheading]	**OR**	congenital* OR bathing trunk* OR garment OR giant OR tierfell* OR gigantic OR inborn OR hereditary OR newborn OR "congenital" [Subheading]		
NOT					
			connective tissue[tiab] OR anaemicus[tiab] OR elasticus[tiab] OR inelasticus[tiab] OR depigmentosus[tiab] OR mucinosis[tiab] OR lipomatosus[tiab] OR sebaceus[tiab] OR blue[tiab] OR comedonicus[tiab] OR spindle[tiab] OR sponge[tiab] OR woolly[tiab] OR spilus[tiab] OR spider[tiab] OR flammeus[tiab] OR Jadassohn[tiab] OR Ota[tiab] OR Becker[tiab] OR Sutton[tiab] OR Unna[tiab] OR neurofibromatosis[tiab] OR pancreas*[tiab] OR placenta[tiab]		
NOT					
Study design			case report*[ti]	**OR**	"Case Reports" [Publication Type]

Embase (Ovid)

# Searches		
1	exp nevus/ or (nevus or nevi or naevus or naevi or birthmark*).	ti,ab,kw.
2	(congenital* or bathing trunk* or garment or giant or tierfell* or gigantic or inborn or hereditary or newborn).	ti,ab,kw. or cn.fs.
3	1 and 2	
4	(connective tissue or anaemicus or elasticus or inelasticus or depigmentosus or mucinosis or lipomatosus or sebaceus or blue or comedonicus or spindle or sponge or woolly or spilus or spider or flammeus or Jadassohn or Ota or Becker or Sutton or Unna or neurofibromatosis or pancreas* or placenta).	ti,ab,kw.
5	3 not 4	
6	limit 5 to conference abstract status	
7	5 not 6	
8	case report/ or case report*.	ti,ab,kw
9	7 not 8	

Cochrane Library

ID	Search
#1	(nevus or nevi or naevus or naevi or birthmark*):ti,ab,kw (Word variations have been searched)
#2	(congenital* or bathing trunk* or garment or giant or tierfell* or gigantic or inborn or hereditary or newborn):ti,ab,kw (Word variations have been searched)
#3	#1 and #2

Abbreviations

Ab: abstract

Ti: Title

Kw: keyword

Tiab: Title/abstract

Appendix 2. Characteristics of the included SR

Author	Total number of studies	Number of CMN studies	Number of CMN studies not included in our study*	CMN patients
Bray et al. 2015[29]	12	12	12	148
Eggen et al. 2017 [30]	24	24	21	434
Tapia et al. 2016 [21]	155	2	1	39
Vogelaar-Burghout et al. 2016[75]	10	10	8	-
Vourc'h-Jourdain et al. 2013[23]	14	14	11	-

*Studies that did not met the inclusion criteria

Appendix 3. Characteristics of included studies

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Adjadj et al. 2016 [47]	France	Re	4	Peri-orbital CMN excision	51	30/21	19y	-	-	H:51
Adler et al. 2009 [79]	Israel	Re	4	Auricular CMN excision	14	6/8	4.5y (7m-13y)	-	-	H/N: 14
Al-Hadithie et al. 2012 [49]	UK	Re	4	Laser	52	43/9	12	< 5cm: 33 5-10cm: 9 >10cm: 2 G: 8	No definition	H/N: 26 T:7 E: 19
August et al. 2011 [50]	UK	Re	4	Laser	55	45/10	18y (9y-43 y)	M: 55	Kopf et al.	H/N: 27 T: 10 E: 22
Bekiesinska-Figatowska et al. 2014 [62]	Poland	Re	4	Neurocutaneuos melanosis	24	-	- (12d-7y)	-	-	-
Bellier-Waast et al. 2007 [35]	France	Re	4	Psychological impact of interventions	105	58/47	1y -	G: 105	G: Face: > 1% BSA Other: > 2% BSA	H/N: 46 T: 33 E: 26
Bray et al. 2015[29]	US	SR	3	Laser	148	-	- (1m-55y)	-	Various	-
Chan et al. 2006 [63]	Singapore	Re	4	Melanoma risk	39	16/23	18.8y (23m-60 y)	L: 29	L: >5% BSA	-

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Ciampo et al. 2008 [77]	Italy	Re	3	Spontaneous pigment loss	207	99/108	5.4y	-	-	H/N: 41 T: 61 E: 105
Dai et al. 2016[64]	China	Re	4	Excision with SG	20	8/12	3.8y (6 m-9 y)	L/G	L/G: Infants/ toddlers: > 2% BSA Adults: > 20 cm	H/N:10 E:10
Eggen et al. 2017 [30]	Netherlands	SR	3	Laser	434	-	- (1m-28y)	M: 187 G: 37	Krengel et al.	-
Ekinci et al. 2016[72]	Turkey	Re	3	Spontaneous pigment loss	92	-	- (0y-25y)	L: 92	> 20 cm	-
El -Sabbagh et al. 2017[56]	Egypt	Re	4	Excision with SG	16	12/4	8.17y (4m-22y)	G:16	G: face: >1% BSA other: >2% BSA	H: 9 T: 4 E: 3
Errichetti et al. 2017[73]	Italy	Pr	3	Dermatoscopic characteristics	73	33/40	12y (11y9m - 12y2m)	All < 3 cm	Kopf et al.	-
Fahmy et al. 2010[39]	Egypt	Re	4	Excision with TE	12	3/9	6.5y (2y-12y)	G:12	G: >20 cm PAS	T: 12

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Fernandes et al. 2009[74]	Brazil	Re	4	CMN monitoring in children/ adolescence	60	35/25	- (1y-12y)	S: 45 M: 20 L: 4 G:5	S: <1,5 cm M: 1.5-10 cm L: 10-20 cm G: >20 cm	H/N:17 T:36 E: 22
Gatibelza et al. 2012[46]	France	Re	4	Curettage	29	17/12	- (1w -7w)	G: 29	G > 20 cm	H/N: 10 T: 14 E: 5
Gonzalez Ruiz et al. 2017[40]	Spain	Re	4	Excision with TE	14	10/4	5.94y (0,98y-20,8y)	-	-	-
Goil et al. 2018 [19]	India	Re	4	Excision (TE and SG)	17	10/7	18,8 y (14y-24y)	G:17	G: primary closure not possible	H: 17
Hassanein et al. 2014[57]	USA	Re	4	Excision (primary closure)	21	10/11	6m (3m-11y)	-	% BSA	H/N: 7 T: 3 E: 11
Ingordo et al. 2008[81]	Italy	Pr	3	Dermatoscopic characteristics	52	0/52	19y (18y-22y)	M: 41 L: 11	Kopf et al.	H/N: 0 T: 55 E: 9
Jacobs et al. 2013[55]	USA	Re	4	Peri-orbital CMN excision	12	7/5	20.5y (3y-26y)	-	-	H: 12
Jakchairoognruang et al. 2018[71]	USA	Re	3	Neuroimaging	80	-	22m (1d-22y)	-	-	-

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Kinsler 1 et al. 2009[26]	UK	Pr	3	Evaluation of etiological factors of CMN patients and family	349	206/143	9.2y (0.0y-36.1y)	0-10 cm: 127 10-20 cm: 49 20-40 cm: 43 40-60 cm: 38 >60 cm: 25 multiple: 10 missing: 9	cm PAS	H/N: 128 T: 125 E: 70 H/N/T: 10 Multiple: 9 Missing: 7
Kinsler 2 et al. 2009[52]	UK	Pr	3	Evaluation of patients with intervention and no intervention	301	169/132	2.9y (0.0y -36.1 y)	0-10 cm: 149 10-20 cm: 55 20-40 cm: 50 40-60 cm: 44 > 60cm: 28 multiple: 13 missing: 10	cm PAS	-
Kryger et al. 2008 [36]	US	Re	4	Excision on lower extremity	50		- (1y- 19y)	-	-	E: 50
Lee et al. 2017[27]	Korea	Re	4	Laser	26	16/10	- (2m-28y)	S: 1 M: 25	Kopf et al.	H/N: 9 T: 3 E: 14
Lim et al. 2008 [58]	Korea	Pr	4	Excision and laser	13	11/2	16.6y (7y-25y)	-	-	H: 4 T: 2 E: 7

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Lim et al. 2018[44]	Korea	Re	4	Excision and Laser	119	66/53	16y (0y-59y)	S: 36 M:82	Krengel et al.	H: 59 T:21 E:39
Lovett et al. 2006 [42]	Canada	Re	4	Risk factors for Neurocutaneuos Melanosis	54	29/25	15.2 m (0m-169m)	M:2 L:52	M: 1.5-19.9 L: Adults: >20cm Infants: Head: >9cm Other: > 6 cm	H: 9 T: 17 E: 0
Ma et al. 2017 [45]	China	Re	4	Excision with TE	11	6/5	6.6y (3y-11y)	-	-	-
Maillet-Declerck et al. 2012 [51]	France	Re	4	Excision with TE of the scalp	15	6/9	5.25y (2.25y-8.58y)	-	-	H:15
Mandal et al. 2006[76]	Scotland	-	4	Laser	10	10/0	-	S: 10	% BSA	-
Margilethet al. 2018[34]	US	Re	3	Spontaneous regression	45	22/23	-	S:5 M:35 L:2 G: 3	L: > 20 cm G: > 40 cm	H/N: 18 T:13 E:14
Margulis et al. 2009[41]	Israel	Re	4	Peri-orbital CMN excision	44	-	- (6m -17y)	-	-	H: 44

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Masnari et al. 2012[38]	Switzerland	Pr	3	QoL in patients with facial differences	10	-	- (0.9y-6.117)	-	-	-
Merigou et al. 2009[28]	France	Re	4	Intervention (excision and curettage) compared with no intervention	108	56/52	-	S: 26% M: 68% L/G: 6%	Kopf et al.	H/N: 35% T: 28% E: 37%
Minagwa et al. 2011[65]	Japan	Re	4	Dermatoscopic characteristics	24	11/13	6.8y (0 y-27y)	S: 22 M: 2	Kopf et al.	E: 24
Nguyen van Nuoi et al. 2013[59]	France	Re	4	Excision with TE	33	-	4.5y (0.3y-15.5y)	-	-	H: 17 T: 10 E: 6
Oh et al. 2013[25]	Korea	Pr	4	Excision on the face (primary closure)	82	34/48	- (6m-31y)	-	-	H/N: 82
Oztas et al. 2010[78]	Turkey	Re	4	Dermatoscpopic characteristics	239	125/114	- (1m-63y)	S: 77 M: 150 L: 12	Kopf et al.	H/N: 54 T: 80 E: 105
Phadke et al. 2011 [70]	US	Pr	4	Comparison of proliferative nodules with melanoma	41	27/14	- (0y-84y)	S/M: 14 G: 27	-	H: 12 T: 22 E: 8

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Price et al. 2015[17]	US	Pr	-	New classification system	45	28/17	-	G2: 20 G1: 13 L2: 5 L2: 2 M2: 3	Krengel et al.	H/N: 10 T: 37 E: 24
Qian et al. 2018[43]	China	Re	4	Neuroimaging	13	4/9	36,5y (18y-59y)	-	-	Kopf
Rasmussen et al. 2015[48]	Denmark	Re	4	Curettage and excision (with TE, SG, primary closure)	35	20/15	5.5y 2d-49y	G: 35	Head/neck: >1 % BSA Other: > 2%	H/N: 13 T: 15 E: 15
Roldan et al. 2013[22]	Spain	Re	3	Costs of different management strategies	113	60/53	7.6y (1y - 16y)	-	-	-
Romo Munoz et al. 2018[37]	Spain	Re	4	Excision with TE on the face	10	6/4	- (8m-36m)	>10 cm: 10	-	H/N: 10
Rothfus et al. 2009[53]	Germany	Re	4	Excision with TE	51	-	3.2y (<6y)	-	-	H/N: 10 T: 16 E: 25
Sawicka et al. 2014[66]	Poland	Re	4	Analysis of diagnostics, treatment and follow up	24	14/10	- (2d – 7y)	-	-	H/N: 6 T: 18

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Schiestl et al. 2009[60]	Switzerland	Re	4	Excision (artificial SG)	12	8/4	3.8y (0.6y-11y)	-	BSA%	H/N: 3 T: 6 E: 3
Simons et al. 2017[69]	US	Re	3	Histological characteristics	176	-	17m (0m-35m)	S: 3 M1: 91 M2: 31 L1: 18 L2: 6 G: 9 Missing: 21	Krengel et al.	H: 71 T/N: 57 E: 49
Stanganelli et al. 2013[18]	Italy	Re	-	National monitoring management	-	-	-	S/M	Kopf et al.	-
Tapia et al. 2016 [21]	US	SR	3	QoL op facial differences patients	39	-	-	-	-	-
Tokuda et al. 2010[80]	Japan	Re	4	Histological characteristics of acquired nevi and CMN	73	-	24.3y (1y-16y)	S: 57 M: 20 G: 7	Kopf et al.	H/N:20 T: 28 E: 25
Viana et al. 2011[67]	Brazil	Pr	3	Melanoma risk	57	28/29	8.3y -	L: 57	Kopf et al.	H/N: 10 T: 39 E: 8

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Vogelaar-Burghout Et al. 2016[75]	Netherlands	SR	3	Dermatoscopic characteristics	-	-	-	-	-	-
Vourc'h-Jourdain et al. 2013[23]	France	SR	3	Melanoma risk, therapeutic assessment and life impact	-	-	-	-	-	-
Waelchli et al. 2015[54]	England	Re	3	Endocrinological assessment	202	-	5.2y -	-	cm PAS	-
Warner et al.2008[61]	US	Re	4	Excision (primary closure, SG, TE)	40	25/15	4.75 (0.4–15)	G: 40	G: >20cm	-
Wramp et al. 2017[33]	Germany	Pr	3b	QoL	83	41/42	11.2y	M: 30 L: 27 G: 26	Krengel et al.	-
Yun et al. 2012[68]	Korea	Re	4	Clinical characteristics and risk of melanoma	131	64/67	10.3y (0-70y)	G: 131	G: Infants and children: > 5% BSA Adults: > 20 cm	H: 15 T: 227 E: 66
Zaal et al. 2009[24]	Netherlands	Pr	4	Excision with TE of the scalp/face	17	11/6	- (4m-36y)	G: 17	BSA%	H: 17

Appendix 3. (continued)

Author	Country	Study design	Level of evidence	What is studied	Patients	female male ratio	Mean age and (Age range)	Size	Size measurement (diameter in cm or BSA %)	Location
Zhu et al. 2009[20]	China	Re	4	Peri-orbital CMN excision	10	4/6	11.8y (5y-18y)	-	-	H: 10

Re: retrospective, Pr: prospective, SR: systematic review, - not mentioned, d: days, m: months, y: year, S: small, M: medium, L: large, G: giant, SG: skin graft, TE: tissue expander, QoL: quality of life, BSA: body surface area. H: head, N: neck, T: trunk, E: extremities.

Gustav Klimt

Portrait of Adele Bloch-Bauer I, "Woman in Gold"

1907

This is the most popular work of Klimt's 'Golden Phase', aside from 'The Kiss' (1907). Many of his paintings from this period make use of gold leaf. The Woman in Gold is the wife of a Jewish banker and sugar producer. Klimt's trips to Venice and Ravenna, both cities famous for their beautiful mosaics, most likely inspired his use of gold and his Byzantine style.

Reference: Wikipedia

6

DEVELOPMENT OF AN INTERNATIONAL CORE DOMAIN SET FOR MEDIUM, LARGE AND GIANT CONGENITAL MELANOCYTIC NEVI AS A FIRST STEP TOWARDS A CORE OUTCOME SET FOR CLINICAL PRACTICE AND RESEARCH

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ABSTRACT

Background

Medium, large and giant congenital melanocytic nevi (CMN) can impose a psychosocial burden on patients and families, and are associated with increased risk of developing melanoma or neurological symptoms. Lack of consensus on what outcomes to measure makes it difficult to advise patients and families about treatment and to set up best practice for CMN. Fostering consensus amongst patient representatives and professionals, we aim to develop a core outcome set (COS), i.e. the minimum set of outcomes to measure and report in care and all clinical trials of a specific health condition. We focused on the 'what to measure' aspect, the so-called core domain set (CDS), following COMET and CS-COUSIN guidelines.

Methods

We conducted a systematic review to identify outcomes reported in literature. Focus groups with patient representatives identified patient-reported outcomes. All these outcomes were classified into domains. Through e-Delphi surveys, 144 stakeholders from 27 countries iteratively rated the importance of domains and outcomes. An online consensus meeting attended by seven patient representatives and seven professionals finalized the CDS.

Results

We reached consensus on six domains, four of which were applied to both care and research: 'quality of life', 'neoplasms', 'nervous system' and 'anatomy of skin'. 'Adverse events' was specific to care and 'pathology' to research.

Conclusion

We have developed a CDS for medium-to-giant CMN. Its application in reporting CMN care and research will facilitate treatment comparisons. The next step will be to reach consensus on the specific outcomes for each of the domains and what instruments should be used to measure these domains/outcomes.

Keywords: Core outcome set, outcome domains, congenital nevi, melanoma, clinical research

What is already known about this topic?

- Medium, large and giant congenital melanocytic naevi (CMN) are associated with psychosocial burden for patients and their families because of their unusual appearance and increased risk of melanoma and/or neurocutaneous melanocytosis.
- Outcome reporting of treatment options for CMN is heterogeneous. Current lack of consensus in outcome reporting hinders the development of evidence-based treatment guidelines for CMN.
- Development of a core outcome set (COS) may enhance standardized reporting.

What does this study add?

- We focus on the core domain set, the 'what to measure', for the COS.
- By following the guidelines of COMET and CS-COUSIN, we reached consensus on six domains.
- Four of the domains were applied to both care and research: 'quality of life', 'neoplasms', 'nervous system' and 'anatomy of skin'. 'Adverse events' was specific to care and 'pathology' to research.

What are the clinical implications of this work?

- Uptake of the core domain set in future clinical care of, and research about, medium-to-giant CMN should facilitate comparisons across different treatment choices for both patients and professionals.

INTRODUCTION

Background and objectives

Congenital melanocytic nevi (CMN) are pigmented birthmarks that can cover large areas of the body.[1-3] CMN are present at birth or become visible within the first year of life (so-called "tardive" CMN). An estimated 1% of infants worldwide are born with small CMN. Large and giant CMN are much rarer, with an estimated incidence of 0.005% and 0.0002%, respectively.[4] CMN are described in size as well as other parameters by the classification system of Krengel et al.[5] Medium (> 1.5 cm projected adult size [PAS] CMN on the face, and ≥10cm PAS for the rest of the body), large (> 20 cm PAS) and giant (>40 cm PAS) CMN may be associated with a psychosocial burden for patients and their families due to their unusual appearance and the extra medical care CMN may require.[6] Large and giant CMN or multiple CMN, are also associated with increased risk of malignant melanoma, soft-tissue tumors or neurologically symptomatic neurocutaneous melanocytosis.[1-3,7-10] Adequate treatment and monitoring of CMN are therefore crucial. Different interventional treatments for CMN such as laser, curettage and excision are available, but conservative treatment such as watchful surveillance is also possible.[3,11-13] Patients with CMN may undergo several surgical interventions, sometimes dozens, which do not always yield satisfactory cosmetic and functional results. It is also not established that such treatment reduces the risk of melanoma.[3,12,14]

Scientific evidence for the best treatment policies for different kinds of CMN is unfortunately still lacking.[15] Multiple case-series articles describe the impact of having CMN, including the effects of treatment, on the lives of patients and their families. However, wide heterogeneity of outcomes reported in these articles makes it difficult to combine, compare or contrast the results.[16] Furthermore, outcomes important for patients and patient-reported outcomes are often missing.[16] Development of a 'core outcome set' (COS), i.e. the minimum set of outcomes that should be measured and reported in all care settings and clinical trials for a specific health condition, is a potential solution to reduce heterogeneity in outcome selection, measurement, and reporting in future CMN care and research. This may facilitate evidence synthesis for conservative and interventional treatment recommendations.[17]

Scope

The Outcomes for Congenital Melanocytic Nevi (OCOMEN) project aims to develop a COS for care and research of CMN. A COS consists of 'what' (domains and outcomes) and 'how' to measure (outcome measurement instruments).[18] This article focuses on the development of the core domains sets (CDS) (the 'what to measure').

We aimed to reach consensus on a CDS for care and a separate CDS for research settings. We distinguished the CDS for the care setting, i.e. to be used in every consultation with physicians, as these may or may not be similar to the CDS for the research setting, i.e. to be reported in every research of CMN. We also aimed to initiate the selection of the specific outcomes for each of the domains in the CDS. Fine-tuning the outcomes will be done in a separate project. Such exercises, i.e. fine-tuning the outcomes during the process of reaching consensus on the instruments, have been followed before in other studies.[19-21]

We defined a "domain" as an aspect of disease that should be measured, such as cognitive functioning,[22] whereas an "outcome" describes a concept or construct which is a part of a domain, such as learning difficulties or memory lapse for the domain "cognitive functioning".[23]

Specific objectives were:

1. to identify domains and outcomes that
   a. have been reported in the literature through a systematic review
   b. are considered important by patient representatives, i.e. patients or the parents of minor patients in focus group discussions
2. to compare the domains and outcomes considered critically important by professionals with those of the patient representatives
3. to reach consensus on a CDS of the COS for future use in care and research of CMN,
4. to initiate the selection of the specific outcomes for each domain in the CDS.

We focused on patients with medium, large and giant sizes of CMN as defined by a recent consensus classification study,[5] of any age, without, during, or after treatments.

METHODS

Our approach was described in a protocol.[24] In brief, we followed the guidelines of the Core Outcome Measures in Effectiveness Trials (COMET) initiative,[25-27] and the Cochrane Skin-Core Outcomes Set Initiative (CS-COUSIN).[28] Results reporting followed the Core Outcome Set-STAndards for Reporting (COS-STAR).[29]

Protocol registration and ethical approval

This study has been registered on the COMET website (http://www.comet-initiative.org/studies/details/1124) and the CS-COUSIN website (http://cs-cousin.org/cos-project-groups/). Ethical approval was obtained from the Ethical Review Board at the Erasmus MC Rotterdam and from the Ethical Board at the Amsterdam UMC. Prior to their participation, consent was obtained from each of the participants.

Stakeholders recruitment

We included two English-speaking stakeholder groups from 27 countries: one of patient representatives and one of professionals. We reached out to patient representatives through patient advocacy groups, hospital registries in the Netherlands, publicity through Naevus International (https://www.naevusinternational.com/2018/09/26/the-outcome-measures-for-congenital-melanocytic-naevi-ocomen-project/) and at its meetings in 2017 and 2018, word-of-mouth and social media. We involved professionals from various backgrounds (dermatologists, plastic surgeons, pediatricians, psychologists, pathologists, and basic researchers). Invitations were sent to all patient representatives and professionals who had earlier expressed interest in participation. Detailed recruitment is described in the protocol.[24]

In the development of the CDS, we were supported by a study advisory group. This group consisted of experts in COS development and in the field of CMN, including a patient representative, researchers, dermatologists and a plastic surgeon. The study advisory group provided input considering protocol development, stakeholder recruitment, design of the e-Delphi, and the consensus meeting.

Identifying an initial list of outcomes

Our methods in identifying the initial list of outcomes have been described in the protocol.[24] Briefly, we listed the outcomes from systematic review, focus group discussions and guidelines (Figure 1). We looked at a list of outcomes in the taxonomy published by the COMET initiative website[22,26] to ensure that we did not miss any relevant outcomes that were not reported by the review or focus groups. Several domains of the COMET taxonomy that were generally irrelevant for our aim, such as cardiac, ear and labyrinth, or hepatobiliary outcomes, were excluded. Since CMN is a specific skin malformation, and the COMET taxonomy provides a high-level classification covering various diseases, we also consulted the WHO International Classification of Functioning, Disability and Health (ICF) for a more detailed classification of skin anatomy and functions.[30]

An overview of the selection of domains and outcomes is summarized in Figure 1.

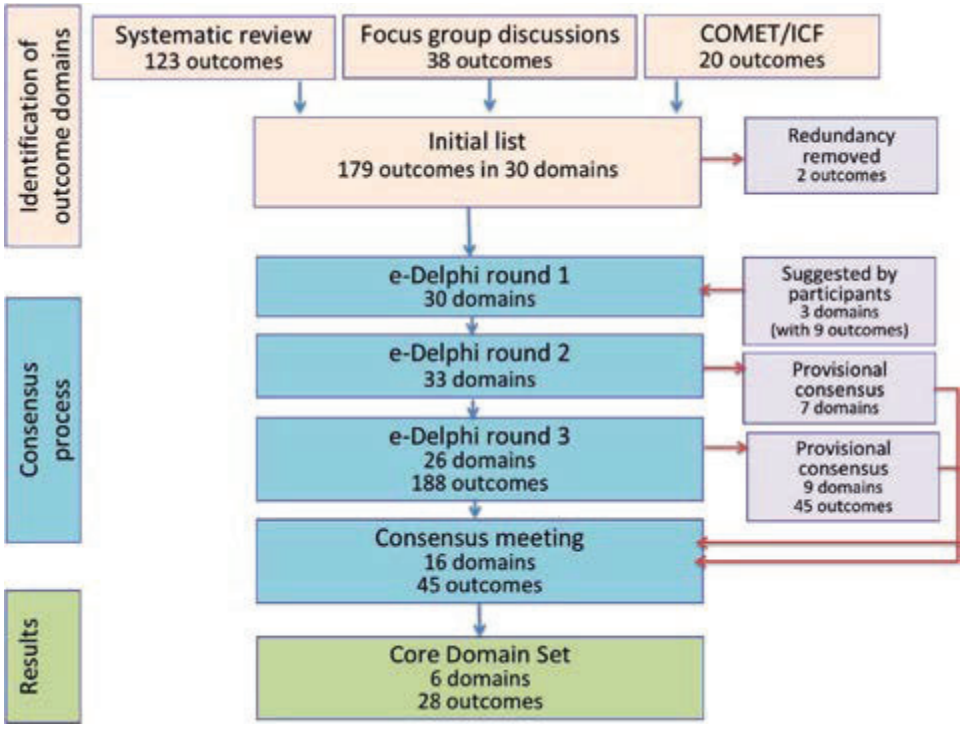

Figure 1. Overview of CDS development

Consensus process: e-Delphi

Delphi surveys are a well-recognized and increasingly used consensus method for COS development.[31-33] We conducted three rounds of e-Delphi, using the Lime Survey platform. Participants were given three weeks to complete a survey. Reminders were sent frequently after the first week. The ratings from the two stakeholder groups (patient representatives and professionals) were evaluated separately. During the first two rounds, we also recorded characteristics of the patient CMN associated with the representatives, including size, colour, location, and treatment history. For the professional group, we recorded the type of profession and years of experience.

In the first round, participants from the two groups were asked to rate the importance of domains for clinical care and for the research setting separately. During the first two rounds, participants could suggest additional domains. The results of the previous round were fed back to the participants. In the second round, participants could alter their votes. In the third round, participants were only asked to vote again for those domains for which no consensus had been reached. Moreover, in the third round, participants were asked to also rate the list of outcomes as proposed for each domain.

The consensus definitions for the domains and outcomes are specified in the protocol. Briefly, domains were rated on 9-point Likert scales, where 1 signifies no importance and 9 very important. Domains scored 7, 8, or 9 by at least 70% of one of the stakeholder groups were considered to be 'important domains' for that stakeholder group and domains that were scored 1, 2 or 3 by at least 70% of one stakeholder group were considered 'unimportant domains'. Domains that were considered 'important domains' by both stakeholder groups, were considered to have met the consensus definition and were eligible for provisional inclusion in a CDS and named 'provisional consensus domains'. Domains that were considered 'unimportant domains' by both stakeholder groups, were dropped.

For the outcomes that describe the domains, those that were selected by at least 70% of participants of the third round of the e-Delphi were considered to be 'important outcomes' and eligible for a vote for inclusion in the CDS during the consensus meeting.

Consensus process: consensus meeting

An online consensus meeting involving the study advisory group and representatives of e-Delphi completers was planned to review and discuss the 'provisional consensus domains' from the e-Delphi surveys. Patient representatives and professionals were intentionally sampled in equal proportion from the e-Delphi completers to ensure representation of patient representatives with various geographical backgrounds as well as types of profession (dermatologists, surgeons, pathologists, researchers). This intentional sampling deviated from the protocol.

During the meeting, participants discussed and voted on the domains for which the abovementioned consensus definition was reached, and on domains that were considered important by at least a stakeholder group during the e-Delphi process, for inclusion in the CDS, separately for care and for research settings. The importance of domains was voted on during the online consensus meeting. Participants filled out the voting form for each domain, and the forms

were sent to the organizer directly. The responses were calculated immediately and fed back to the participants. After a break of 15 minutes, we used this vote result to deliberate and narrow down the top 5 domains through another direct voting session by e-mail. Several studies recommended to be very selective about the number of consensual domains to be included in the CDS, to promote feasibility and future uptake.[26,34] The average (median) number of domains reported in COS studies was five.[26] Therefore, participants were asked to also select their top five from the list of 'provisional consensus domains' for the CDS. Moreover, participants had the opportunity to discuss the classifications of domains and could make suggestions to lump or split the domains.

Besides the rating of domains, participants were asked to vote on those shortlisted outcomes considered 'important' during the last e-Delphi round for inclusion in the CDS. Outcomes that received favorable votes from at least 70% of meeting participants were included in the CDS. For practical reasons, the outcome voting was done by e-mail.

Statistical analyses

Descriptive statistics were used to summarize the results of each round, including the percentage of stakeholder groups who had given a high score (7, 8, or 9) per domain. The analysis was done in R, version 3.5.1.

RESULTS

Identifying an initial list of outcomes

An initial list of 123 outcomes reported in the literature of CMN was found in a systematic review.[16] Through seven focus group discussions (five in the Netherlands and two international), we identified 38 additional outcomes that are important for patient representatives.[24] From the COMET and the ICF we obtained additional 20 outcomes. After removal of redundancies (2 outcomes), we grouped the 179 outcomes into domains by following the COMET taxonomy.[22,26] The selected domains (30) and outcomes (179) were fed into the e-Delphi study (Appendix 1- List of domains and outcomes for the e-Delphi).

Delphi survey

In total, we identified 138 professionals and 134 patient representatives. Among those, 186 confirmed their interest in participation by mail and thus, received the invitation link to access the first survey. The response rate and the characteristics of participants are presented in Table 1. In each round, around 70% of participants completed the e-Delphi. The median age of participants is 43 years old (parents of young patients filled out the e-Delphi on behalf of their children) and around 70% of the participants are female. There was equal representation of patient representatives and professionals. The geographical spread of the participants from 27 countries on six continents has been described elsewhere.[24]

During the first round three domains (itch, sweating, overheating) were suggested to be added by participants but were not rated as sufficiently important in the subsequent rounds.

Table 1. Core domains and outcomes of the Core Outcome Set (COS) of care and research

	First round n=186	Second round n=144	Third round n=111
Responses (%)*	144 (77)	111 (77)	70 (63)
Stakeholder group			32 (46)
Patients representatives (%)**	81 (56)	62 (56)	38 (54)
Professionals (%)**	63 (44)	49 (44)	

* percentage indicates proportion of responders of a round among those invited (n) for that round.

** percentage indicates proportion of a stakeholder group among those responders.

To give an overview of the rating of all domains, Figure 2 summarizes the rating of the complete list of domains during the second round of the e-Delphi. The rating during this second round showed that the preferences of patient representatives and of professionals on important domains for care were rather similar to that for the research setting, with a few exceptions such as family function or pain. After the second round, seven 'provisional consensus domains' were eligible for inclusion in the CDS.

Table 2 summarizes the rating of 'important domains', i.e., domains that had ever scored 7, 8, or 9 by at least 70% of a stakeholder group, for a particular setting (care or research), during the three rounds of e-Delphi. No domains were voted to be 'unimportant' during the three rounds of e-Delphi. It appeared that the preferences of patient representatives and professionals for the 'important' domains were consistent throughout the e-Delphi rounds. Despite the few changes in preference of domains such as cognitive functions, social function and psychiatric outcomes, most stakeholders agreed on the importance of the selected domains.

After the third round, there were 15 'provisional consensus domains' eligible for inclusion in the CDS for the care and 9 for the research setting (Table 3), with quite some overlap. In total, there were 16 unique provisional consensus domains. For those 16 unique domains, 45 outcomes were selected by at least 70% of stakeholder groups. A summary of results of the first, second, and third e-Delphi rounds can be found in Appendix 2, Appendix 3, and Appendix 4, respectively.

Consensus meeting

Detailed descriptions of the consensus meeting can be found in Appendix 5. Seventeen people participated in the consensus meeting, including seven patient representatives and seven professionals, and three (no vote) project members. Fourteen participants reviewed and voted on the 'provisional consensus domains' for inclusion in the CDS (Table 3). They also voted on the 'important domains' for which consensus had not been reached during the e-Delphi (Appendix 5-Table A2A and Table A2B); none of these 'important domains' were added to the 'provisional consensus domains'. During the discussion, re-classifications of a number of domains were suggested by either lumping or splitting domains. Since it was unanimously agreed to lump the 'social', 'family', 'emotional', and 'physical function' into a new domain called 'quality of life', this idea was immediately implemented. Other suggestions included categorization of 'death',

Table 2. Percentage of score 7, 8, or 9 given by patient representatives (PP) and professionals (Pro) on domains for clinical care or for the research setting during each e-Delphi round

		First round				Second round				Third round			
	Domains that are scored as	Care		Research		Care		Research		Care		Research	
No	important by a stakeholder group	PP	PRO	PP	PRO	PP	PRO	PP	PRO	PP	PRO	PP	PRO
1	Delivery of care	73	83	68	73	85	94	73	88	*	*	*	*
2	Cognitive function	41	53	62	41	57	50	67	53	74	44	71	36
3	Emotional function	86	87	75	75	90	88	71	75	*	*	*	*
4	Family function	73	83	68	73	78	77	60	52	*	*	62	44
5	Social function	70	76	67	60	96	80	71	60	*	*	55	53
6	Neoplasms	83	90	85	87	89	98	89	98	*	*	*	*
7	Nervous system	83	86	85	79	84	90	83	87	*	*	*	*
8	Psychiatric outcomes	72	60	65	52	76	60	78	44	85	71	76	53
9	Pain	79	81	72	63	81	86	70	67	*	*	81	71
10	Anatomy characteristics of skin	90	94	89	84	87	90	92	86	*	*	*	*
11	Anatomy characteristics of hair	71	78	78	62	76	67	71	52	57	44	57	24
12	Histopathology	83	73	84	86	71	63	87	75	69	84	*	*
13	Protective function	75	67	74	51	76	61	79	40	76	58	33	62
14	Repair function	81	68	81	51	75	71	79	44	*	*	74	53
15	Sensation of skin	78	59	77	44	81	65	75	38	76	49	67	31
16	Other function	67	38	77	44	46	17	40	13	36	16	36	11
17	General adverse events	79	84	77	75	84	94	81	79	*	*	*	*
18	Infection	79	67	69	52	89	67	76	44	90	82	76	49
19	Death	80	86	83	83	82	94	90	94	*	*	*	*
20	Information provision	91	81	77	60	92	86	78	52	*	*	79	51

* not rated in the third round because that domain for a given setting became a 'provisional consensus domain' after the second round; *i.e.* already rated 7, 8, or 9 by at least 70% of both stakeholder groups in the second round.

'neoplasms', 'nervous system', and '(histo)pathology' into the domain 'malignancy'; and 'signs/symptoms' into the domain 'adverse events'. These suggestions were not unanimously accepted and thus not included. Furthermore, the domain 'histopathology' was renamed as 'pathology' because 'pathology' does not only describe histological findings but also molecular findings. The selection of the top five domains for the CDS and the opportunity to alter the classification of domains was an additional step to promote future uptake, and had not been specified in the initial protocol.[24]

The top five domains that were considered crucial for care and for the research setting are shown schematically in Table 4 and Figure 3. The core domains of the COS for CMN comprise the categories 'quality of life', 'neoplasms', 'nervous system', and 'anatomy of skin' for both the care and research settings, and the domains 'general adverse events' or 'pathology' for clinical care or research, respectively. There was a thorough discussion on whether or not general adverse events should be included in the COS for the research setting, given it was considered crucial but did not get sufficient votes to be among the top five domains. There was a concern that if we were to make an exception here, it would be hard to draw the line for other domains that were also not included in the COS. Therefore,

Table 3. List of 'provisional consensus domain' (X) from the e-Delphi for inclusion in the CDS during the consensus meeting.

Domains	Care	Research
1. Delivery of care	X	X
2. Emotional function	X	X
3. Social function	X	
4. Family function	X	
5. Physical functioning	X	
6. Malignancy (neoplasms)	X	X
7. Nervous system	X	X
8. Psychiatric outcomes	X	
9. Pain	X	X
10. Anatomy of skin	X	X
11. (Histo)pathology		X
12. Repair function of skin	X	
13. General adverse events	X	X
14. Infection	X	
15. Death	X	X
16. Information provision	X	

Table 4. Results of vote on the provisional consensus domains; The top 5 domains (highlighted) were included in the CDS for the care or research setting.

No	Domains for the care setting	Vote %	No	Domain for the research setting	Vote %
1	Quality of life (including social, family, emotional and physical function)	86	1	Pathology	93
2	Neoplasms	79	2	Neoplasms	79
3	Nervous system	64	3	Nervous system	71
4	Anatomy of skin	71	4	Quality of life (emotional function)	71
5	General adverse events	57	5	Anatomy of skin	64
6	Delivery of care	50	6	General adverse events	43
7	Infection	21	7	Death	43
8	Pain	21	8	Pain	21
9	Death	14	9	Delivery of care	14
10	Psychiatric outcomes	14			
11	Repair function	7			

we decided to follow the consensus meeting protocol sent to participants prior to the meeting, in which it was stated that we would include only the top five domains for each setting.

For the domains included in the CDS, 44 outcomes describing these domains were considered to be 'important by stakeholders during the third e-Delphi round. During the consensus meeting, fourteen of the seventeen participants re-voted for these outcomes. Table 5 presents a list of 28

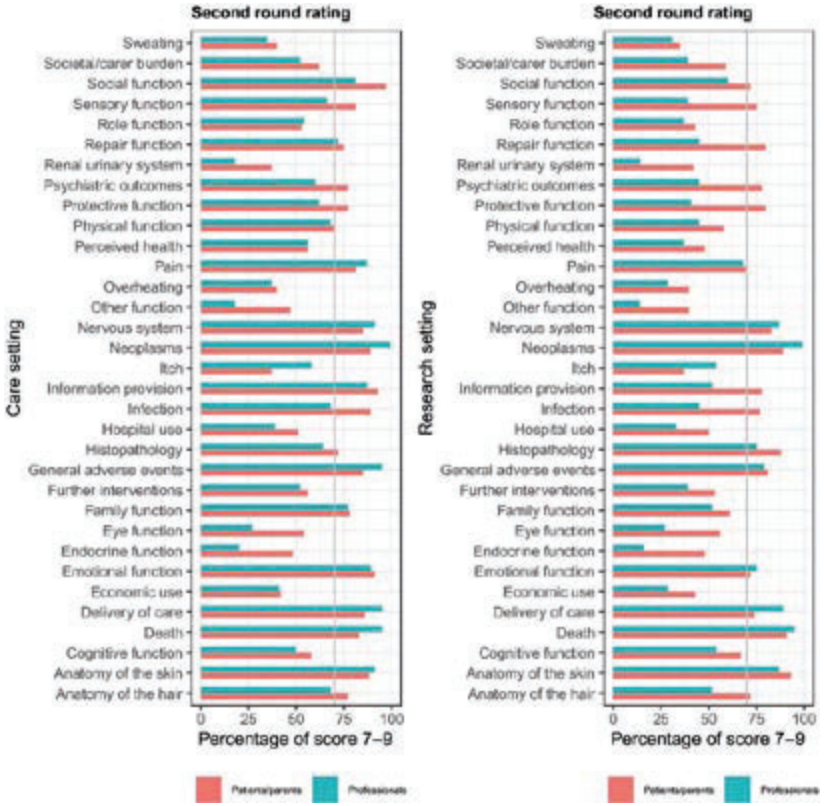

Figure 2. The proportion of patient representatives (red bars) or professionals (blue bars) who assigned a score of 7, 8 or 9 to each of the domains for care (left) and for the research (right) settings during the second round of e-Delphi.

outcomes that were selected by at least 70% of the consensus meeting participants for inclusion in the CDS. One outcome, 'brain complications', was re-classified from the domain 'general adverse events' to the domain 'nervous system' since they may not be related to treatment.

DISCUSSION

Our project presents the first part of the COS development for medium, large and giant CMN that considers the opinions of patient representatives and uses transparent methods planned *a priori*.

Table 5. List of domains and outcomes selected for the COS

Domains	Outcomes
1. Quality of life*	Acceptance of CMN as part of identity
	Satisfaction with treatment choice
	Coping mechanisms
	Esthetic issues
	Perceived stigmatization
	Social relations*
	Acceptance by parents/family members of having CMN*
2.Neoplasms/malignancy	Incidence of melanoma
	Incidence of other malignancy
	Frequency of monitoring for malignancy
	Biopsy findings/ histological characteristics
3. Nervous system	Epilepsy
	MRI findings
	Hydrocephalus
	Motor development
	Brain complications due to melanocytosis, melanoma, or metastasis
4. Anatomical characteristics of skin	Color of the CMN (hypo-, hyperpigmentation, vitiligo)
	Hairiness
	Lumpiness
	Spontaneous regression of nevi
	New satellite nevi
	Change of nevus over time
	Rugosity
5. General adverse events[$]	Growth-related problem in the area of operated nevus
	Skin graft issues (flap, graft failure)
	Change in scar (keloid, hypertrophic, atrophic, widening, contracture)
	Cranial or facial deformation by treatment
6. Pathology[&]	Histo-pathological characteristics

* Quality of life entails emotional, physical, family, and social functioning for the care setting where as for the research setting it entails only emotional functioning.

[$] General adverse events was chosen by vote within the care setting only.

[&] Pathology was chosen by vote within the research setting only.

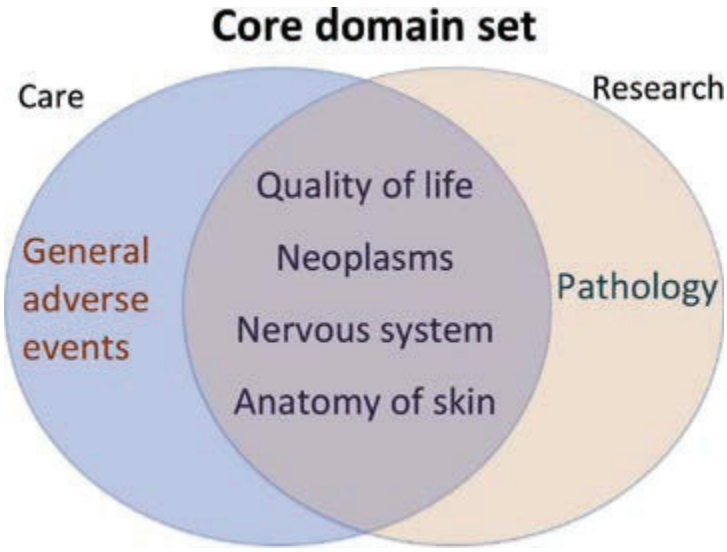

Figure 3. Core domains of the COS for reporting clinical care of CMN and research into CMN.

The purpose of this study was to develop an international consensus-based CDS to be applied in care of or in research about medium-to-giant CMN patients of any age, with or without treatment. We managed to include participation from six continents.

To date, there is no outcome classification specifically designed for skin conditions.[35] Several COS studies on skin diseases set examples of outcome classification.[20,34,36,37] We chose to enrich the COMET domain classification by adding the classification from the WHO ICF for skin anatomy and functions. Domains that were classified as 'Functioning' in the COMET taxonomy were grouped into 'quality of life' during our consensus meeting.

Participants frequently brought up the importance of providing vetted information about CMN throughout the focus group discussions and it was rated highly during the e-Delphi process. However, during the consensus meeting, information provision was removed from the 'provisional consensus domains' since it was not considered to be directly influenced by either conservative or interventional treatment.

The consensus meeting took place online to allow participation of people around the globe. We successfully reached consensus on many domains within a limited time of online discussion. It does, however, require great concentration to participate in an online discussion in a non-native language, time zones were not equally convenient for all, and participants did not always have a stable internet connection, which can interrupt the discussion. Nevertheless, we found that the online consensus meeting provided a complementary opportunity to the surveys to directly discuss, debate and finally agree on the important domains.

In COS development, adoption of an internationally accepted outcome domain classification is supposed to facilitate literature searches and synthesis of evidence.[38] The COMET taxonomy[25,26] that we chose to follow is open to more detailed classification relative to clinical and methodological

areas.[26] Too much detail, however, might cause confusion when one needs to formulate specifically what a domain should entail. We attempted to identify which outcomes should be considered when looking at each of the core domains through two selection processes, i.e., during the last e-Delphi and by email after the consensus meeting. Some outcomes were classified under one domain but remained related to another. Moreover, participants did not have the opportunity to vote separately for the specific outcomes they considered important. Therefore, the selected outcomes in this study were used to illustrate what a core domain could consist of. To facilitate further consensus on finding or developing the instruments to measure these outcomes and to promote future uptake, it may be necessary to reorganize or reduce the number of outcomes in each setting.[39]

There were some limitations of the COS development in this study. Participation from North America and Europe was over-represented in our study. In part, this might be due to the requirement to conduct the development process online and in English. The essential votes included 14 intentionally selected participants, in contrast to the random sampling stated in the protocol. We thought that equal representation of patient representatives and professionals was essential, but there were more professionals who were available to participate in the consensus meeting. Furthermore, "general adverse events" was excluded from the CDS of research and "delivery of care" from the CDS for the clinical setting after the consensus meeting. These findings may be contested by participants who had voted for these domains by e-mail but could not participate in the consensus meeting. We have sent these interim results to all participants who were involved in the second round of the e-Delphi, and none has objected to the CDS selected by the online consensus meeting participants.

In conclusion, the present study reports the development of a comprehensive CDS for use in care and in research on medium-to-giant CMN. The final CDS includes the top five domains for care and top five for research, with four in common. A set of outcomes was selected to illustrate these domains. Future research is needed to reach a consensus on the core outcomes of each domain in the CDS, to validate and/or to develop instruments, and to reach a consensus on the appropriate outcome measurement instruments. Uptake of this CDS in future clinical care of, and research about medium-to-giant CMN should facilitate comparisons across different treatment choices for both patients and professionals.

SUPPORTING INFORMATION

Additional Supporting Information can be found in the online version of this article at the publisher's website.

Link: https://onlinelibrary.wiley.com/doi/ftr/10.1111/bjd.19694

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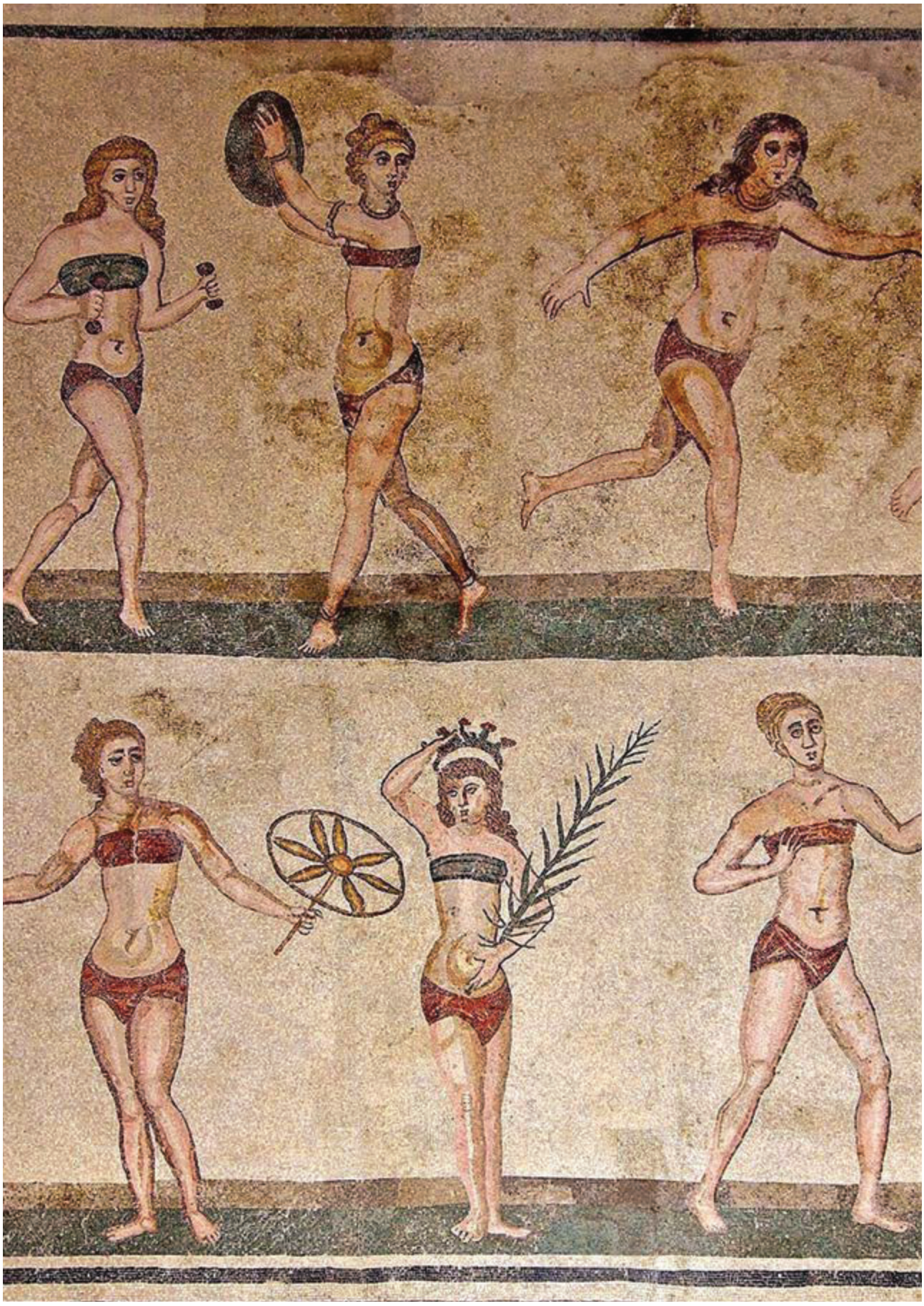

“Bikini Girls”, Villa Romana del Casale, Piazza Armerina, Sicily

300 AD

The famous “Bikini Girls” are formed by a floor mosaic showing women exercising, running, or receiving the palm of victory for winning an athletic competition. Note that the bikinis are shown as sportswear and not as swimwear.

7

DOMAINS AND OUTCOMES OF THE CORE OUTCOME SET OF CONGENITAL MELANOCYTIC NAEVI FOR CLINICAL PRACTICE AND RESEARCH (THE OCOMEN PROJECT): PART 2

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ABSTRACT

Background

Congenital melanocytic naevi (CMN) can have a great impact on patients' lives owing to perceived stigmatization, and the risk of melanoma development and neurological complications. Development of a core outcome set (COS) for care and research in CMN will allow standard reporting of outcomes. This will enable comparison of outcomes, allowing professionals to offer advice about the best management options. In previous research, stakeholders (patients, parents and professionals) reached consensus on the core domains of the COS. To select the appropriate measurement instruments, the domains should be specified by outcomes.

Methods

A list of provisional outcomes (obtained earlier) was critically reviewed by the Outcomes for COngenital MElanocytic Naevi (OCOMEN) research team and by relevant stakeholders through an online questionnaire, to refine this list and provide clear definitions for every outcome. When needed, discussion with individual participants was undertaken over the telephone or by email. During an online consensus meeting, stakeholders discussed the inclusion of potential outcomes. After the meeting, participants voted in two rounds for the inclusion of outcomes.

Results

Forty-four stakeholders from 19 countries participated. Nine core outcomes were included in the COS relative to clinical care and 10 core outcomes for research.

Conclusion

These core outcomes will enable standard reporting in future care and research of CMN. This study facilitates the next step of COS development: selecting the appropriate measurement instruments for every outcome.

What is already known about this topic?

- Congenital melanocytic naevi (CMN) can be associated with psychosocial burden and increased risk of melanoma and/or neurological complications.
- Outcomes measured for research and care in CMN are heterogeneous, impeding comparison.
- A core outcome set (COS) may enhance standardized use and reporting, and reduce selective reporting bias.
- In previous research, relevant stakeholders reached consensus on what domains should be included in the core domain set (CDS).

What does this study add?

- To select the appropriate measurement instruments for the domains included in the CDS, the domains should be further specified by outcomes.
- We reached consensus on what outcomes should describe the domains of the CDS of CMN care and research.
- Through a consensus procedure, including online discussions, online consensus meeting and voting, relevant stakeholders reached consensus on a limited number of core outcomes describing the core domains.

What are the clinical implications of this work?

- Development of a COS will allow standard reporting of outcomes in future care and research of CMN.
- This will enable pooling and comparison of outcomes, allowing guideline development of optimal management policy.

INTRODUCTION

Owing to their unusual appearance, congenital melanocytic naevi (CMN) can have a great impact on patients' lives.[1] In addition, people with CMN with large or giant [> 20 cm projected adult size (PAS)], or multiple CMN have an elevated risk of developing melanoma and neurological complications.[2,3] Comparison of management strategies is currently hindered by the lack of standard and uniform outcome reporting.[4,5] This impedes guidance on the optimal management policy based on high-evidence research.[6] To address this problem, a core outcome set (COS) needs to be developed, i.e. a consensus-derived minimum set of outcomes that should be measured and reported in all care of or clinical research concerning a certain health condition.[7] Ideally, a COS describes both what should be measured (domains and outcomes) and how this should be measured (measurement instruments)[7]. The Outcomes for COngenital MElanocytic Naevi (OCOMEN) project aims to develop a COS for CMN. Currently, the project is focused on the 'what' to measure. The first step was performed in 2020, i.e. consensus was reached on which domains should be included in the core domain set (CDS) of care of, and research on, CMN.[8]

In this study, we define 'domains and outcomes' as aspects of disease that could be measured to evaluate different management strategies. 'Domains' are broader aspects of a disease like 'neoplasm', whereas 'outcomes' are defined as more precise aspects of a disease on a lower hierarchical level, for example 'presence of melanoma' is an outcome on a lower hierarchical level of the domain 'neoplasm'. We define a 'baseline characteristic' as a demographic, clinical or prognostic aspect of the patient, like age, sex or the location of their CMN. To be able to select the right measurement instrument the domains should be defined in terms of measurable specific outcomes.

Table S1 (see Supporting Information) shows the list of domains and provisional outcomes obtained in previous research.[8] To promote future uptake of the CMN CDS, only a limited set of core outcomes should be measured. These are the ones agreed to be most necessary to measure and report in all future care or research concerning CMN management. A limited number of outcomes makes the CDS feasible to use in daily practice and research. Of course, researchers and professionals could always measure additional outcomes that they deem relevant.

The aim of this study was to reach consensus on outcomes describing the core domains that are most necessary to measure and report in all future care or research encompassed by the core domains.

METHODS

Scope and applicability of the core outcome set

The target population is patients with medium-to-giant CMN: patients with a CMN of 1·5 cm in diameter or larger PAS on the face, and CMN > 10 cm diameter PAS elsewhere on the body.[9] The COS is intended for use in all types of interventions of CMN: interventional management (excision, laser, curettage and dermabrasion), as well as conservative management (watchful waiting). Distinct COS are being developed for care (clinical practice) and for research (clinical observational studies and trials), each for international use.[10]

Ethical approval was obtained from the Ethical Review Board at Erasmus MC Rotterdam and from the Ethical Board at Amsterdam UMC. The OCOMEN project was registered in the Core Outcome Measures in Effectiveness Trials (COMET) database. We followed the guidelines of the COMET initiative[7,11,12] and the Cochrane Skin-Core Outcomes Set Initiative (CS-COUSIN).[13] We reported this article according to the Core Outcome Set – STAndards for Development (COS-STAD) and Core Outcome Set – STAndards for Reporting (COS-STAR).[12,14] The protocols of consensus meetings of other COS research groups were used for the CMN consensus meeting.[15,16] A protocol of the consensus procedure was sent to CS-COUSIN, who provided methodological feedback.[17] The participants were asked for their consent to publish their names in the acknowledgements. None of the participants objected [see also Table S2 (see Supporting Information)].

Table 1 shows the ways in which we involved relevant stakeholders, including patients, parents and health professionals in this project.

Finding the core outcomes that describe the core domains involved four steps: (i) reviewing the provisional list of outcomes by the OCOMEN team (i.e. defining and reordering outcomes); (ii) reviewing the provisional list of outcomes with relevant stakeholders; (iii) an online consensus meeting with relevant stakeholders to discuss the inclusion/exclusion of outcomes that are core and most necessary to measure and report in all future care or research; and (iv) voting for inclusion/exclusion of outcomes, resulting in a list of outcomes per domain.

Table 1. Stakeholder groups and methods of approaching potential participants

Stakeholder groups	Details	Methods of approach
Patients/ parents	Patients Parents/caregivers* Family members	Identified patients who participated in previous research of the OCOMEN project Call for participation on social media and websites of the patient support organizations (around 4000 views) Collaboration with national and international patient advocates who used their network to invite patients Call for participants on the Naevus Global patient representative meeting (12 September 2019)
Professionals	Dermatologists Plastic surgeons Pathologists Neurologists Psychologists Researchers	Identified professionals who participated in previous research of the OCOMEN project Identification of names from the literature, attendance of meetings/ conferences in paediatric dermatology/plastic surgery and trough personal network of the OCOMEN team Participants were asked to suggest names of other professionals who may be interested to participate.

* Parents could fill out the survey based on their own personal perspective or on behalf of their young child, in that case they needed to do the rating based on the child's perspective.

Reviewing the provisional list of outcomes by the Outcomes for Congenital Melanocytic Naevi team

The provisional list of outcomes (list 1; Table S1) was obtained in previous research that aimed to reach consensus on the core domains. In this research, participants could give their provisional vote on which outcomes should describe the domains during the last round of an e-Delphi study and during a consensus meeting.[8] These outcomes were obtained through a previously performed systematic review and focus groups.[5,10]

We aimed to prepare this provisional list of outcomes to enable an easier discussion of inclusion and exclusion of outcomes during the consensus meeting. The OCOMEN team critically reviewed the following aspects for every separate outcome of list 1: (i) Is the name and definition of the outcome clear? (ii) Was the outcome classified in the right domain? (3) Is it an outcome and not a baseline characteristic like age, sex or body location of the CMN? (4) Could the outcome be lumped together with another outcome? A clinical psychologist (L.H.) was consulted to review the outcomes concerning 'quality of life'. Definitions were provided in order to make the outcomes clear for all participants. We used the Patient Reported Outcomes Measurement Information System (PROMIS) definitions for the definitions of the outcomes of the 'quality of life' domain.[18,19] Two parents of children with CMN were consulted to ensure that all outcomes and definitions were written in lay language. These alterations resulted in list 2: 'provisional list of outcomes reviewed by the OCOMEN team' (Table S3; see Supporting Information).

Reviewing the provisional list of outcomes with relevant stakeholders

We asked relevant stakeholders to give their feedback on list 2 (Table S3). They were sent an online questionnaire, where they could state their opinion. When needed, discussion was performed by email or telephone. One week before the consensus meeting, participants received list 3 ['provisional list of outcomes reviewed by the OCOMEN team and relevant stakeholders' (Table S4; see Supporting Information)]. When participants disagreed with alterations made, they were offered an opportunity to discuss this with one of the OCOMEN team members by telephone before the consensus meeting, to ensure that everyone's opinion was heard. Participants did not have the opportunity to discuss these alterations during the consensus meeting. This deviation of the protocol was made to shorten the discussion during the online consensus meeting by only discussing the inclusion/exclusion of outcomes.

Online consensus meeting to discuss inclusion/exclusion of outcomes

An online consensus meeting was held on 21 January 2020 via Zoom (https://zoom.us), with the aim of discussing the inclusion and exclusion of potential outcomes. Patients, parents and professionals specialized in CMN were able to participate in this meeting (Table S2). A meeting protocol with a timetable was made beforehand, to ensure that all outcomes could be discussed in the 2-h consensus meeting.

Before the meeting, participants received the following information: (i) what a COS is vs. a CDS and why they are necessary;[7] (ii) information about previously conducted research in

CDS development;[5,8,10] (iii) the list of domains included in the CDS for care and research; (iv) the provisional list of outcomes per domain; (v) the list of outcomes excluded during the Delphi round and consensus meeting for the CDS in 2019; (vi) a definition list of outcomes in lay language for patients who participated; (vii) explanation of what should be expected of the meeting; and (viii) explanation that when an outcome is included in the CDS, it should always be measured in all care or all research.

The consensus meeting started with personal introductions from all participants, which was followed by a presentation repeating the information listed above. After the presentation we started a plenary whole-group discussion. An audio discussion was moderated by one of the OCOMEN team members. In the meantime, there was a written chat discussion moderated by another OCOMEN team member. We discussed whether the domain 'adverse event' should be included in the CDS of research, because it was only included in the CDS of care. Subsequently, we discussed each outcome of list 3 ('provisional list of outcomes reviewed by the OCOMEN team and relevant stakeholders'; Table S4).

Voting for inclusion/exclusion of outcomes, resulting in a list of outcomes per domain

The voting was done in two rounds to enable participants to see the first judgement of the group after the first round of voting and revise their earlier answers in light of the replies of other participants. The first round was performed at the end of the consensus meeting by the anonymous voting option in Zoom. The second vote was the final round of voting and was done via email. Participants who attended the consensus meeting received a Microsoft Word document with results of the first voting. In this document they could vote for which outcomes they considered to be core. When at least 70% of participants considered an outcome to be core in the final voting, the outcome was included in the CDS.

RESULTS

Participants

We initially contacted 193 stakeholders, of whom 79 were initially interested in participating. Forty-four stakeholders participated in the study, i.e. gave feedback on the list of outcomes (n = 33) and/or participated in the consensus meeting (n = 32). Twelve of the participants who gave their feedback on the provisional list of outcomes were not able to attend the meeting and 11 participants who attended the meeting did not give their feedback on the provisional list of outcomes. A total of 30 participants gave their final vote for the care setting and 31 participants for the research setting. Table S2 shows the details of the participants from 19 different countries.

Reviewing the provisional list of outcomes

The OCOMEN team critically reviewed the 26 outcomes of list 1 ('provisional list of outcomes'; Table S1). The alterations made are shown in list 2 ('a provisional list of outcomes reviewed by the OCOMEN team'; Table S3). A total of 33 participants gave feedback on list 2 (Table S3).

Based on the participants' feedback, alterations were made to prepare the list of outcomes for the consensus meeting (list 3: 'provisional list of outcomes reviewed by the OCOMEN team and relevant stakeholders'; Table S4). Definitions of lists 2 and 3 are given in Appendix S1 (see Supporting Information).

Online consensus meeting to discuss inclusion/exclusion of outcomes

A total of 32 stakeholders participated in the consensus meeting. We first discussed whether the domain 'adverse events' should be included in both the care and research CDS. In previous research, this domain was excluded for the research CDS. All participants agreed that 'adverse events' is a core domain for research and was therefore also included in the research CDS.

Some outcomes that were discussed during the consensus meeting could be interpreted as both an outcome (i.e. aspects to evaluate change by management) or as a baseline characteristic (i.e. demographics, clinical or prognostic aspects). For instance, size, colour, texture or number of CMN can be considered to be baseline characteristics by which to classify the CMN. These baseline characteristics are important in estimating the risk of melanoma or neurological involvement. However, these aspects of the appearance of the CMN can also be used to evaluate different types of management. For instance, the 'size of CMN' can reduce after (partial) excision; the 'colour of CMN' can lighten after laser treatment; the 'texture of CMN' can change as a result of scarring; and 'satellite naevi number' can increase during watchful waiting in the first years of life. After discussion with the entire group, we decided that these mutable aspects themselves should be considered as outcomes.

In our previous report, the outcome 'ability to cope' was classified as a core outcome for CMN. This outcome is also considered to be core in other conditions like bereavement support in palliative care.[20] We explained that 'ability to cope' is something that is influenced by personality and learned coping strategies, and not by the usual direct treatments of CMN (surgery or watchful waiting). Therefore, 'ability to cope' is a difficult outcome to use to evaluate the usual treatments of CMN. It could be used as a baseline characteristic to predict other outcomes like 'emotional distress' or 'satisfaction with treatment'. During the group discussion, it was suggested that 'ability to cope with stigmatization' could be influenced by treatment such as complete excision of CMN. However, we agreed that the outcome measured in this case would be 'stigmatization' and not the 'ability to cope'.

The most serious clinical threats of CMN are the development of melanoma and neurological complications. Consequently, most participants agreed that these outcomes 'presence of melanoma' and 'neurological symptoms and signs' are most necessary to measure for both care and research. Therefore, in all future CMN studies, the presence of melanoma or neurological symptoms/signs need to be explicitly documented.

The outcome 'molecular characteristics' was proposed during the consensus. Molecular characteristics can be assessed to evaluate (malignant) changes in the CMN tissue.[21-23] Research on COS uptake emphasized that outcomes should be feasible to measure (easily measurable and requiring minimal resources) and responsive to interventions.[24] Testing molecular characteristics could be costly and may hinder researchers in measuring this outcome as standard. Moreover,

a skin biopsy is needed to investigate malignancy, which can be a burden for patients in the absence of a clinical rationale. Therefore, we decided with the consensus of the whole group that 'molecular characteristics' should be reported in research when such tests were already performed for clinical care. This will increase the standard publication of 'molecular characteristics' found in patients with CMN and will improve knowledge on this topic.

Voting for inclusion/exclusion of outcomes, resulting in a list of outcomes per domain

A total of 22 participants voted in the first round at the end of the consensus meeting. Ten participants did not vote because they had to leave the meeting before the end (n = 7), had a bad internet connection (n = 1), had expertise in only one domain (n = 1) or voted together with another participant (n = 1).

Of the 32 people who participated in the consensus meeting, the final vote was made by 30 participants for the care setting and by 31 for the research setting. One participant only voted for research as this participant was only involved in research of CMN. Another participant in the consensus meeting had expertise about only one domain and therefore chose not to vote. Table 2 shows the reviewed provisional list of outcomes and the results of voting in the first and second rounds. Figure 1 shows the list of core outcomes per domain for care and research. The following core outcomes were included in both the CDS of care and research: satellite naevi number; colour of the CMN; texture of the CMN; size of CMN; emotional distress; presence of melanoma; neurological symptoms and signs; wound problems in the CMN; and scar problems. In the research CDS, the outcome 'molecular characteristics' was also included.

Table 2. Reviewed list of provisional outcomes per domain and voting results

Domains and provisional outcomes for the COS of care	Voting round 1 Care % n	Voting round 2 Care % n	Voting round 1 Research % n	Voting round 2 Research % n
1. Anatomy of skin				
Satellite nevi number	95 (21/22)	**87 (26/30)**	95 (21/22)	**97 (30/31)**
Colour of the CMN	91 (20/22)	**73 (22/30)**	86 (19/22)	**74 (23/31)**
Texture of the CMN	91 (20/22)	**83 (25/30)**	86 (19/22)	**77 (24/31)**
Size of CMN	91 (20/22)	**93 (28/30)**	86 (19/22)	**81 (25/31)**
Hairiness of the CMN	86 (19/22)	57 (17/30)	86 (19/22)	55 (17/31)
2a. Quality of life				
Emotional distress	95 (21/22)	**87 (26/30)**	82 (18/22)	**77 (24/31)**
Body image	55 (12/22)	40 (12/30)	45 (10/22)	26 (8/31)
Perceived stigmatization	45 (10/22)	10 (3/30)	36 (8/22)	3 (1/31)
Ability to cope	41 (9/22)	7 (2/30)	27 (6/22)	6 (2/31)
Social relations: satisfaction with participation in social activities	64 (14/22)	30 (9/30)	NA	NA
Social relations: ability to participate in social roles and activities	64 (14/22)	13 (4/30)	NA	NA

Table 2. Reviewed list of provisional outcomes per domain and voting results

Domains and provisional outcomes for the COS of care	Voting round 1 Care % n	Voting round 2 Care % n	Voting round 1 Research % n	Voting round 2 Research % n
General physical functioning	68 (15/22)	30 (9/30)	NA	NA
2b. Quality of life of family; Delivery of care				
Satisfied with treatment	68 (15/22)	57 (17/30)	68 (15/22)	39 (12/31)
2c. Quality of life of family; Family function				
Acceptance of parents/family members of having child/family member with CMN	32 (7/22)	10 (3/30)	NA	NA
3. Neoplasms (Cancer)				
Presence of melanoma	100 (22/22)	**97 (29/30)**	95 (21/22)	**100 (31/31)**
Presence of other malignancy	86 (19/22)	53 (16/30)	86 (19/22)	58 (18/31)
4. Nervous system				
Neurological symptoms and signs	95 (21/22)	**93 (28/30)**	91 (20/22)	**94 (29/31)**
Neuroimaging findings (documented/ measured when neuroimaging is performed)	77 (17/22)	53 (16/30)	82 (18/22)	61 (19/31)
Brain complications due to melanosis, melanoma or metastasis	45 (10/22)	23 (7/30)	36 (8/22)	19 (6/31)
5. General adverse events (problems)				
Wound problems of the CMN (after treatment and when spontaneous wounds of the CMN occur)	91 (20/22)	**83 (25/30)**	95 (20/21)	**77 (24/31)**
Scar problems	91 (20/22)	**78 (24/30)**	95 (20/21)	**74 (23/31)**
Anatomic deformation	86 (19/22)	63 (19/30)	90 (19/21)	58 (18/31)
6. Pathology				
Histological characteristics (documented/measured when skin removal is performed)	NA	NA	68 (15/22)	65 (20/31)
Molecular characteristics (documented/ measured when available) (outcome proposed during consensus meeting)	NA	NA	NA	**71 (22/31)**

Provisional list of outcomes reviewed by the OCOMEN team and relevant stakeholders and the results of voting after the first and second voting round. Outcome included in the core domain set are presented in bold.

One participant did not vote for the care setting in the second round.

NA; not applicable.

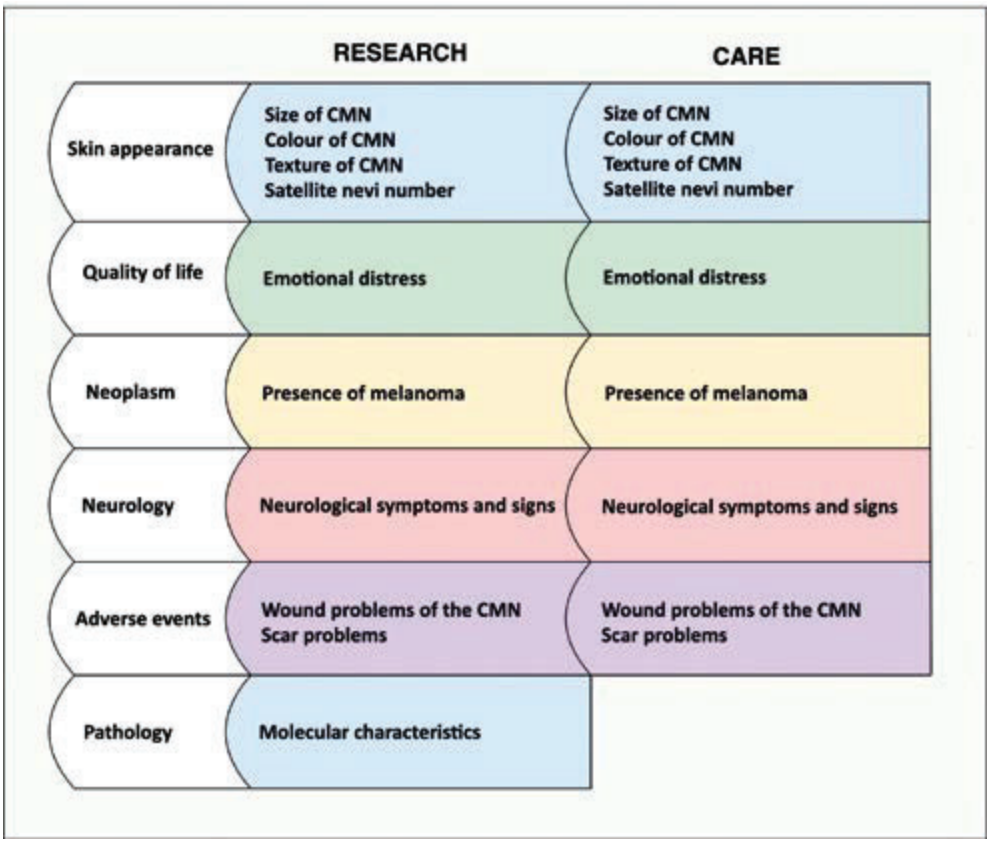

Figure 1. Core domains (white) and outcomes (coloured) of the core domain set of congenital melanocytic naevi (CMN) of care and research

DISCUSSION

In this study, we reached consensus on which outcomes should describe the CDS of care and research in CMN. The provisional list of 28 possible outcomes was reordered and limited to nine core outcomes for care and 10 mostly redundant core outcomes for research. This limited number of outcomes makes the CDS feasible for use in all future care and research settings.[25] As the outcomes included in the CDS are 'core', they are of the highest priority for inclusion in all clinical and research outcome evaluations. Of course, other outcomes beyond those considered as core may always be measured additionally.

The size, colour and texture of the CMN, as well as a proxy for the number of 'satellite' (disseminated) naevi, are included in the CDS. These aspects are also recommended as baseline characteristics to be reported by a consensus-derived, internationally used classification developed by Krengel et al.,[9] and qualified (the '6B' and 'biker glove' distributions)[26,27] for the location of the CMN. We highly recommend using these classifications in all CMN reports to obtain uniform descriptions of CMN. However, these classifications are not themselves outcome measurement instruments

and are not designed to evaluate responses to interventional treatment or spontaneous changes after watchful waiting. In future research, outcome measurement instruments must be identified or developed, and validated, to measure the dynamics of size, colour, texture and number of additional naevi in order to evaluate CMN management.

We did not identify specific neurological symptoms/signs that should be measured. We believe that specific outcomes should be decided with stakeholders experienced in neurological outcomes in patients with CMN. Future research may refine this recommendation by defining how this should be measured (e.g. examination by neurologist/physician or a patient-reported outcome measurement instrument). In this process, it should be decided which specific neurological symptoms and signs should always be assessed in care and research. To assist this process, the OCOMEN team has conducted a systematic review to identify which specific neurological symptoms/signs have been described in patients with CMN (PROSPERO ID: CRD42020177555).

Some outcomes that were highlighted as important during the consensus meeting (e.g. 'neuroimaging findings' were not voted for by > 70% of stakeholders). It is not feasible to measure too many outcomes, and stakeholders voted other outcomes to be of greater importance.[25] When possible, the excluded outcomes could be measured/documented alongside the core outcomes in research and care.

We used a broad network to involve patients, parents and professionals, attempting to reach and engage everybody who wanted to participate. All participants had the opportunity to state their opinions via a questionnaire, email, telephone and during the consensus meeting. All the feedback was considered to improve the list of outcomes.

A limitation was that the group of patients and parents became under-represented in the group of participants. We tried to reach as many patients and parents as possible; however, there were more professionals willing to participate in this project. Social media posts in patient support groups were viewed by an estimated 4000 subscribers, but only four of these subscribers showed an interest in participating. We did not exclude professionals to maintain equal proportions, as we did not want to exclude anybody who was willing to participate. Most of these professionals were dermatologists and surgeons, which may have influenced the choice of outcomes. Nevertheless, a large representation of dermatologists and plastic surgeons tallies with the prominent role of these professionals in the care and research of CMN, and also reflects their voluntary participation in interdisciplinary meetings devoted to CMN.[6,28] Only a limited number of outcomes were included in the CDS. Many questions are still unanswered concerning outcomes for such fields as neuroimaging or psychological functioning. Standard reporting of outcomes in these different fields will greatly improve knowledge about the impact and treatment of CMN. However, when too many outcomes are recommended to be measured, the CDS may not be widely adopted, which could impede uniformity in outcome reports.[24,25]

The next step is to define the core outcome measurement set for CMN. To reach uniformity, the core outcomes should be measured by standard outcome measurement instruments. Relevant stakeholders should try to reach consensus on which outcome measurement instruments should be used to measure the domains and outcomes included in the CDS of CMN.

SUPPORTING INFORMATION

Additional Supporting Information can be found in the online version of this article at the publisher's website.

Link: https://onlinelibrary.wiley.com/doi/10.1111/bjd.20437

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Battistero di San Giovanni

Baptistery of Saint John, Florence

1225 - 1250

This artwork was selected by a patient representative of the CMN patient association of Italy.
The Baptistery is one of the oldest buildings in the city and is sheltered by a mosaic ceiling.
The different zones of the ceiling are created in different periods. The upper, oldest part shows choirs of angels. The other rings show stories from the Book of Genesis, Joseph, Mary, Christ, and John the Baptist. The front part with the figure of Christ represents the Last Judgement.
Reference: Wikipedia

8

MEASUREMENT INSTRUMENTS FOR THE CORE OUTCOME SET OF CONGENITAL MELANOCYTIC NAEVI AND AN ASSESSMENT OF THE MEASUREMENT PROPERTIES ACCORDING TO COSMIN: A SYSTEMATIC REVIEW

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Submitted

ABSTRACT

Background

Congenital melanocytic naevi (CMN) can impact patients' lives due to their appearance and the risk they carry of neurological complications or melanoma development. Development of a core outcome set (COS) will allow standardised reporting and enable comparison of outcomes. This will help to improve guidelines. In previous research, relevant stakeholders reached a consensus over which core outcomes should be measured in any future care or research. The next step of the COS development is to select the appropriate measurement instruments.

Aim

Step 1: to update a systematic review identifying all core outcomes and measurement instruments available for CMN. Step 2: to evaluate the measurement properties of the instruments for the core outcomes.

Methods

This study was registered in PROSPERO and performed according to the PRISMA checklist. Step 1 includes a literature search in EMBASE (Ovid), PubMed and the Cochrane Library to identify core outcomes and instruments previously used in research of CMN. Step 2 yields a systematic search for studies on the measurement properties of instruments that were either developed or validated for CMN, including a methodological quality assessment following the COSMIN methodology.

Results

Step 1 included twenty-nine studies. Step 2 yielded two studies, investigating two quality of life measurement instruments.

Conclusion

Step 1 provided an overview of outcomes and instruments used for CMN. Step 2 showed that additional research on measurement properties is needed to evaluate which instruments can be used for the COS of CMN. This study informs the instrument selection and/or development of new instruments.

Keywords: Congenital melanocytic naevi; Core outcome set; Measurement instruments; Patient reported; Melanoma; Measurement properties

INTRODUCTION

Congenital melanocytic nevi (CMN) are birthmarks present at birth or soon after birth. CMN are associated with an increased risk of melanoma, neurological complications and/or psychological burden due to their appearance.[1-3] Treatment of CMN is either conservative (watchful waiting including histology) or interventional (full thickness: excision, partial thickness: laser, curettage, or dermabrasion). Outcomes measured to evaluate treatment of CMN are heterogeneous in care and research, which impedes the comparison and pooling of these outcomes.[4] This complicates guidance of optimal management policy.

The aim of the Outcomes for Congenital Melanocytic Naevi (OCOMEN) project is to develop a core outcome set (COS) for measuring the outcomes of all treatment options for medium, large and giant CMN for care and research.[5,6] A 'core outcome set' (COS) is a consensus-derived minimum set of outcomes that should be measured and reported in all care and clinical trials of a certain health condition.[7,8] The use of a COS may enhance homogeneity in outcome and measurement instrument reporting in future studies and could therefore facilitate evidence synthesis for conservative and interventional treatment recommendation in the future.

In this study, we define 'domains and outcomes' as aspects of a disease that could be measured to evaluate different management strategies. 'Domains' are broader aspects of a disease, whereas 'outcomes' are defined as more precise aspects of a disease on a lower hierarchical level, like 'presence of melanoma' is an outcome of the domain 'neoplasm'.

Patients included in the OCOMEN project are those presenting with either at least M1 (1.5–10 cm projected adult size (PAS)) on the face or at least M2 (10–20 cm PAS) elsewhere, either single or multiple. The COS will be developed for international use, to evaluate both interventional treatment and conservative treatment. In a recent consensus procedure, relevant stakeholders reached a consensus on the core domains and outcomes that need to be measured in the COS (Table 1).[5,6,9] The next step in the development of the COS is to reach a consensus on how these domains must be measured (the core outcome measurement set (COMS)). The first step of developing the COMS is to identify all instruments previously used to measure core domains and outcomes and to evaluate the quality of the measurement properties of the instruments available for the core outcomes. A previous systematic review was performed summarizing all outcomes and measurement instruments used in research for CMN between 2006 and 2019 including sixty-three individual studies.[4] This study, as part of the OCOMEN project, aims to update this previously performed systematic review summarising all outcomes and their measurement instruments available for CMN. The second aim of this study is to critically appraise the measurement properties of all available measurement instruments that are developed and/or used in CMN patients, measuring the core outcomes.

METHODS

This study consists of two steps:

Step 1: A systematic review to identify and describe the outcomes and instruments used in previously published studies for CMN, an update from a previously performed systematic review.[4] The previously systematic review included all outcomes and instruments used, the update only focusses on the outcomes of the COS and their instruments.

Table 1. Core domains and outcomes of the Core Outcome Set (COS) of care and research

Domains	outcomes for the COS of care	outcomes for the COS of research
1. Anatomy of skin	Size of CMN	Size of CMN
	Colour of the CMN	Colour of the CMN
	Texture of the CMN	Texture of the CMN
	Satellite nevi number	Satellite nevi number
2. Quality of life	Emotional distress	Emotional distress
3. Neoplasms	Presence of melanoma	Presence of melanoma
4. Nervous system	Neurological symptoms and signs	Neurological symptoms and signs
5. General adverse events	Wound problems of the CMN	Wound problems of the CMN
	Scar problems	Scar problems
6. Pathology		Molecular characteristics

Step 2: A systematic review to evaluate the quality of the measurement instruments developed or validated for domains and outcomes of the COS of CMN.

Both these steps were registered in PROSPERO, registry number CRD42021238242, and reported according to the PRISMA checklist. The design of the systematic review was based on the guidelines of the Core Outcome Measures in Effectiveness Trials (COMET) initiative and the Cochrane Skin Group Core Outcomes Set Initiative (CS-COUSIN). The Consensus-based Standards for the Selection of Health Status Measurement Instruments (COSMIN) methodology and guidelines were used to critically appraise the measurement properties of instruments. The OCOMEN project was registered in the COMET initiative database.

Step 1: Identification and description of instruments used in previously published studies

Search strategy, quality assessment and data extraction

This first step is an update of a previously performed systematic review in which a list of domains, outcomes and measurement instruments used in CMN research published between 2006 and 2019 were identified.[4] The search strategy used the current and previously performed systematic review was developed with the help of an information specialist (FE) and was performed in EMBASE (Ovid), PubMed, and the Cochrane Library. The complete search strategy can be found in Appendix 1. The research for the current systematic review was performed between January 2019, which marked the end date of the previously performed systematic review,[4] and February 2021.

The same inclusion criteria from the previous systematic review were adopted for this study. We included all studies with ten or more patients that were written in English or Dutch. We excluded case reports, conference reports, and books. Study selection was performed by two independent reviewers (ACF and TB) and disagreements were discussed with a third reviewer. Quality assessment of the included studies was performed independently by two researchers (ACF and TB) according to the level of evidence guidelines set by the Oxford Centre for Evidence-based Medicine.[10] Any disagreement regarding a study's level of evidence was resolved by discussion.

We extracted the following data: study characteristics (author, year, country, study design, intervention, number of subjects with CMN, classification system used for CMN), core domain, core outcomes, and their measurement instruments. Unlike the previously performed review, we only extracted the core outcomes and the measurement instruments for the core outcomes. When diagnoses other than CMN were included in the studies, only data from CMN subjects was extracted. Data extraction was conducted independently by two reviewers (ACF and TB). Disagreements were resolved by discussion, or a third reviewer was consulted.

Data synthesis

Data on domains, outcomes and measurement instruments were extracted. Descriptive statistics were used to calculate the frequency of outcomes. Measurement instruments were labeled as clinician reported or patient reported outcome measurement instruments (PROMs).

Step 2: Evaluation of the quality of measurement instruments developed or validated for CMN

Search and study selection

A search was performed in MEDLINE and EMBASE to identify development and validation studies of instruments for CMN, measuring the core outcomes. It used the same controlled terms and words for the concepts of CMN that were used for the search strategy of Step 1 (Appendix 1) including a validated search filter for finding studies on measurement properties, developed by Terwee et al. (sensitive version, Appendix 2).[11]

Only studies reporting on the evaluation of at least one measurement property of an instrument used or developed for CMN, were included. The COSMIN-taxonomy was used to select which of the following measurement properties of an instrument were evaluated: structural validity, internal consistency, reliability, hypotheses testing, cross-cultural validity and/or responsiveness.[12,13] We included both clinician reported and PROMs instruments including rating systems, questionnaires, medical devices, or other instruments.

The following data were extracted independently by two reviewers (ACF and TB): study characteristics, patient characteristics, evaluated instruments, aspects of the measurement properties investigated and feasibility aspect of the instruments. Discrepancies were discussed with a third reviewer until a consensus had been reached.

Evaluation of the methodological quality of the included studies

The COSMIN Risk of Bias checklist was used to evaluate methodological quality of the included studies.[12,13] Studies were stratified as having very good, adequate, doubtful, or inadequate methodological quality.

Assessment of measurement property results, best evidence synthesis and generating recommendations

Two authors (ACF and CML) independently rated the results of each study on a measurement property against the criteria for good measurement properties as either sufficient (+), insufficient (-), or indeterminate (?) as recommended by COSMIN.[14,15]

Results were summarized to produce an overall rating for each individual measurement property of every instrument. Next, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to grade the quality of the evidence and thereby the trustworthiness of the results. A risk of bias (as determined using the COSMIN Risk of Bias checklist), the consistency of the study results on measurement properties across studies and the sample size could all downgrade the evidence quality rating.[14]

Methods for generating recommendations for the measurement instruments of outcomes used for CMN were based on the methodological quality of the included studies and on the adequacy of an instrument. Four degrees of recommendation were assigned to the instruments included in this review (A-D) and adopted from previously performed studies:[16,17] category A, meets all requirements (positive rating for all boxes/measurement properties in the best evidence synthesis) and is recommended for use; B, meets two or more required quality items, but performance in all other required quality items is unclear, so the instrument has the potential to be recommended, depending on the results of further validation studies; C, exhibits low quality in at least one required quality criterion (≥1 rating of 'minus') and therefore is not recommended for further use; D, almost not validated, its performance in all or most relevant quality items is unclear, so further validation studies are needed.

RESULTS

Results Step 1: Identification and description of instruments used in previously published studies

Search strategy, quality assessment and data extraction

The update from the previously performed systematic review yielded a total of 450 unique references after deduplication. A total of 29 studies met the inclusion criteria including 27 original studies with a total of 1938 patients and two systematic reviews. The selection procedure is illustrated in the flow-chart of Figure 1.

Patient and CMN characteristics of the included studies are listed in Appendix 3. Most studies were conducted in Asia (45%), followed by Europe (35%) and the USA/Canada (10%). Two studies were conducted in the Middle East and one in Egypt. Thirteen studies had a prospective study design (45%). A total of 12 studies were retrospective (41%). Two studies were cross-sectional (7%). Two systematic reviews (7%) were detected with a total of 35 studies.

Similar to the previously performed systematic review, the quality of the studies included in the update was generally low. Most studies (55%) were rated as level 3 evidence (low evidence). All other studies, 13 in total (44%), were rated as level 4 (very low evidence). The level of evidence was mainly low because of small patient groups, the absence of control groups and retrospective study designs.

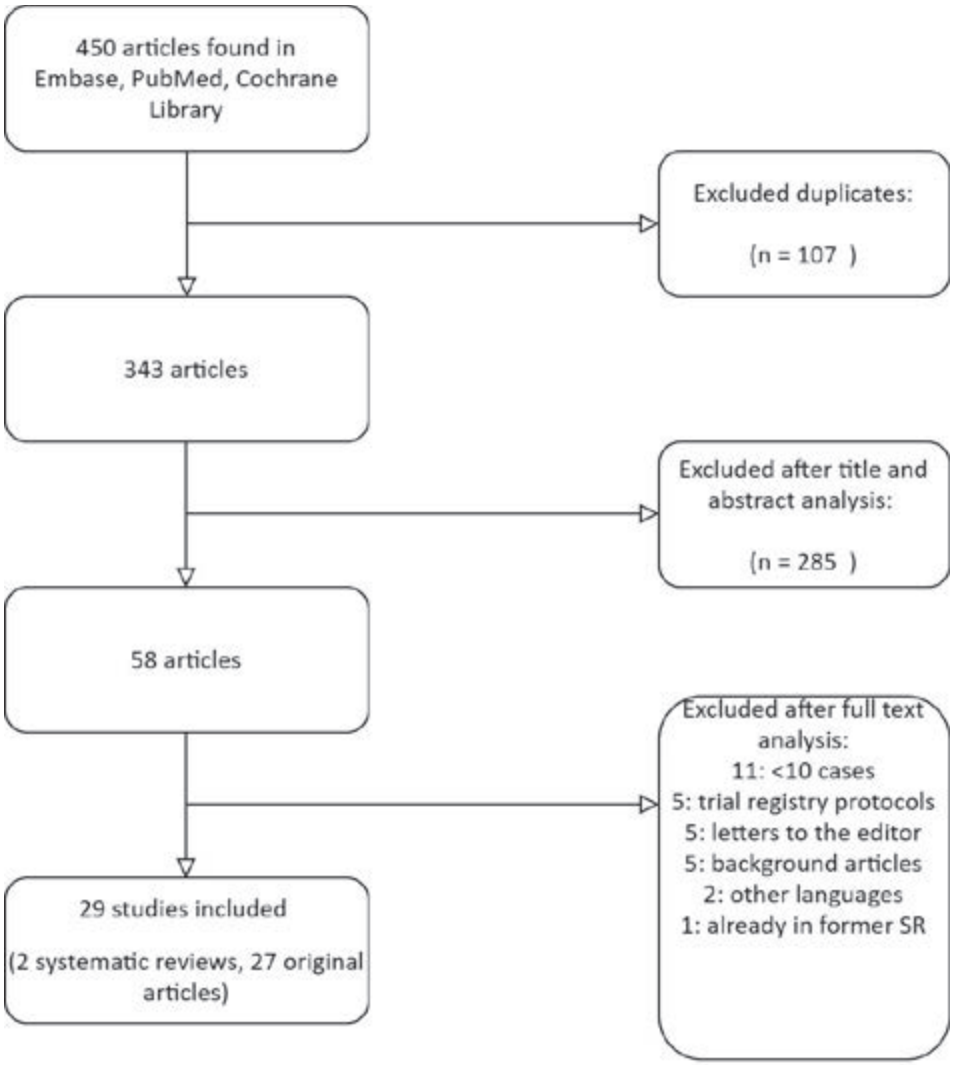

Figure 1. Search 1: Flow diagram

The number of included patients ranged from 15 to 293 CMN patients in the update, and the female to male ratio was 1.35:1. The mean patient age was 15.2 years (range 0–73 years) mentioned in 16 out of 29 studies.

We found different classification systems used for CMN, equally to the previous systematic review. For location, most studies reported a particular part of the body, but body parts were sometimes classified together. Size was defined in the following ways: the diameter in centimetres in PAS (11 studies) and the percentage of the total body surface area (TBSA) (four studies). The classification of Krengel et al. was used in five studies. Two studies used the '6B rule' to classify the location of giant CMN. Twelve studies did not define size according to a certain classification system.

Data synthesis

Table 2 shows the frequency of the core outcomes reported in the 29 studies of the update and their frequency in the sixty-three studies performed in the previous systematic review.[4] Table 3 shows the measurement instruments used to measure the core outcomes found in the previously performed systematic review and the update, including information on the instrument, the target population and whether it was a PROM or clinician reported.

Results Step 2: Evaluation of the quality of measurement instruments developed or validated for CMN

Search and study selection

The search provided 677 unique studies; Figure 2 shows the flow diagram of the study selection. Two studies met our inclusion criteria, with both evaluating one measurement property, internal consistency, of an instrument measuring the domain 'quality of life'.[18,19]

We did not find any development studies. Besides 'quality of life', there were no studies available for instruments measuring the core domains and outcomes developed or validated for the CMN population. Moreover, no clinician reported instruments nor rating systems, medical devices, or other instruments were developed or validated for CMN.

Evaluation of the methodological quality of the included studies

Both studies had scored a 'very good' for their methodological quality regarding the measurement property they assessed (Appendix 4).

Evaluation of the quality of the measurement properties, evidence synthesis and generating recommendations

The included studies evaluated the measurement property 'internal consistency' of the Paediatric Quality of Life Inventory (PedsQol) and the Children's Dermatology Life Quality Index (CDLQI) to

Table 2. Frequency of outcomes

		Reported previous SR		Reported update SR	
Core Domain	**Core outcome used in research**	**n**	**%**	**n**	**%**
Anatomy of skin	Size of CMN	1/63	2	3/29	10
	Colour of the CMN	31/63	49	5/29	17
	Texture of the CMN	21/63	33	3/29	10
	Satellite nevi number	10/63	16	0/29	0
Quality of life	Emotional distress	6/63	10	7/29	24
Neoplasm	Presence of melanoma	21/63	33	14/29	48
Nervous system	Neurological symptoms and signs	11/63	17	5/29	17
General adverse events	Wound problems of the CMN	32/63	51	11/29	38
	Scar problems	10/63	16	12/29	41
Pathology	Molecular characteristics	2/63	3	7/29	26

n: number of studies reporting the outcome; SR: systematic review

Table 3. Measurement instruments

Measurement instrument	Outcome measured*	Description of instrument	Target population	CR/ PROM
Anatomy of the skin (domain)				
Digital assessment of length in cm[45]	CMN lesion size and postoperative scar size	Digital measurement of the size of the lesion in two dimensions	S, M, L CMN Age NR	CR
Length in cm measured by a ruler[46]	Long diameter of nevi	To measure the long diameter in centimetres by using a ruler.	Size NR Age range: 10-103 m	CR
Rating system, self or proxy reported[47]	Percentage of nevus removal	Patients or caregivers were asked to rate removal percentages (<10%, 10–25%, >25–50%, >50–75%, >75%)	S, M, L, G CMN Mean age: 17.5 y [self] and 6.3 y [proxy]	PROM
Tracing on transparent film (area of resection in cm^2)[46]	Area of nevi before resection in cm^2	To measure the area by tracing the total nevus area onto a transparent film, being transposed onto paper divided into millimetres	Size NR Age range: 10-103 m	CR
L*a*b-colour space model (CIE-LAB) on clinical photos[48]	Lightening / colour change of CMN	A program using mathematical descriptions of all perceivable colours in three dimensions	S, M, L, G CMN Age range: 0-17.4 y	CR
Kilmer & Lee 5 point lightening scale[49,50]	Lightening of CMN	A 5-step scale to measure lightening of CMN colour after laser treatment: poor, fair, good, excellent, clear	S, M CMN Median age: 9 m Age range: 0-28 y	CR
Zaal & van der Horst 7-point repigmentaion scale[51]	Repigmentation	A 10-step scale to measure repigmentation after treatment: 1-4 mild, 5-7 moderate, 8-10 severe.	G CMN Age range: 0.4-36 y	
Self-made questionnaire by Kinsler et al.[52]	Colour lightening or darkening, hairiness, lumpiness, new CMN in unaffected skin at the edge of the treated area and development and number of new satellite lesions.	A questionnaire to measure changes in CMN appearance and development of new satellites	S, M, L, G CMN Mean ag: 2.9 y	PROM

Table 3. (continued)

Measurement instrument	Outcome measured*	Description of instrument	Target population	CR/ PROM
Estimation by specialist[53]	Hypopigmentation, hyperpigmentation, repigmentation, infection, erythema, scarring,	Reviewing of clinical photographs by clinician	Size NR Age range: 7-25 y	CR
Evaluation by specialist blinded to study[54]	Reduction pigmentation after treatment	Independent third party reviewed clinical photographs	Size NR Mean age: 12 y	CR
Investigator's Global Assessment (IGA) score for skin appearance[55]	Pigment clearance, erythema, hypopigmentation, hypertrophic scarring and texture irregularity	A 7-point scale to assess improvement of clinical outcomes before and after intervention: 1 worsened - 7 total improvement	Size NR Mean age 13.4 y	CR
Quality of life				
Paediatric Outcomes Data Collection Instrument (PODCI)[56]	Physical functioning, mobility, sports, pain/comfort, and happiness	To estimate functional health outcomes, musculoskeletal health, and QoL. It has been extensively reported in the orthopaedic surgery literature. Number of items: 86 Scoring method: Likert-scale, scores range from 0–3 for some items and 0–6 for others Total score range: 0 worse -100 best	Size/age NR	PROM
Children's Dermatology Life Quality Index (CDLQI)[19,57,58]	Skin discomfort, emotional, social and physical functioning, teasing/ bullying/ asking questions, sleep, effect of treatment on QoL	To assess proxy- and self-reported skin-related QoL No of items: 10 questions Scoring methods: 4-Point Likert scale Total score range: sum score, range, 30 best - 0 worst	S, M, L, G CMN Age range: 4-18 y	PROM

Table 3. (continued)

Measurement instrument	Outcome measured*	Description of instrument	Target population	CR/ PROM
Pediatric Quality of Life Inventory 4.0 (PedsQol)[18]	Health related QoL, Emotional functioning, Social functioning	To assess self- and proxy reported Health related QoL Number of items: 21 Scoring method: 5-point Likert scale Total score range: 0 never - 4 almost always	S, M, L, G CMN Mean age: 6.3 y	PROM
Strengths and Difficulties Questionnaire (SDQ)[18]	Psychological adjustment, emotional conduct, hyperactivity, inattention	To assess self- and proxy-reported emotional and behavioural problems Number of items: 25 Scoring method: 3-options, not true – somewhat true – certainly true Total score range: sum score 0 - 40	S, M, L, G Mean age: 6.3 y	PROM
Post-Traumatic Stress Disorder Semi structured Interview (PTSDSSI)[59]	Anxiety, depression, withdrawal, somatic complaints, attention problems, thought problems, social problems, rule-breaking behaviour, and aggressive behaviour	To assess the frequency of PTSS Number of items: 29 Scoring method: mixed response no 0, sometimes 1, yes 2	Size NR Mean age: 4.2 y	PROM
Teacher Report Form[60]	Academic competence, adaptive functioning, inattention, hyperactivity, impulsivity, social problems, thought problems, anxious, and depressed	To rate the child's behavioural competence and behavioural/emotional problems Number of items: 113 Scoring method: 3-point Likert scale 0 Not True, 1 Somewhat or Sometimes True, and 2 Very True or Often True and fill-in blanks questions	L CMN Mean age: 12.6 y	PROM
Estimation by parents[61]	Estimation by parents of global QoL	Global QoL	S, M, L, G CMN Age NR	

Table 3. (continued)

Measurement instrument	Outcome measured*	Description of instrument	Target population	CR/ PROM
Neoplasms (Cancer)				
Questionnaire for presence of malignancy (proxy report)[18,19,47]	Presence of Melanoma	To indicate the patients' health status concerning chronic diseases such as the presence of melanoma.	S, M, L, G CMN Various ages	PROM
Histopathological biopsy (unspecified assessor)[62,63]	Presence of Melanoma	To assess histologically for melanoma presence in biopsied CMN lesions	S, M, L, G CMN Various ages	CR
Clinical photos and Dermascopy[64]	Presence of Melanoma	A noninvasive and in vivo diagnostic tool to visualize subtle clinical patterns of skin structures invisible to the unaided eye.	Size NR Mean age: 39.2 y	CR
Nervous system				
Questionnaire (proxy report), presence of neurological problems[18,19,47]	Neurological symptoms and signs	To indicate the patients' health status concerning chronic diseases such as the presence of neurological problems.	S, M, L, G CMN Various ages	PROM
EEG, and classification criteria of ILAE[65]	Focal epilepsy	To assess diagnosis of focal epilepsy an EEG was performed and was classified according to the ILAE criteria.	G CMN, Median age: 5 m	CR
Developmental milestones assessment[65]	Cognitive developmental delay	To distinguish cognitive development as normal or delayed the developmental milestones in children were used.	G CMN, Median age: 5 m	CR
Physical evaluation by physician[66]	Neurological symptoms and signs	Assessment of neurological symptoms and signs by a clinician	M CMN Age range: 9-43 y	CR
Adverse events				
Clinical photographs and visual assessment (surgeons)[45,53,67]	Wound problems of the CMN Scar problems	Based on photographs, the scars and wound problems were visually assessed by clinicians	S, M, L CMN and 'kissing naevus' Various ages	CR

Table 3. (continued)

Measurement instrument	Outcome measured*	Description of instrument	Target population	CR/ PROM
Vancouver Scar Scale (VSS) (3 independent evaluators)[68]	Scar appearance, scar pigmentation, scar height/ thickness, scar pliability, and scar vascularity	A tool for scar assessment, with the highest score indicating the worst scar formation and 0 suggesting the best outcome 0 best outcome – 4 worst outcome)	M CMN Mean age: 20.4 y	CR
Investigator's Global Assessment (IGA) score for skin appearance[55]	Pigment clearance, erythema, hypopigmentation, hypertrophic scarring and texture irregularity	A 7-point scale to assess improvement of clinical outcomes before and after intervention: 1 worsened - 7 total improvement	Size NR Mean age: 13.4 y	CR
Own assessment (self/proxy report)[18,47]	Healing issues or infections	Patients or parents could indicate if they had wound healing problems through a questionnaire	S, M, L, G CMN Various ages	PROM
Patient and Observer Scar Assessment Scale (POSAS-score)[45,47,51,69]	Scar appearance	Observer and patient scale Number of items: 6 Scoring method: 10-step score, 10 worst imaginable scar Total score range: 6 reflects normal skin – 60 the worst imaginable scar	S, M, L, G CMN Various ages	CR/ PROM
Physical examination[70]	Infection, hypertrophic or atrophic scarring	To assess occurrence of adverse events a physical examination was performed during follow up.		CR
Self-made questionnaire by August et al.[66]	General adverse events	Participants could indicate if they had any side-effects from the treatment? Rating: 1-10 (10 being worst)	M CMN Age range: 9-43 y	CR
Pathology				
Electrochemiluminescence immunoassay[71]	Molecular characteristic	To determine S-100B protein concentrations in peripheral blood in a blinded manner	M, L, G CMN Mean age: 5.7 y	CR
Phosphokinase-array[72]	Molecular characteristic	To analyse expression of effector proteins of the MAPK/Akt-signalling pathways	L, G CMN Median age 8 m	CR

Table 3. (continued)

Measurement instrument	Outcome measured*	Description of instrument	Target population	CR/ PROM
PCR - MC1R screening blood/saliva samples[73]	Molecular characteristic	To amplify two overlapping fragments of the MC1R-coding region in blood and saliva samples	M, L, G CMN Mean age: 16.8 y	CR
Sanger sequencing[48]	Molecular characteristic	Germline MC1R-genotyping was undertaken on leucocyte DNA	S, M, L, G CMN Age range: 0.0-17.2 y	CR
Immunohistochemistry[63]	Molecular characteristic	To assess the proliferative indices in Giant CMN lesions by using proliferation markers (Ki67, Melan-Am S-100, HMHB-45, SOX-10)	G CMN Median age: 6 y	CR
Single-base extension SNaPshot assay PCR[74]	Molecular characteristic	To analyse recurrent point mutation in KRAS codons G12, G13, and Q61; NRAS codons G12, G13, and Q61; HRAS codons G12, G13, and Q61; GNAQ exon 5; and BRAF codon V600 in proliferative nodule tissue	S, M, L, G CMN Age range: 0-84 y	CR

*The specific core outcome of the core domain in underlined

CR: clinician reported, PROM: patient reported outcome measure, S: small, M: medium, L: large, G: giant, NR: not reported, y: years, m: months, QoL: quality of life

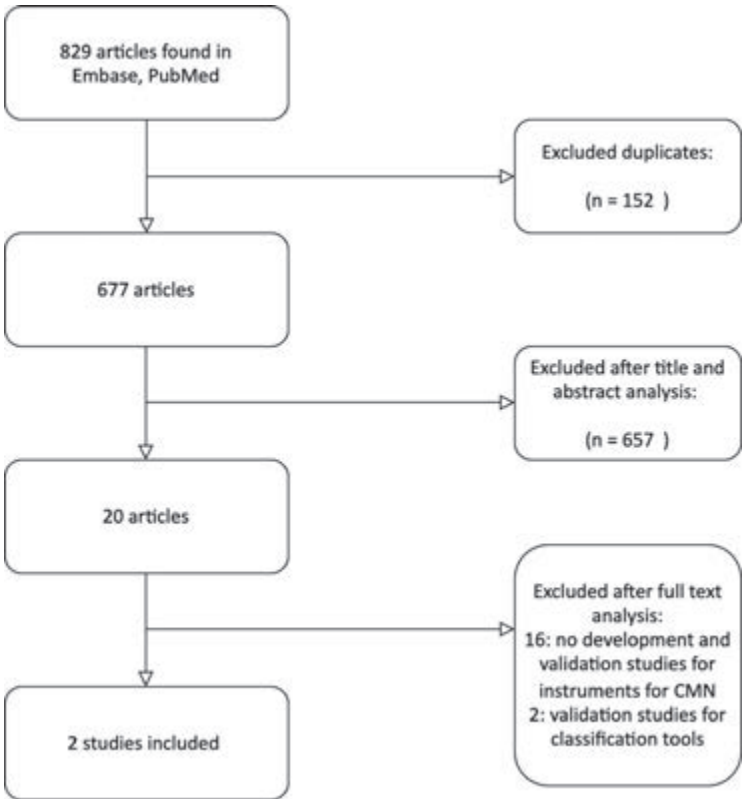

Figure 2. Search 2: Flow diagram

measure the domain 'quality of life' including the outcome 'emotional distress'.[18,19] The following measurement properties were not evaluated: structural validity, reliability, hypotheses testing, cross-cultural validity and/or responsiveness. We did not find any study evaluating these measurement properties in other instruments used for the CMN population.

Masnari et al studied internal consistency of the PedsQol. They recruited their patients worldwide and included 235 children with a mean age of 6.3 years and a mean TBSA score of 13.14 per cent. About half of the included children did not have any surgery to remove the CMN.

Neuhaus et al. studied internal consistency of the CDLQI and recruited their patients worldwide as well. They included 163 patients. The mean age of children in their proxy report group (4-18 years) was 9.3 years and in the self-report group (14-18 years) was 16.3 years. They had a mean TBSA score of 13.6 and 16.1, respectively. More than half of the patients underwent partial removal of their CMN.

Table 4 shows the rating of the results and level of evidence.

Despite most Cronbach's alpha item scores being >0.7, all ratings were scored as indeterminate due to the absence of "at least low evidence for sufficient structural validity", which is a requirement for a sufficient rating for internal consistency. Table 5 shows the feasibility aspects of these instruments. The best evidence synthesis is shown in Table 6. As only the internal constancy of

these questionnaires had been evaluated, they receive recommendation D, almost not validated. Its performance in all or most relevant quality items is unclear, further validation studies are needed.

DISCUSSION

This study is the first step of selecting the core measurement instruments for the COS of CMN. We showed a systematic overview of the instruments used to measure core outcomes for CMN published in addition to a previously performed study.[4] In addition, studies on measurement properties of instruments used for the CMN population were evaluated. We found a wide heterogeneity in outcomes and measurement instruments in the included studies and there were

Table 4. Study characteristics and rating of internal consistency

Measurement instrument	Sample size	Results (Cronbach's α)	COSMIN Risk of Bias score[2]	Level of evidence[3]	Rating of results[6]
PedsQol[18]					
1-12m	31	0.76 - 0.94[1]	Very good	Low[4]	?[7]
13-24m	32	0.72 - 0.91[1]	Very good	Low[4]	?[7]
2-18y	170	0.53 - 0.94[1]	Very good	Moderate[5]	?[7]
CDLQI[19]					
Proxy	135	0.83	Very good	High	?[7]
Self- report	28	0.87	Very good	Low[4]	?[7]

1: Range of Cronbach's α: for each item, Cronbach's α was measured separately.
2: Based on the COSMIN risk of bias tool (Appendix 4).
3: After application of the GRADE approach.
4: Downgraded because of the sample size.
5: Downgraded because of the indirectness, as the exact sample size of the size of the 5–18 years and < 5 years group is not reported.
6: Rating of results was either sufficient (+), insufficient (–), or indeterminate (?).
7: Rated as indeterminate due to the absence of evidence for sufficient structural validity.

Table 5. Aspects of feasibility

Instrument	Available for ages	Available translations	Completion time	Licensing/costs
CDLQI Self- and proxy reported	4-12 years proxy and self-reported Adult version available (DLQI)	115 Languages	2 minutes	Free for clinicians, free for nonacademic research (not funded externally); external funded trial fees dependent on sample size
Self- and proxy PedsQoL	2-18 years proxy and self-reported	176 translations	4 minutes	The costs are determined based on, the type of research, the source of funding for the research and the sample size.

Table 6. Best evidence synthesis and recommendations

Evaluated measurement properties according to the COSMIN taxonomy[12]	PedsQol	CDLQI
	Masnari et al. (2019)[18]	Neuhaus et al. (2020)[19]
Internal consistency	?	?
Reliability	NA	NA
Measurement error	NA	NA
Content validity	NA	NA
Structural validity	NA	NA
Hypotheses testing	NA	NA
Cross-cultural validity	NA	NA
Responsiveness	NA	NA
Recommendation	Category D	Category D

For each measurement property, the methodological quality of the study is reported as sufficient (+), insufficient (−), or indeterminate (?), *NA* not available (analysis was not performed for this measurement property).

Recommendations: category A, meets all requirements (positive rating for all boxes in the best evidence synthesis) and is recommended for use; B, meets two or more required quality items, but performance in all other required quality items is unclear, so that the instrument has the potential to be recommended, depending on the results of further validation studies; C, low quality in at least one required quality criteria (≥1 rating of 'minus') and therefore is not recommended to be used anymore; D, almost not validated. Its performance in all or most relevant quality items is unclear, further validation studies are needed.

no studies reporting all core outcomes. We showed that research on measurement properties of these instruments is limited. Therefore, none of the instruments could be recommended based on the quality of their measurement properties and further validation studies are needed.

Research on CMN is growing; this current update included twenty-nine studies published in a period of two years, while the previously performed systematic review includes sixty-three studies in a period of twelve years.[4] Uniformity is therefore of utmost importance to enable combination and comparison of studies. However, heterogeneity in outcomes still exists, highlighting the importance of a COS. Besides heterogeneity in outcomes, we found heterogeneity in CMN classifications as well. To enhance uniformity in CMN care and research, we recommend using the consensus derived, internationally used classification developed by Krengel et al[20] and qualified (the "6B"[21] and "biker glove" distributions[22]) for the CMN location.

Relevant stakeholders should reach consensus over which instruments should be validated for CMN. In this process, the feasibility of instruments should be considered as well; instruments should be easy and quick to use and should be low-cost or free of charges. Similar systematic reviews investigating the measurement properties according to the COSMIN checklist are available for diseases similar to CMN such as vitiligo, vascular malformations, capillary malformation and burn scars.[17,23-25] Although these studies also revealed a low quality of measurement instruments validated for their particular patient population, some of their recommendations may inform which instruments should be validated for CMN.

The domain 'anatomy of the skin' or 'skin appearance' is often measured by disease specific measurement instruments, a probable result of the unique manifestations of every skin disease. For CMN, we found both objective instruments, such as L*a*b* colour-space model (CIE-LAB) measurements, as well as subjective rating systems (Table 3). The systematic reviews of similar

anomalies revealed that 'skin appearance' is generally measured by questionnaires or rating systems completed by both clinicians and patients. These types of instruments are often low-cost and quick and easy to use. For vitiligo, the most effective instrument that measures the size of a lesion was the disease specific (Self-Assessment) Vitiligo Extent Score ((SA)-VES).[26] For capillary malformation there were only low-quality clinician reported rating systems available.[25] None of these rating systems were developed by asking patients (or their parents) which outcomes are important to them.[25] The systematic review for vascular malformations also showed low-quality rating systems.[17] Therefore, a new PROM questionnaire is now in development; the Outcome Measures for Vascular Malformations (OVAMA) questionnaire.[27] For burn scars, both PROMs, clinician reported rating systems and objective measurement instruments are available.[28] For instance, objective instruments to measure colour of burn scars include: reflectance spectroscopy (colourimetry/ spectrophotometry), laser imaging or computerized analysis of digital photographs.[29]

Various questionnaires are available to measure the domain 'quality of life', including the outcome 'emotional distress', in patients with a skin disease. To measure health related 'quality of life', disease specific and generic instruments are available. In addition, for skin conditions, dermatology specific questionnaires are available.[30] Disease specific instruments measure the impact of a specific condition on the different aspects of 'quality of life', while generic instruments measure the overall 'quality of life' of a subject allowing comparison between a group of patients with a certain disease and their peers of the general populations. The systematic review evaluating 'quality of life' instruments for burn scars showed that burn scar specific instruments have the best measurement properties.[24]

No disease specific questionnaires are available for CMN. Rare diseases may be best measured with a generic 'quality of life' measurement instrument, as the development of a high-quality disease specific instrument is hindered by the limited number of subjects to validate the instrument. An existing generic instrument may be the best option for CMN, as there are various generic quality of life PROMs available. The systematic review for capillary malformations provisionally recommends the PROMs Perceived Stress Questionnaire (PSQ) or the DLQI. The DLQI was proposed by the vitiligo group as well.[23] The systematic review for vascularity malformations states that the Short Form-36 (for adults) and PedsQol (for children) seem to be the most appropriate generic instrument.[17] However, this same research group showed in a subsequent study that these questionnaires do not sufficiently measure effectiveness i.e., change in the 'quality of life' before and after treatment. They therefore advise using Patient-Reported Outcomes Measurement Information System (PROMIS).[27,31] The use of PROMIS is advised for rare diseases and may be suitable to use for CMN.[32-34] PROMIS consists of item banks for every subdomain of 'quality of life' which have been extensively validated in large populations. An item bank is a large set of questions for multiple 'quality of life' outcomes. These item banks are available in short form and with computer adaptive testing. With computer adaptive testing, the most relevant questions for an individual will be asked based on their previous answers. This decreases the number of questions and causes accurate and person-centred outcomes. In contrast to other generic instruments, PROMIS facilitates the measurement of the outcome 'emotional distress' without measuring the outcomes 'social and physical functioning'.

For measuring the domain 'neoplasm' a panel of stakeholders agreed that the core outcome 'presence of melanoma' should always be measured in care and research. In this study, we found

'presence of melanoma' to be measured by self/proxy report of patients or their parents through online questionnaires or by pathological confirmations. In future research, a consensus should be reached regarding whether melanoma should be confirmed by pathology for all research or if an anamnesis of patients or parents is sufficient for survey studies.

The domain 'neurology' is defined by the outcome 'neurological symptoms and signs'. A consensus procedure with international stakeholders should be held to decide how neurological symptoms and signs should be measured. For instance, a questionnaire screening for the most common symptoms or signs could be used and/or stakeholders could decide that neurological examinations should as a standard be performed by, for example, a neurologist or paediatrician. None of the studies included in this study or the previously performed systematic review used a questionnaire for specific symptoms and signs of CMN patients.[4] Questionnaires to measure developmental delay or epilepsy are available for clinicians and for patients.[35-38] Questionnaires to measure general neurology disorders are available and are frequently developed for patients in low- and mid-income countries.[39-41] If relevant stakeholders decide that a neurological questionnaire should be used for the core outcome set, future research should assess the accuracy and feasibility of the questionnaires for neurological involvement in CMN patients or decide to develop a CMN specific instrument.

The domain 'general adverse event' includes the core outcomes 'wound problems of the CMN' and 'scar problems'. Classifications such as The Common Terminology Criteria for Adverse Events (CTCAE), the Medical Dictionary for Regulatory Activities (MedDRA) or the Clavien-Dindo Classification can be consulted to classify the severity or define the adverse events. A consensus should be reached over which classification should be used to report adverse events. For the outcome 'scar problems' the Patient and Observer Scar Assessment Scale (POSAS) is used in four CMN studies. A new version of the POSAS is now in development, in which the patients' opinion on scar appearance is implemented. A consensus with international stakeholders should be reached over which standard instrument and classification system should be used to report adverse events.

The importance of the outcome 'molecular characteristics' of the domain 'pathology' is growing in the research of CMN. A quarter of the studies included in this systematic review measured this outcome. Increasing knowledge regarding molecular characteristics of CMN could help in the future to estimate the risk of melanoma or neurological complications.[42]

Moreover, new pharmacological therapies may be developed that could be offered to patients with a certain DNA mutation.[43,44] We showed that various molecular characteristics are reported in literature. For now, alongside all relevant stakeholders, we have decided that all molecular characteristics that are already measured for care purposes should be standard documented in research of CMN in a standardised manner.

Strength and limitations:

We systemically reviewed the availability and quality of measurement instruments of CMN according to the COMET, CS-COUSIN and COSMIN guidelines. We included a broad range of studies on CMN including both outcomes and instruments for studies of intervention treatment and watchful waiting. A limitation could be that we only included studies written in English or Dutch, however,

there is a wide geographical spread in the included publications. Because of the heterogeneity in the classification of CMN, we could not describe differences between measurement instruments used for different CMN size or location (visible/non-visible) categories.

Future perspectives

This systematic review was the first step of developing the COMS of the COS of medium-to-giant CMN care and research. Relevant stakeholders should reach a consensus over which measurement instruments should be used for the domains and outcomes of CMN. Firstly, relevant stakeholders should decide whether every domain and outcome should be clinician and/or patient reported and if questionnaires, rating systems, clinical devices or other instruments are needed. In addition, they should consider the feasibility of an instrument. Secondly, relevant stakeholders should decide which measurement instruments should be developed or validated for the CMN patient population. This study informs the instrument selection and/or the development of new instruments.

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SUPPORTING INFORMATION

Appendix 1 - Search 1

Pubmed:

("Nevus"[Mesh] OR nevus OR nevi OR naevus OR naevi OR birthmark*)
AND
(congenital* OR bathing trunk* OR garment OR giant OR tierfell* OR gigantic OR inborn OR hereditary OR newborn OR "congenital" [Subheading])
NOT
(connective tissue[tiab] OR anaemicus[tiab] OR elasticus[tiab] OR inelasticus[tiab] OR depigmentosus[tiab] OR mucinosis[tiab] OR lipomatosus[tiab] OR sebaceus[tiab] OR blue[tiab] OR comedonicus[tiab] OR spindle[tiab] OR sponge[tiab] OR woolly[tiab] OR spilus[tiab] OR spider[tiab] OR flammeus[tiab] OR Jadassohn[tiab] OR Ota[tiab] OR Becker[tiab] OR Sutton[tiab] OR Unna[tiab] OR neurofibromatosis[tiab] OR pancreas*[tiab] OR placenta[tiab])
NOT
("Case Reports" [Publication Type] OR case report*)

Embase(Ovid):

#	Searches
1	exp nevus/ or (nevus or nevi or naevus or naevi or birthmark*).ti,ab,kw.
2	(congenital* or bathing trunk* or garment or giant or tierfell* or gigantic or inborn or hereditary or newborn).ti,ab,kw. or cn.fs.
3	1 and 2
4	(connective tissue or anaemicus or elasticus or inelasticus or depigmentosus or mucinosis or lipomatosus or sebaceus or blue or comedonicus or spindle or sponge or woolly or spilus or spider or flammeus or Jadassohn or Ota or Becker or Sutton or Unna or neurofibromatosis or pancreas* or placenta).ti,ab,kw.
5	3 not 4
6	limit 5 to conference abstract status
7	5 not 6
8	case report/ or case report*.ti,ab,kw.
9	7 not 8

Cochrane Library:

ID	Search	Hits
#1	nevus or nevi or naevus or naevi or birthmark*:ti,ab,kw (Word variations have been searched)	
#2	congenital* or bathing trunk* or garment or giant or tierfell* or gigantic or inborn or hereditary or newborn:ti,ab,kw (Word variations have been searched)	

Appendix 2 - COSMIN filter

COSMIN sensitive search filter for measurement properties

(instrumentation[sh] OR methods[sh] OR Validation Studies[pt] OR Comparative Study[pt] OR "psychometrics"[MeSH] OR psychometr*[tiab] OR clinimetr*[tw] OR clinometr*[tw] OR "outcome assessment (health care)"[MeSH] OR outcome assessment[tiab] OR outcome measure*[tw] OR "observer variation"[MeSH] OR observer variation[tiab] OR "Health Status Indicators"[Mesh] OR "reproducibility of results"[MeSH] OR reproducib*[tiab] OR "discriminant analysis"[MeSH] OR reliab*[tiab] OR unreliab*[tiab] OR valid*[tiab] OR coefficient[tiab] OR homogeneity[tiab] OR homogeneous[tiab] OR "internal consistency"[tiab] OR (cronbach*[tiab] AND (alpha[tiab] OR alphas[tiab])) OR (item[tiab] AND (correlation*[tiab] OR selection*[tiab] OR reduction*[tiab])) OR agreement[tiab] OR precision[tiab] OR imprecision[tiab] OR "precise values"[tiab] OR test–retest[tiab] OR (test[tiab] AND retest[tiab]) OR (reliab*[tiab] AND (test[tiab] OR retest[tiab])) OR stability[tiab] OR interrater[tiab] OR inter-rater[tiab] OR intrarater[tiab] OR intra-rater[tiab] OR intertester[tiab] OR inter-tester[tiab] OR intratester[tiab] OR intra-tester[tiab] OR interobserver[tiab] OR inter-observer[tiab] OR intraobserver[tiab] OR intra-observer[tiab] OR intertechnician[tiab] OR inter-technician[tiab] OR intratechnician[tiab] OR intra-technician[tiab] OR interexaminer[tiab] OR inter-examiner[tiab] OR intraexaminer[tiab] OR intra-examiner[tiab] OR interassay[tiab] OR inter-assay[tiab] OR intraassay[tiab] OR intra-assay[tiab] OR interindividual[tiab] OR inter-individual[tiab] OR intraindividual[tiab] OR intra-individual[tiab] OR interparticipant[tiab] OR inter-participant[tiab] OR intraparticipant[tiab] OR intra-participant[tiab] OR kappa[tiab] OR kappa's[tiab] OR kappas[tiab] OR repeatab*[tiab] OR ((replicab*[tiab] OR repeated[tiab]) AND (measure[tiab] OR measures[tiab] OR findings[tiab] OR result[tiab] OR results[tiab] OR test[tiab] OR tests[tiab])) OR generaliza*[tiab] OR generalisa*[tiab] OR concordance[tiab] OR (intraclass[tiab] AND correlation*[tiab]) OR discriminative[tiab] OR "known group"[tiab] OR factor analysis[tiab] OR factor analyses[tiab] OR dimension*[tiab] OR subscale*[tiab] OR (multitrait[tiab] AND scaling[tiab] AND (analysis[tiab] OR analyses[tiab])) OR item discriminant[tiab] OR interscale correlation*[tiab] OR error[tiab] OR errors[tiab] OR "individual variability"[tiab] OR (variability[tiab] AND (analysis[tiab] OR values[tiab])) OR (uncertainty[tiab] AND (measurement[tiab] OR measuring[tiab])) OR "standard error of measurement"[tiab] OR sensitiv*[tiab] OR responsive*[tiab] OR ((minimal[tiab] OR minimally[tiab] OR clinical[tiab] OR clinically[tiab]) AND (important[tiab] OR significant[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR (small*[tiab] AND (real[tiab] OR detectable[tiab]) AND (change[tiab] OR difference[tiab])) OR meaningful change[tiab] OR "ceiling effect"[tiab] OR "floor effect"[tiab] OR "Item response model"[tiab] OR IRT[tiab] OR Rasch[tiab] OR "Differential item functioning"[tiab] OR DIF[tiab] OR "computer adaptive testing"[tiab] OR "item bank"[tiab] OR "cross-cultural equivalence"[tiab])

COSMIN FILTER adapted for EMBASE(Ovid)

methodology/ or exp health status indicator/ or Sickness Impact Profile/ or clinical assessment/ or clinical assessment tool/ or outcome assessment/ or outcomes research/ or medical assessment/ or measurement/ or exp measurement precision/ or exp measurement accuracy/ or measurement

error/ or exp systematic error/ or exp performance measurement system/ or exp measurement repeatability/ or intermethod comparison/ or data collection method/ or system analysis/ or validation study/ or feasibility study/ or exp quality control/ or rating scale/ or scoring system/ or summated rating scale/ or qualitative analysis/ or quantitative analysis/ or correlation analysis/ or "constants and coefficients"/ or correlation coefficient/ or cronbach alpha coefficient/ or kappa statistics/ or correlation function/ or exp reliability/ or discriminant analysis/ or exp validity/ or valid*.hw. or factorial analysis/ or observer variation/ or psychometry/ or (audit or audits or psychometr* or clin?metr* or ((outcome* or clinical or observer* or utility or satisfaction or QoL or quality of life or score or scores or method or methods or physicians or dermatologists or modelling or objective) adj3 assessm*) or clinical asses* or outcome measure* or observer variation* or reproducib* or reliab* or unreliab* or valid* or coefficient or homogeneity or homogeneous or ((internal or external) adj3 (consistency or inconsistency)) or cronbach* or (item and (correlation* or selection* or reduction*)) or ((item or items) adj3 (discriminant* or convergent* or divergent*)) or agreement or precision or imprecision or (precise adj values) or (test and retest) or accuracy test* or stability or interrater or intrarater or intertester or intratester or interobserver or intraobserver or intertechnician or intratechnician or interexaminer or intraexaminer or interassay or intraassay or interindividual or intraindividual or interparticipant or intraparticipant or ((inter or intra) adj (rater or tester or observer or technician or examiner or assay or individual or participant)) or kappa or kappa's or kappas or repeatab* or ((replicab* or repeated) and (measure or measures or findings or result or results or test or tests)) or generaliza* or generalisa* or concordance or (intraclass and correlation*) or discriminative or (known adj group) or (factor adj (analy* or structure*)) or dimension* or interscale or inter-scale or interscales or inter-scales or subscale* or sub-scale* or ((multitrait* or multi-trait*) and (scaling or scale*)) or error or errors or ((individual or interval or rate) adj variability) or (variability adj5 (analy* or values)) or (uncertainty and (measurement or measuring)) or sensitiv* or responsive* or ((limit or limits) and detection) or ((minim* or lowest) adj2 detectable adj2 (concentration* or dose* or level* or amount*)) or interpretab* or (small* and (real or detectable) and (change or difference)) or meaningful change* or ((minimal* or minimum) adj2 (meaningful or important or detectable or real or identifiable or relevant) adj3 (change* or difference* or improvement*)) or ((minimal or minimally or clinical or clinically) and (important or significant) and (change* or difference* or improvement*)) or (MDC adj2 value*) or MCID or MCIDs or MICD or MICDs or MCII or MCIC or MCICs or ((ceiling or floor) adj2 effect*) or item response* or IRT or rasch or ((differential or fit) adj2 item*) or DIF or computer adaptive test* or item bank* or cross-cultural equivalen*).tw,ot,kw.

Appendix 4. Study characteristics

Primary author	Year	Medical Center	Country	Study design	No. of patients	Patient Age (if possible: mean (range; median))	Female: male ratio
AL Mutairi H. et al.(1)	2020	Multicenter	Saudi-Arabia	Systematic Review	595	Unreported	Unreported
Alkureishi L. et al.	2018	Shriners Hospital for Children Chicago	USA	Retrospective	19	Unreported	Unreported
Ben-Ari A. et al.	2020	Hadassah Medical Center	Israel	Prospective	30	Range 1 to 13 years (mean 4.23 years, median 3.1 years)	1,1:1
Calbet-Llopart M. et al.	2020	Multicenter	Spain, France	Prospective	166	(mean 16.81 years, median 16.54 years)	1,63:1
Carmen Ceballos-Rodríguez, M. et al.	2021	La Paz University Hospital - Madrid	Spain	Retrospective	136	Range 1 month to 59 years; median 9 years	1,56
Cho H. et al.	2019	Hanyang University Seoul Hospital	South-Korea	Prospective	15	Range 13 to 73 years (mean 26.0 years)	02:01
Elmelegy N. et al.	2020	Tanta University - Gharbia	Egypt	Prospective	25	Range 2 to 45 years (mean 18 years)	1,5:1

Size CMN	Location CMN	Classification system used	Aim Intervention used	Mean follow up (range)	Level of evidence
small to giant CMN	Unreported	PAS	Evaluation of treatment	Unreported	3-
			Watchful waiting		
			Surgical intervention (excision, serial excision, curettage, tissue expander, dermabrasion)		
			Laser		
Unreported	Unreported	Unreported	Evaluation of treatment	14 years (range 2 to 21 years)	3
			Surgical intervention (Excision with reconstruction with skin flap)		
Unreported	Back, head, abdomen, buttocks and other (knee, groin, arm, shoulder blades, hand)	Unreported	Post-traumatic stress symptoms evaluation	4 months	3
			Surgical intervention (not specified)		
medium to giant CMN	Head, Head and Trunk, Extremities	Krengel: medium to giant CMN, 6B: giant CMN only	Association of MC1R variants with CMN characteristics	Unreported	3
			Unreported		
giant CMN	Craniofacial, Extremities, Trunk	PAS/6B	Evaluation of treatment	Unreported	4
			Surgical intervention (Excision)		
small to medium kissing nevus	eyelids	PAS	Evaluation of treatment	10 months (range 3–19 months)	4
			CO2 Laser		
small to medium CMN	Nasal and perinasal region	PAS	Evaluation of treatment	1.0 year (range 6 months to 1.5 years)	4
			Carbon dioxide cryotherapy		

Appendix 4. (continued)

Primary author	Year	Medical Center	Country	Study design	No. of patients	Patient Age (if possible: mean (range; median))	Female: male ratio
Fahradyan A. et al.	2019	Multicenter	USA	Retrospective	32	Range 3.3 months to 15.8 years (mean 4.4 years; median 4.5 years)	1,46:1
Funayama E. et al.	2019	Hokkaido University Hospital	Japan	Prospective	19	Range 1 month to 6 years (median 9 months)	Unreported
Gu Y. et al.	2019	Shanghai Ninth People's Hospital	China	Prospective	20	Unreported	2,3:1
Han J. W. et al.	2021	Inje University School of Medicine	Korea	Retrospective	78 (42 anchoring/36 conventional)	n=42 (mean 14.2 years, SD 3.7 years) n=36 (mean 17.6 years, SD 4.7 years)	Unreported
Hong S. et al.	2019	National Hospital of Dermatology and Venereology and Saint Paul Hospital	Vietnam	Prospective	20	Unreported	Unreported
Kim J. et al.	2019	Ajou University Hospital	South-Korea	Prospective - observational	100	Range 10 months to 103 months	1,7:1
Kim M. J. et al.	2020	Ajou University School of Medicine	Korea	Retrospective	55 (24 single/31 serial)	mean 6.59 years, SD 7.76 years	1,38
Malladi N. et al.	2020	KEM Hospital - Mumbai	India	Cross-sectional	44	Range 0 to 20 years	unspecified

Size CMN	Location CMN	Classification system used	Aim Intervention used	Mean follow up (range)	Level of evidence
small to giant CMN	Face (eyebrows, eyelid margins, nasal alae)	Krengel (PAS)	Estimate prevalence of melanoma Surgical intervention	5.6 years (range 1.0 to 14.4 years)	3
medium CMN	head, neck, trunk, limb	Unreported	Evaluation of treatment Laser (PDL & QSRL)	1 year	4
Unreported	Face (eyelid, peri-orbital region)	Unreported	Evaluation of treatment Laser (CO2/ER:YAG/ combination)	20.5 months (range 6 to 48 months)	4
small to large CMN	Face, Arm, Leg, Back, Abdomen	Unreported	Evaluation of treatment Surgical intervention (de-epithelialized dermal flaps)	n=42 (mean 12.2 months, SD 2.4 months) n=36 (mean 14.8 months, SD 4.7 months)	3
giant CMN	Unreported	Unreported	Evaluation of treatment Surgical intervention (Excision)	6.0 months	4
area before resection (in cm2) & long diameter (in cm)	trunk, face, scalp, extremities	Total Body Surface Area (TBSA) and long diameter	Evaluation of treatment Surgical intervention (Excision)	Unreported	4
giant CMN	Head, Lower extremity, Upper extremity, Back, Trunk	Unreported	Evaluation of treatment Surgical intervention (Excision)	Mean 23.74 months, SD 28.20 months	4
Unreported	Unreported	Unreported	Evaluation of Clinical, epidemiological and dermoscopic patterns Unreported	no follow up	4

Appendix 4. (continued)

Primary author	Year	Medical Center	Country	Study design	No. of patients	Patient Age (if possible: mean (range; median))	Female: male ratio
Masnari O. et al.	2019	University Children's Hospital - Zurich	Switzerland	Cross-sectional	235	Range 1 month to 18 years (mean 6.3 years; median 5.0 years)	0,93:1
Mosa A. et al.	2019	Hospital for Sick Children - Toronto	Canada	Prospective	30	Range 1 to 25 years (mean 9.2 years, median 10 years)	1,73:1
Neuhaus K. et al.	2020	University Children's Hospital - Zurich	Switzerland	Prospective	163	Range 4 to 18 years	1,46:1
Neuhaus K. et al.	2020	University Children's Hospital Zurich	Switzerland	Retrospective	44 patients (self-report) and 249 (proxy-report)	n=44 Range 14 to 24 years (mean 17.50 years, median 2.25 years) n=246 Range 0-18 years (mean 6.34 years, median 5.08 years)	4,5:1 and 0,98:1
Oh Y. et al.	2019	Severance Hospital and Gangnam Severance Hospital	South-Korea	Retrospective	67	(mean 13.42 years)	2,04:1

Size CMN	Location CMN	Classification system used	Aim Intervention used	Mean follow up (range)	Level of evidence
all sizes CMN	face, scalp, neck, collar, arms/ shoulders, hands, chest, abdomen/ flank, back/ buttocks, genitals, and legs/feet	Total Body Surface Area (TBSA)	Evaluation of health-related quality of life and psychological adjustment Surgical intervention (Excision)	Unreported	3
small to large CMN	Head and neck, trunk, extremities	Unreported	Perspectives and expectations of patients and families Unreported	Unreported	3
Unreported	face, scalp, neck, collar, arms/ shoulders, hands, chest, abdomen/ flank, back/ buttocks, genitals, legs/feet	Total Body Surface Area (TBSA)	Skin-related Quality of Life Surgical intervention (Excision)	Unreported	3
All sizes	Face, Scalp, Neck, Collar, Arms/ shoulders, Hands, Chest, Abdomen, Back, Legs/feet, Genitals	Total Body Surface Area (TBSA)	Treatment evaluation Surgical intervention (Excision)	unreported	4
mean 36.57 cm²	face, trunk, extremities	Unreported	Treatment evaluation Laser only group (ablative laser/ pigment specific laser) Combination group (partial excision with laser)	3.40 years	3

Appendix 4. (continued)

Primary author	Year	Medical Center	Country	Study design	No. of patients	Patient Age (if possible: mean (range; median))	Female: male ratio
Pellino G. et al.	2020	Multicenter	Italy	Systematic Review	24	Range 12 to 322 months (median 5 months)	01:02
Polubothu S. et al.	2020	Great Ormond St. Hospital - London	United Kingdom	longitudinal cohort - prospective	110	Range 0.0 to 17.4 years	1,62:1
Qiao C. et al.	2019	Shanghai Ninth People's Hospital	China	Retrospective	35	Range 3 to 36 years (mean 20.4 years; median 8.4 years)	3,38:1
Roh D. et al.	2020	Pusan National University Hospital	South-Korea	Retrospective	43	(mean 15.9 years; median 14.6 years)	1,18:1
Rouillé T. et al.	2019	Unreported	France	Prospective	17	Range 4 months to 8 years (median 18 months)	2,4:1
Sakhiyah J. et al.	2019	New Civil Hospital - Asarwa	India	Retrospective	17	Range 22 to 52 years (mean 31.7 years)	7,5:1
Tomás-Velasqués A. et al.	2020	Multicenter	Spain	exploratory case control - Prospective	24	(mean 5.7 years; median 3.4 years)	03:01

Size CMN	Location CMN	Classification system used	Aim Intervention used	Mean follow up (range)	Level of evidence
giant CMN	Unreported	PAS	Evaluation of neurological symptoms	50 months (range 6 to 286 months)	3-
			Parenchymal neurocutaneous melanosis specific interventions (anti-epileptic drug [AED] therapy or surgical epilepsy therapy)		
all sizes	Unreported	PAS	CMN lightening over time	Mean 5.3 years (range 0.2-16.0 years)	3
			Watchful waiting		
			Surgical intervention (superficial removal techniques)		
medium CMN	Unreported	PAS	Evaluation of treatment	1 year	4
			Surgical intervention (vertical/near vertical linear closure)		
small to medium CMN	palm/sole	Unreported	Evaluate difference between acquired and congenital melanocytic naevi	Unreported	3
			Unreported		
large to giant CMN	head, trunk, arm, leg	Krengel (PAS)	Evaluation of treatment	Unreported	4
			MEK-inhibitors AKT-inhibitors		
small CMN	Face	Krengel	Evaluation of treatment	Unreported	4
			Carbon dioxide laser ablation performed by a surgeon		
medium to giant CMN	Unreported	Krengel (PAS)	Level of S-100B	Unreported	3
			Unreported		

Appendix 4. (continued)

Primary author	Year	Medical Center	Country	Study design	No. of patients	Patient Age (if possible: mean (range; median))	Female: male ratio
Wu M. et al.	2020	Shanghai Ninth People's Hospital	China	Retrospective	98	Range 0.25 - 37 years (median 6 years)	0,72:1
Zalaudek I. et al.	2020	Multicenter	Austria and Italy	Retrospective	47	(mean 39.02 years; median 17.63 years)	1,04:1

Size CMN	Location CMN	Classification system used	Aim Intervention used	Mean follow up (range)	Level of evidence
giant CMN	Head and Neck, Trunk, Extremities	PAS	Histopathological characteristics	Unreported	3
(15.13±21.33 mm) C-NAM	Unreported	Unreported	Unreported Histopathological characteristics Unreported	Unreported	3

		PedsQL			CDLQI		
		Masnari 2019			Neuhaus 2020		
3. Structural validity		**rater 1**	**rater 2**	**Consensus**	**rater 1**	**rater 2**	**Consensus**
	unidimensionality or structural validity?						
1	For CTT: Was exploratory or confirmatory factor analysis performed?						
2	For IRT/Rasch: does the chosen model fit to the research question?						
3	Was the sample size included in the analysis adequate?						
4	Were there any other important flaws?						
	TOTAL *Lowest score of items 1-4*	**NA**	NA	**NA**	**NA**	**NA**	**NA**
4. Internal consistency		**rater 1**	**rater 2**	**Consensus**	**rater 1**	**rater 2**	**Consensus**
1	Was an internal consistency statistic calculated for each unidimensional (sub)scale separately?	VG	VG	VG	VG	VG	VG
2	For continuous scores: Was Cronbach's alpha or omega calculated?	VG	VG	VG	VG	VG	VG
3	For dichotomous scores: Was Cronbach's alpha or KR-20 calculated?	NA	NA	NA	NA	NA	NA
4	For IRT-based scores: Was standard error of the theta (SE (θ)) or reliability coefficient of estimated latent trait value (index of (subject or item) separation) calculated?	NA	NA	NA	NA	NA	NA
5	Were there any other important flaws?	NA	NA	NA	NA	NA	NA
	TOTAL *Lowest score of items 1-5*	**VG**	**VG**	**VG**	**VG**	**VG**	**VG**

Appendix 4. COSMIN Risk of Bias checklist. Score: V= very good; A = adequate; D = doubtful; I = inadequate; N= not applicable. We present the risk of bias scores of structural validity and internal consistency. Structural validity was not evaluated, what influences the rating of internal consistency (shown in Table 4). Like structural validly, all other measurement properties were not evaluated by the two included studies.

THE OUTCOMES FOR CONGENITAL MELANOCYTIC NAEVI (OCOMEN) PROJECT

WHAT IS THE PROBLEM?

At the moment, studies on Congenital Melanocytic Naevi (CMN) often measure different outcomes. Imagine two studies about treatment for CMN:
Study A measures the color of CMN after treatment and Study B measures the number of complications.

When the two studies are finished, their results cannot be compared or combined, because different outcomes were used. This lack of uniformity makes it difficult to decide what the best management options are.

AIM OF THE PROJECT

To agree on a set of outcomes that should be measured in all research and clinical practice: the so-called CMN Core Outcome Set.

This Core Outcome Set will be developed with the help of people with CMN, their families and professionals.

HOW CAN YOU HELP US?

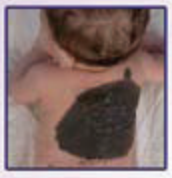
Let us know what outcomes are important for you by participating in different meetings or completing questionnaires.

If you are interested in participating, please e-mail Neavus Global or our OCOMEN research team.

Contact: a.c.fledderus@amsterdamumc.nl

Erasmus MC

Amsterdam UMC




GENERAL DISCUSSION AND SUMMARY

Street art, South Africa

Picture made by the head of the South African patient association for congenital melanocytic naevi.

9

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In this thesis an overview is presented of the current understanding and clinical challenges of the management of congenital melanocytic naevi (CMN). While trying to fill the gaps in current knowledge, professionals are restricted by small patient samples and heterogeneity in CMN care and research. Therefore, the main focus of this thesis was on increasing uniformity in and standard reporting of outcomes in clinical practice and research regarding CMN. In this general discussion, we reflect on clinical considerations and our research findings, and deliberate about possible future perspectives.

CLINICAL CONSIDERATIONS

The first chapter of this thesis presents a general explanation of the aetiology, diagnosis, classification, and management of CMN. Illustrated by a case report, we elucidate the clinical considerations and the ongoing discussion among specialists responsible for the care of patients with CMN. Although different management strategies have been described, many more research questions still need to be answered. It is recommended that patients with larger or multiple CMN are monitored regularly by a specialist to detect malignant transformation or neurological complications at an early stage. However, there is no international consensus on what exact size or number of CMN defines the "high-risk group" that should be frequently monitored.[1-3] Risk of neurological complications increases with CMN size but particularly with number of CMN or satellite nevi.[1-3] In Chapter 2 we showed an estimated prevalence of neurological symptoms and signs in 6.26% (95% CI: 3.85–10%) of patients with a CMN >6 cm. Unfortunately, it was not possible to estimate the risk of neurological involvement in CMN patients due to the heterogeneity and the high risk of bias in the available studies. Regarding melanoma risk, the Dutch guideline describes the various risk estimations. Firstly, the risk of developing melanoma in smaller CMN (<20 cm PAS) is hardly increased compared with the general population (<1%).[2,4] In patients with larger CMN (>20 cm PAS) the estimated increased risk is 1~3%.[2,4] In giant CMN, however, the estimation of the risk is much higher, estimated to be up to 8~14%.[2,4] As these risks are estimated from small sample size studies, they are vulnerable to bias and could therefore be overestimated as patients with malignant transformations may visit the expertise centres more often compared with asymptomatic patients. Other features of CMN, such as the number, location, texture or molecular characteristics of a CMN may also be predictors for melanoma or neurological involvement. Certain mutations may be associated with typical clinical or pathological features of the lesions.[5-7] BRAF mutations are, for instance, commonly associated with a multinodular phenotype.[7] In the future, research on risk factors may enable risk profiling of CMN groups, thus facilitating patient-tailored management.

In Chapter 2 we evaluated the different management strategies regarding MRI screening for neurological involvement. This is a topic much discussed among international specialists and on the social media platforms of patient associations. On one hand, discovering neurological involvement at an early stage is important to inform parents and establish a prognosis.[1,8,9] A baseline MRI could help to pinpoint radiological changes when symptoms and signs develop. Routine MRI screening might also benefit care and research on understanding neurological involvement.[10] At the other hand, it might be debated whether the advantages of routine MRI

screening outweigh the inconveniences, including extra costs, false positive/negative results and the creation of uncertainties. MRI abnormalities found in asymptomatic patients will mostly not change the management of these patients, which questions the additive value of MRI screening. The Dutch guidelines recommend that in asymptomatic patients, routine MRI screening should not be performed as part of care, but that patients with larger CMN (>20 cm PAS) should be monitored annually by a paediatrician and, when needed, by a neurologist, at least in the first five years of life.[2] Discussion on optimal management regarding neurological involvement is still ongoing. Weighing the advantages of routine MRI screening against the disadvantages depends on the individual's experience, personal opinion and cultural differences, which complicates the development of standard international guidelines. Standard reporting in CMN research and a prospective multi-centre study are needed to evaluate different management strategies, including watchful monitoring and routine MRI screening. The literature overview in Chapter 2 may support clinicians in deciding on the management on the neurological involvement and informing the patient adequately to enable shared decision-making.

Surgical treatment

The indications for excision of a CMN have shifted from prevention of malignant transformation towards improvement of appearance to prevent psychosocial problems.[11,12] Consequently, the risks and burden of excision should be weighed against its benefits to assist patients and their families in deciding which treatment best suits their personal needs.

Several plastic surgery techniques are available to remove and reconstruct the lesion, including serial excision, excision and grafting, reconstruction with artificial skin, and tissue expansion. Formerly, curettage and dermabrasion were performed as well, but this is no longer recommended due to the frequent wound complications and cosmetically unfavourable outcomes, including hypertrophic scarring and repigmentation.[13] In Chapter 3 we showed a high satisfaction rate with surgical resection results, as rated by both patients and clinicians. The following complications were documented: wound-related complications, scar-related complications, and anatomic deformations. Moreover, we revealed that published studies on surgical treatment of CMN are of low methodological quality as they are mainly retrospective case series with a high risk of bias, with only a few descriptions of outcomes, and limited regarding patient-reported outcomes and unvalidated outcome measures. Also, the patient characteristics are not always clear (size and localization of the CMN), and the studies' outcomes are often heterogeneous.

Deciding on the best surgical technique depends on many factors, including shape, size, location of the CMN, experience of the surgeon and the desire of the patient or parents. Scientific evidence on surgical interventions is associated with several methodological and practical challenges, for example surgeon-related factors, complexity of interventions, range of outcomes, or the fact that there is no standard treatment that fits all patients.[14] To tackle these challenges it is of the utmost importance to document the factors that influence the interventions, such as patient characteristics, characteristics of the lesion (when possible using standardized classifications), surgeon's experience, descriptions of intervention and long-term outcomes[14]. This PhD thesis has

stressed the importance of ensuring uniformity in the outcomes used in care and research to enable the comparison and combination of studies, something that is especially important for rare diseases such as CMN as the study sample sizes are generally small.

UNIFORMITY IN CMN CARE AND RESEARCH

As already pointed out previously, uniformity in CMN care and research would be a big step forward towards improving the quality of care and treatment of patients born with a CMN in the future. As described in Part 3 of this thesis, the Outcomes for Congenital Melanocytic Naevi (OCOMEN) project is a critical step enabling standardization and adequate international collaboration between clinicians and researchers in this field. The OCOMEN project aims to reach consensus on the core outcome set (COS) of medium-to-giant CMN to improve and standardize outcome assessment and implement the patients' perspective. If and when international clinicians and researchers implement the COS, care and research will be more consistent, enabling comparison and combination of results. The importance of COS is stressed by recognized entities in research, such as the Cochrane Institute.[15] The Core Outcome Measures in Effectiveness Trials (COMET) initiative was launched to promote and facilitate the development and application of COS. COMET provides COS development guidelines, maintains a database of COS studies and facilitates the exchange of ideas and methodological research to enhance the quality and uptake of COS (*www.comet-initiative.org*). The Cochrane Skin–Core Outcome Set Initiative (*CS-COUSIN*) initiative and the Consortium for Harmonizing Outcomes Research in Dermatology (CHORD) initiative are both independent initiatives that support the development and implementation of the COS for dermatological conditions.[16-18] These two initiatives have considerable overlap in terms of aims and ambitions; therefore, discussion is ongoing to form a combined initiative. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative focuses on the development and validation of outcome measurement instruments for the COS.[19]

Involvement of patients

Patient empowerment and patient-centred medicine is an emerging concept in medical care and research, recommended by the World Health Organization. The shift from provider-centred healthcare towards a more patient-centred healthcare is evident from an increasing focus on patient communication, shared decision-making, evaluation of patient experiences, patient-centred outcomes and patient involvement in development of guidelines for both care and research.[20-22] Regarding the OCOMEN project, patients had a key role in deciding what domains and outcomes should be involved in the COS. In addition, the president of an international patient association of CMN was part of the OCOMEN research team. The international patient association Naevus Global supported the OCOMEN project and helped us to recruit and inform patients and their families.

Including patients in COS development is crucial as evidence indicates that opinions on the priority of certain outcomes can differ between patients and clinicians.[23,24] When patients are not involved, important outcomes can be overlooked.

The COMET Initiative and, in particular, the COMET Patient Participation, Involvement and Engagement (PoPPIE) Working Group provide recommendations and guidance on patient involvement, including appropriate recruitment methods, finding the best way to explain the concept of a COS, using a suitable method to obtain perspectives, maintaining participant input over time, and enabling the inclusion of patients in meetings with clinicians (*www.comet-initiative.org/Patients*).[22,25]

Definition and classification of outcome measures

Definitions, domains and outcomes differ in COS studies. There are no strict guidelines on what hierarchic level a domain or an outcome should be, complicating this process. In this thesis we define "domains" as broader aspects of a disease such as "neoplasm", whereas "outcomes" are defined as the more precise aspects of a disease on a lower hierarchical level; for example, "presence of melanoma" is an outcome of the domain "neoplasm". In other studies, "outcomes" are named "sub-domains" or "domain items". Sometimes, sub-sub-domains are described as well, i.e. aspects on a lower hierarchic level than "outcomes".

We learned in Chapters 4 and 6 that the classification of outcomes can be challenging. We used the classification of the COMET taxonomy, but other guidelines are available as well to assist this process.[26-28] One of the challenges was that some outcomes can be classified in more than one domain. For instance, perceived stigmatization can be classified as both an emotional and a social problem. The other challenge was how to classify outcomes on the same hierarchical level as other outcomes. For instance, "psychosocial issues" is a broader concept compared with "colour of the lesion". "Psychosocial issue" should be further specified; for instance, "emotional distress" could be more on the same hierarchical level as "colour of lesion". Another option is to lump outcomes together; for example, "colour of lesion" and "texture of the lesion" could be lumped together as the outcome "appearance of lesion". We recommend classifying outcomes with a team of experts and reaching consensus on the best classifications.

We define a "baseline characteristic" as a demographic, clinical or prognostic aspect of the patient, such as age, gender or the location of the lesion. For some aspects it is complicated to determine whether it is a baseline characteristic or an outcome. For instance, "size of CMN" can be an aspect of the classification (baseline characteristic), but it can also change after treatment (size reduction as an outcome of partial excision). There is currently no consensus on the definitions/ names of the domains, outcomes, different hierarchical levels, and baseline characteristics. Therefore, we recommend that COS developers should clearly define the definition used by the research team in every study.

Uptake of the COS

The uptake of the COS in care and research is an important factor to improve uniformity in future outcomes.[17] To promote uptake, the COS should be implementable and easy to use. Similar to many other COS groups, we experienced the problem that numerous domains and outcomes are considered to be "important", as presented in the Delphi study in Chapter 6. CS-COUSIN strongly

advises that only a limited number of "core" outcomes be included in a COS to make the COS feasible for all care and research.[17] To address this, we followed the advice of the CS-COUSIN methodological specialists and made a protocol deviation by asking participants to indicate the top five domains that should be included in the COS as presented in Chapter 6. To increase feasibility it is recommended that only one instrument per domain is used, and preferably an instrument covering multiple domains.[17]

Various dissemination strategies to promote the future uptake of COS are proposed, including publications in medical journals, presentations at conferences, the organization of journal clubs, developing a website for the COS, newsletters, webinars, dissemination of social media, and dissemination through patient associations.[29] Moreover, technological assistance to simplify routine data collection will support the implementation of the standard set of outcomes.[30] For instance, 22 practice sites of a specialized treatment centre for hand and wrist conditions across The Netherlands routinely measure the outcome of treatment by using an online system that automatically distributes measurements among patients, which can be accessed by healthcare professionals and used for research.[30] The European Reference Network-SKIN (ERN-SKIN) may help enhance the future uptake of this COS for CMN. The ERN-SKIN-subthematic mosaic group aims to offer EU citizens the opportunity to benefit from high-quality and cost-effective CMN care everywhere on European territory (www.ern-skin.eu).

Limitations of core outcome set development

The two major limitations encountered by COS developers are the limited funding sources and the long time needed to develop a COS. Developing a complete COS for a certain condition often needs a couple of years. Faster methods to develop a standard set of outcomes are available,[31] but when there are limited funding sources COS developers rely mainly on the voluntary participation of COS developers and relevant stakeholders. Moreover, sufficient time is needed to ensure the wide and genuine involvement of specialists and patients willing to participate in the project, using robust and evidence-based methods for attaining consensus, and to find and develop valid, reliable and feasible measurement instruments in both care and research. Another limitation is uncertainty about the uptake of the COS. Development of a COS should not result in research being wasted through poor uptake.[17] The editorial board of the *British Journal of Dermatology* has observed either partial or absent COS utilization and reporting in submitted clinical trial manuscripts, despite the existence of a published COS in that field.[18] Over the past years, journals have been progressively formulating requirements to ensure the quality of research, such as protocol registrations, the use of checklists, or availability of data. Requiring the use of standard outcome measures will enhance the quality of future research as well.[18] This will also result in an improvement of care. To increase awareness, COS development should be included in research methodology training and COS research should be prioritized in conference scheduling and in publication in high-impact journals.[18] Moreover, standard outcomes can also form a basis for the evaluation of the quality of care.[32] Healthcare professionals can use the results of standard outcomes to make better choices for the best patient-oriented treatment.[15] In addition, the standard outcomes set can be seen by

patients, patient organisations, managers and reimbursement as valuable information for evaluating and choosing a healthcare provider.[32] However, these standard outcome sets have not yet proved themselves to be valuable as a quality indicator.[32] As a result, they are not yet reliable enough to use for the choice of a healthcare provider.[32]

FUTURE PERSPECTIVES

Uniformity in measurement instruments

The OCOMEN project reached consensus on the core domains and outcomes for CMN care and research, the next step is to reach consensus on the core measurement instrument and to decide when the domains and outcomes should be measured. Chapter 8 presents a systematic review summarizing the instruments used for CMN. This review shows that there is a lack of validation studies for instruments measuring the core outcomes in a group of CMN patients. The results of this chapter may be used as input for a future consensus meeting with all stakeholders, aiming to reach consensus on what measurement instruments could be appropriate for the core outcomes and which ones should be validated first, or whether new measurement instruments should be developed. Progress with the development and/or validation of instruments can be divided among international clinicians and researchers specialized in the different domains of the COS. Different international CMN groups could join the OCOMEN team and help to find reliable and valid instruments.

Uniformity in baseline characteristics

Apart from uniformity in domains and outcomes, standardization should be achieved in baseline characteristics, such as patient characteristics, classification of the lesion and description of intervention. We recommend using the consensus-based standardized categorization of cutaneous features of CMN developed by Krengel *et al*.[33] This classification was developed by the consensus of experts on CMN and has been shown to have an adequate inter-rater agreement.[33] The OCOMEN team started a project together with the University Hospital in La Paz to develop and validate a patient self-classification tool based on the Krengel classification. It may be valuable if patients could classify their own CMN and obtain appropriate information about their condition.[21] Patients could then score their classification before visiting the hospital, which would enable physicians to estimate the risk of complications in these patients and triage to the appropriate specialists. A self-classification tool may also increase the acceptance of the Krengel classification by enabling physicians to do uniform and standard reporting.

Registries

Due to the rarity of large and giant CMN, it takes a single expertise centre decades to include a considerable number of patients in their registry/database. To allow for meaningful analyses, collaboration between CMN expert centres is of the utmost importance. An international standardized registry, allowing all clinical centres to include their patients, will support the collection of data on larger numbers of CMN patients. However, data registration of every evaluated CMN

patient will require extra work for clinicians and researchers. Instead of spending considerable time on data registrations, professionals would probably prefer to publish their data themselves and maintain their own database. To address this, international consensus should be reached on what specific standardized data should be included in the databases/registries in order to create uniform and interoperable data collection. Every clinical centre could publish its own data separately or together with that of other centres in a uniform way. Also, when the data is uniform, the data from different origins could then be combined and analysed to answer other research questions. In this way the databases/registries would be developed according to the FAIR principles: data should be Findable, Accessible, Interoperable and Reusable.[34] These principles emphasise the capacity of machines to find, access, interoperate and reuse data without or with minimal human intervention. The European platform on rare disease registrations provides a standard set of common data elements for rare disease registration to support the FAIR principles.[35]

A patient-driven registry, where patients can register their own data, might be a solution as well. However, some clinical data is difficult for patients to register correctly, such as the types of treatment, presence of melanoma, neurological complications, neuro-imaging reports, or molecular characteristics.

An optimal solution would be for data collected as part of the regular healthcare process to be automatically anonymized and included in an international database. However, this strategy is highly complicated by heterogeneity in the software used by different clinical centres for electronic patient records, especially between different countries. Possibly, the increasing capabilities of technology may offer us a solution in the future.

Treatment

Clinicians' exposure is strictly limited in the case of rare diseases such as CMN. Most surgeons in specialised centres will operate on only a handful of CMN patients every year, which limits the surgeons' personal procedure-based learning. Centralized care in expert centres is therefore important. Moreover, innovative techniques may be beneficial to support surgeons in optimizing the surgical interventions. An innovative technique that might support this surgical intervention may be 3D photogrammetry. 3D photogrammetry can accurately determine surface areas and body part volumes and measure the size of the CMN.[36,37] Furthermore, there could be a role for 3D photogrammetry during preoperative planning of (non-)expanded flaps, as well as in determining the optimal expander type, location and inflation rate of a tissue expander to potentially minimize surgical complications and improve cosmetic outcomes.[36-38]

Pharmacological therapy to improve aesthetics may be available in the future, allowing the avoidance of intensive surgical treatment. Promising pharmacological treatments are being presented in animal or *in vitro* studies, including senolytics, endothelin-1 inhibitors, phosphoinositide 3-kinase (Akt) inhibitors, mitogen-activated protein kinase (MEK) inhibitors (trametinib) and BRAF inhibitors (vemurafenib).[39-41] These therapies have the potential for an alternative non-surgical

approach to CMN treatment. However, clinical studies should be performed to investigate the effect and safety of these pharmacological therapies.

CONCLUSION

We learned during this PhD research that clinical considerations regarding the management of CMN are neither fully clarified nor internationally standardized. Creating uniformity in the use and reporting of domains and outcomes in CMN care and research seems to be the essential first step to enhance medical knowledge in order to advise patients and their families about treatment, and to set up best practice for CMN. The first step towards the harmonization of CMN care and research was presented in this thesis. We have learned that CMN is a condition that has sparked the interest of various clinicians and researchers. Abundant opportunities exist for researchers to investigate further regarding CMN.

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Luca Barberini

Folla 06 (Crowd 06), Rome

2014

Luca Barberini is an Italian artist from Ravenna, a city famous for its paleochristian and Byzantine mosaics. Barberini's art seeks to tie the art of mosaic using the methods and forms of Ravenna's traditional mosaics but portraying ordinary people and everyday scenes, such as romantic dinner, a demonstration in the piazza or a party among friends. Barberini granted me permission to share his artwork in this thesis.

Reference: www.lucabarberini.com

10

SUMMARY

SUMMARY: OUTCOMES FOR CONGENITAL MELANOCYTIC NAEVI

Part I: General introduction

Congenital Melanocytic Naevi (CMN) are birthmarks that can cover large areas of the body. They affect 1:100 newborns, and in large (>20 cm in adulthood) and giant CMN (>40 cm in adulthood), 1:20.000 and 1:500.000 newborns are affected, respectively. The clinical threat of CMN is the risk of developing malignant melanomas or neurological complications. In addition to these complications, the occurrence of CMN can lead to psychosocial problems due to their remarkable appearance or the extra care they may require. **Chapter 1** presents the introduction of this thesis including a general explanation of aetiology, diagnosis, classification, and management of CMN. Illustrated by a case report, we elucidate the clinical considerations and the ongoing discussion among specialists responsible for the care of patients with CMN.

Adequate information and management for patients and their parents are crucial. Although different management strategies have been described, the quality of evidence is generally low which makes it difficult to set up best practice for CMN and to advise patients and their parents. One of the reasons for the low quality of the studies may be the limited patient numbers in studies, owing to the rarity of the disease. Moreover, there is a lack of uniformity regarding the outcomes and measurement instruments used for CMN care and research. Heterogeneity impedes the comparison and pooling of outcomes of the small CMN studies. The aim of this thesis was to evaluate clinical considerations regarding CMN management and to achieve harmonization in the outcomes used in CMN care and research.

Part II: Clinical considerations

CMN can be associated with abnormalities in the central nervous system. The consequences can vary from mild or no symptoms, to death. These anatomical abnormalities can be detected by an MRI scan. To identify central nervous system involvement and how to monitor CMN patients, we present a study in **Chapter 2** that aimed to estimate the prevalence of neurological involvement in CMN patients and to summarize what specific neurological symptoms and signs and MRI abnormalities are reported in the medical literature. In addition, we summarized and evaluated the recommendations reported regarding MRI screening. Studies were included with ten or more CMN patients, reporting outcomes on neurological symptoms, signs or central nervous system MRI characteristics. A meta-analysis was performed to assess the prevalence of neurological symptoms and signs in CMN patients.

A high risk of bias and large clinical heterogeneity were found. The meta-analysis revealed neurological symptoms and signs in 6.26% (95% confidence interval 3.85–10.00%) of patients with a larger CMN (>6 cm in children or >20 cm projected adult size). Neurodevelopmental delay and seizures were most frequently reported. Melanosis and hydrocephalus were the most frequently reported MRI abnormalities. It was not possible to make strong recommendations on routine MRI screening based on current evidence. For now, every clinical centre should decide on its own policy and weigh the advantages and disadvantages of MRI screening. A multi-centre prospective study is needed to understand neurological involvement, with uniform and standard reporting of neurological involvement and MRI screening in CMN patients.

Chapter 3 presents a literature search evaluating the safety and effectiveness of surgical excision of medium-to-giant and/or difficult-to-excise CMN. In the last decade, surgical treatment of CMN has shifted from prevention of malignant transformation towards improvement of appearance to prevent psychosocial problems. Consequently, the risks of excision should be weighed against its benefits. The electronic database search resulted in 1444 unique studies, of which 22 were included. Pooled proportions were 9.8% for major wound-related complications, 1.2% for minor wound-related complications, 1.2% for scar-related complications, and 4.3% for anatomical deformations. Cosmetic outcome was rated by patients as excellent in 24.4%, good in 71.0%, and poor/moderate in 4.6% of cases. Although complications can occur, this literature overview shows that surgical excision of CMN can be safe and effective in many cases.

Part III: Uniformity in domains, outcomes and instruments

At the moment, different studies looking at CMN often measure different outcomes, which makes it impossible to compare and combine the results. To reduce outcome heterogeneity in future research trials, it is imperative to develop a *core outcome set* (COS). A COS is a consensus-based (i.e. developed by patients and professionals) agreed minimum set of outcomes that are recommended to be measured in all research on a certain condition. The Outcomes in Congenital Melanocytic Naevi (OCOMEN) project aims to develop a COS for CMN care and research for medium-to-giant CMN.
The first part of a COS is deciding *what* to measure, the core domain set (CDS). The second part is to decide *how* this should be measured, the core outcomes measurement set (COMS). In this thesis, we define a *domain* as the broader aspects of a disease, whereas *outcomes* are defined as the more precise aspects of a disease on a lower hierarchical level. For example, *presence of melanoma* is an outcome of the domain *neoplasm*. **Chapter 4** presents the protocol developed for the OCOMEN project regarding the CDS. We developed this according to the *Core Outcome Measures in Effectiveness Trials (COMET) initiative* and *the Cochrane Skin Core Outcomes Set Initiative* (CS-COUSIN). This project entailed the following: (1) focus group sessions with national and international patients and parents to identify the outcomes important for patients; (2) a literature review to identify the outcomes previously reported in the medical literature; (3) classification of the outcomes into domains; (4) online surveys in which stakeholders (patients/parents and professionals) could rate the importance of domains and outcomes for research and practice; and (5) an online consensus meeting to finalize the CDSs for both settings. Part from the protocol, Chapter 4 provides the results of the seven focus group sessions and presents a list of outcomes that are considered to be important by international CMN patients and their parents.

Before we were able to reach consensus on what domains and outcomes should be measured, we investigated what outcomes have been used in previous research. **Chapter 5** presents the findings of a systematic literature search which shows the domains, outcomes and measurement instruments used in all studies reporting on ten or more patients with CMN, evaluating interventional and conservative management.

An electronic database search resulted in 1285 individual studies; 63 of these studies were included in our study. We extracted 57 different outcomes and 34 outcome measurement

instruments, showing large heterogeneity. Patient-reported outcomes were included in 38% of the studies used. Our study showed that heterogeneity exists in outcomes and instruments used in CMN research, which underlines the need for a COS.

Chapters 6 and 7 present the consensus procedure followed to decide what domains and outcomes should be measured for the CDS of care and research. The outcomes obtained in Chapters 4 and 5 were classified into the domains that were used for the consensus procedure. Through three e-Delphi survey rounds, stakeholders from 27 countries iteratively rated the importance of domains. An online consensus meeting with patients and professionals was held to discuss the importance of the domains and to vote on which domains should be included in the CDS. The following domains were considered to be core: *anatomy of the skin, quality of life, neoplasm, neurology, general adverse events and pathology*.

To select the appropriate measurement instruments, the domains were further specified by outcomes. First, participants could cast their initial vote on the core outcomes during the last round of the e-Delphi study and could vote for a provisional list of outcomes during the first consensus meeting. Patients, parents and professionals could give feedback on this provisional list of outcomes through an online form. A second online consensus meeting was held to discuss the importance of each outcome. Finally, participants voted on the most important outcomes in two rounds. Patients, parents and professionals from nineteen different countries reached consensus on the following outcomes for the COS of both care and research: *satellite number, texture of the CMN and colour of the CMN, size of the CMN (anatomy of the skin), emotional distress (quality of life), presence of melanoma (neoplasm), neurological symptoms and signs (neurology), wound problems of the CMN and scar problems (general adverse events)*. In addition, the outcome of *molecular characteristics (pathology)* was core for the COS of research.

The next step was to reach consensus on *how* the core domains and outcomes should be measured. For this purpose, we needed to know what outcome measurement instruments were used for CMN and to evaluate their methodological quality. **Chapter 8** presents two systematic reviews: (Step 1) an update of the systematic review in Chapter 5, identifying all core outcomes and their measurement instruments available for CMN; and (Step 2) evaluation of the quality of the measurement properties of the instruments measuring the core outcomes.

Step 1 involved a literature search in EMBASE (Ovid), PubMed and the Cochrane Library to identify core outcomes and instruments previously used in research on CMN. Step 2 involved a systematic search for studies on the measurement properties of instruments that had been either developed or validated for CMN, including a methodological quality assessment following the COSMIN methodology. Step 1 yielded 29 studies, providing an overview of core outcomes and instruments used for CMN. Step 2 yielded two studies, investigating two quality-of-life measurement instruments. We showed that additional research on measurement properties is needed to evaluate which instruments can be used for the COS of CMN. This study informs the instrument selection and/or development of new instruments.

Uniformity and standard reporting in care and research are essential to enable evidence-based management of CMN. This thesis has performed the first step of the development of a COS for CMN care and research.

SAMENVATTING: UITKOMSTEN VOOR CONGENITALE MELANOCYTAIRE NAEVI

Deel I: inleiding

Congenitale melanocytaire naevi (CMN) zijn aangeboren moedervlekken, welke grote delen van het lichaam kunnen bedekken. Van alle pasgeborenen heeft 1:100 een CMN, maar grote CMN (met een diameter van >20 cm op volwassen leeftijd) en reuzen-CMN (>40 cm op volwassen leeftijd) komen minder vaak voor: respectievelijk 1:20.000 en 1:500.000 van de pasgeborenen. Ernstige complicaties die bij CMN-patiënten kunnen optreden zijn melanomen en neurologische complicaties. Als gevolg van deze risico's, het opvallende uiterlijk, en de extra zorg die CMN-patiënten nodig hebben, kunnen CMN psychosociale problemen teweegbrengen. **Hoofdstuk 1** geeft een inleiding van het proefschrift met een uitleg over etiologie, diagnose, classificatie en behandeling van CMN. Aan de hand van een casus belichten wij de klinische overwegingen en de verschillende discussiepunten met betrekking tot de zorg van CMN-patiënten.

Het is van groot belang dat er adequate informatie beschikbaar is ten aanzien van CMN-zorg. Hoewel er verschillende behandelstrategieën zijn beschreven, is het wetenschappelijk onderzoek naar CMN meestal van lage kwaliteit. Dit maakt het moeilijk om de CMN-zorg te optimaliseren en om patiënten en hun ouders volledig te adviseren. De lage kwaliteit van het onderzoek naar CMN kan verklaard worden door de zeldzaamheid van deze aandoening, waardoor er vaak een beperkte aantal patiënten in de studies onderzocht wordt. Bovendien meten verschillende studies vaak verschillende uitkomstmaten met verschillende meetinstrumenten, waardoor deze kleine studies moeilijk of niet gecombineerd of vergeleken kunnen worden. In dit proefschrift richten wij ons op het evalueren van verschillende klinische overwegingen met betrekking tot CMN-zorg en op het creëren van uniformiteit in uitkomstmaten voor CMN-zorg en -onderzoek.

Deel II: klinische overwegingen

De aanwezigheid van een CMN kan gepaard gaan met afwijkingen in het centrale zenuwstelsel. Deze afwijkingen kunnen qua ernst variëren van milde of geen symptomen, tot aan afwijkingen die leiden tot vroegtijdig overleiden. De anatomische afwijkingen in het centrale zenuwstelsel kunnen worden gedetecteerd met behulp van een MRI-scan.

Hoofdstuk 2 presenteert een systematisch literatuuronderzoek naar de prevalentie van neurologische betrokkenheid bij CMN-patiënten. Daarnaast wordt er samengevat welke specifieke neurologische symptomen en MRI-afwijkingen er in de medische literatuur werden gerapporteerd. Verder hebben wij de beschreven aanbevelingen over MRI-screening samengevat en geëvalueerd. Studies werden geïncludeerd wanneer zij tien of meer CMN-patiënten onderzochten en resultaten rapporteerden over neurologische symptomen of MRI-uitkomstmaten. Een meta-analyse werd uitgevoerd om de prevalentie van neurologische symptomen bij CMN-patiënten te bepalen.

De kwaliteit van de gevonden studies was beperkt en de klinische heterogeniteit was hoog. Neurologische symptomen werden gevonden bij 6,26% (95% betrouwbaardheidsinterval 3,85-10,00%) van de patiënten met een groter CMN (>6 cm bij kinderen of >20 cm bij volwassen). Epileptische aanvallen en vertraging in de neurologische ontwikkeling waren de meest

gerapporteerde symptomen. Melanocytose en hydrocephalus waren de meest gerapporteerde MRI-afwijkingen. Op basis van de huidige literatuur was niet mogelijk om aanbevelingen te schrijven met betrekking tot routinematige MRI-screening. Op dit moment behoort elk klinisch centrum zijn eigen beleid te bepalen en de voor- en nadelen af te wegen van MRI-screening. Een multicentrisch prospectief onderzoek is nodig om verder inzicht te krijgen in de neurologische betrokkenheid bij CMN-patiënten. Hiervoor is uniformiteit en gestandaardiseerde rapportage nodig.

Hoofdstuk 3 presenteert een literatuuronderzoek naar de veiligheid en effectiviteit van chirurgische excisie van middelgrote tot reuzen-CMN en/of moeilijk-te-verwijderen CMN. In het afgelopen decennium is de indicatie van chirurgische behandeling van een CMN verschoven van melanoomprofylaxe in de richting van een meer cosmetische indicatie ter voorkoming van psychosociale problemen. Het is daarom van groot belang om de voordelen van excisie af te wegen tegen de risico's. De elektronische zoekactie resulteerde in 1444 unieke studies, waarvan er 22 werden geïncludeerd. Wij vonden gemiddeld 9,8% ernstige wondcomplicaties, 1,2% milde wondcomplicaties, 1,2% complicaties van het litteken, en 4,3% anatomische vervormingen, per patiënt. Cosmetisch resultaat werd door patiënten beoordeeld als uitstekend in 24,4%, goed in 71,0% en slecht/matig in 4,6% van de gevallen. Hoewel er complicaties kunnen optreden, laat dit literatuuroverzicht zien dat chirurgische excisie van CMN in de meeste gevallen veilig en effectief kan zijn.

Deel III: uniformiteit in domeinen, uitkomstmaten en instrumenten

Verschillende studies naar CMN meten vaak verschillende uitkomstmaten. Dit bemoeilijkt het vergelijken en combineren van de resultaten. Om de heterogeniteit van uitkomstmaten in toekomstig zorg en onderzoek te verminderen, is het noodzakelijk om een *core outcome set* (COS) te ontwikkelen. Een COS is een op consensus gebaseerde (ontwikkeld door patiënten en zorgverleners), gestandaardiseerde minimumset van uitkomstmaten die gemeten moeten worden in toekomstige zorg en onderzoek over een bepaald onderwerp. Het project *Outcomes in Congenital Melanocytic Naevi* (OCOMEN) is gericht op het ontwikkelen van een COS voor CMN-zorg en -onderzoek voor middelgrote tot reuzen-CMN. Het eerste deel van de COS-ontwikkeling bestaat uit het beslissen *wat* er gemeten moet worden: de *core domain set* (CDS). Het tweede deel bestaat uit het beslissen *hoe* dit gemeten moet worden: de *core outcomes measurement set* (COMS).

In dit proefschrift definiëren wij een *domein* als de bredere aspecten van een ziekte, terwijl *uitkomstmaten* worden gedefinieerd als specifiekere aspecten van een ziekte op een lager hiërarchisch niveau. Bijvoorbeeld de uitkomstmaat *aanwezigheid van melanoom* is een uitkomstmaat van het domein *maligniteit*.

Hoofdstuk 4 presenteert het protocol van het OCOMEN-project met betrekking tot de CDS. Wij hebben dit ontwikkeld volgens de richtlijnen van het *Core Outcome Measures in Effectiveness Trials* (COMET)-initiatief en het *Cochrane Skin Core Outcomes Set Initiative (*CS-COUSIN). Dit project bestond uit: 1) opzetten van focusgroepen met internationale patiënten en ouders om de uitkomstmaten te identificeren die belangrijk zijn voor patiënten; 2) een literatuuronderzoek om de uitkomstmaten te identificeren die in de literatuur gerapporteerd zijn; 3) indeling van

de uitkomstmaten in domeinen; 4) een online e-Delphi studie waarin patiënten, ouders, en zorgverleners domeinen en uitkomstmaten voor zorg en onderzoek konden beoordelen; en 5) een online consensusvergadering om de CDS te bepalen. Naast het protocol worden in Hoofdstuk 4 de resultaten gepresenteerd van de zeven focusgroepen: een lijst met uitkomstmaten die door internationale CMN-patiënten en hun ouders als belangrijk worden beschouwd.

Voordat wij overeenstemming konden bereiken over welke kerndomeinen en -uitkomstmaten gekozen zouden moeten worden, hebben wij onderzocht welke uitkomstmaten in eerdere studies zijn gebruikt. **Hoofdstuk 5** presenteert een systematisch literatuuronderzoek dat de domeinen, uitkomstmaten, en meetinstrumenten identificeerde van studies over behandelingen van CMN.

Een elektronische zoekactie in de database resulteerde in 1285 individuele studies, waarvan er 63 werden opgenomen in onze studie. Wij hebben hieruit 57 verschillende uitkomstmaten en 34 meetinstrumenten geïdentificeerd, waaruit een grote heterogeniteit in uitkomstmaten en meetinstrumenten tussen individuele studies blijkt. Patiëntgerapporteerde uitkomstmaten werden gebruikt in 38% van de studies. Onze studie toonde aan dat er heterogeniteit bestaat in de in CMN-onderzoek gebruikte uitkomstmaten en instrumenten, hetgeen de noodzaak van een COS benadrukt.

Hoofdstukken 6 en 7 presenteren de consensusprocedure die werd gevolgd om te beslissen welke kerndomeinen en uitkomstmaten gemeten moeten worden voor de CDS van CMN-zorg en -onderzoek. De uitkomstmaten geïdentificeerd in hoofdstukken 4 en 5 werden geclassificeerd in de domeinen die werden gebruikt voor de consensusprocedure. Via een e-Delphi studie hebben patiënten, ouders, en zorgverleners uit 27 landen op de belangrijkste domeinen gestemd. Er is een online consensusvergadering gehouden met patiënten en zorgverleners om het belang van de domeinen te bespreken en te stemmen welke definitieve domeinen in de CDS moeten worden opgenomen. De volgende domeinen werden als kerndomeinen beschouwd: *anatomie van de huid*, *kwaliteit van leven*, *neoplasma*, *neurologie*, *bijwerkingen*, en *pathologie*.

Om de juiste meetinstrumenten te selecteren, behoren de domeinen nader gespecificeerd te worden door uitkomstmaten. Deelnemers konden hun eerste stem uitbrengen op de uitkomstmaten tijdens de laatste ronde van de e-Delphi studie en tijdens de eerste consensusvergadering. Dit resulteerde in een voorlopige lijst van uitkomstmaten. Patiënten, ouders, en zorgverleners konden via een online formulier feedback geven op deze voorlopige lijst. Tijdens een tweede online consensusvergadering werd het belang van elke uitkomstmaat besproken. Tot slot hebben de deelnemers op de belangrijkste kernuitkomstmaten gestemd. Patiënten, ouders, en professionals uit negentien verschillende landen bereikten overeenstemming over de volgende uitkomstmaten voor zorg en voor onderzoek: *aantal satellietmoedervlekken*, *CMN-textuur*, *CMN-kleur*, *CMN-grootte* (anatomie van de huid), *emotioneel ongenoegen* (kwaliteit van leven), *aanwezigheid van melanoom* (neoplasma), *neurologische symptomen* (neurologie*), CMN-wondproblemen*, en *problemen van het litteken* (bijwerkingen). Daarnaast werd de uitkomst *moleculaire karakteristieken* (pathologie) toegevoegd aan de COS voor CMN-onderzoek.

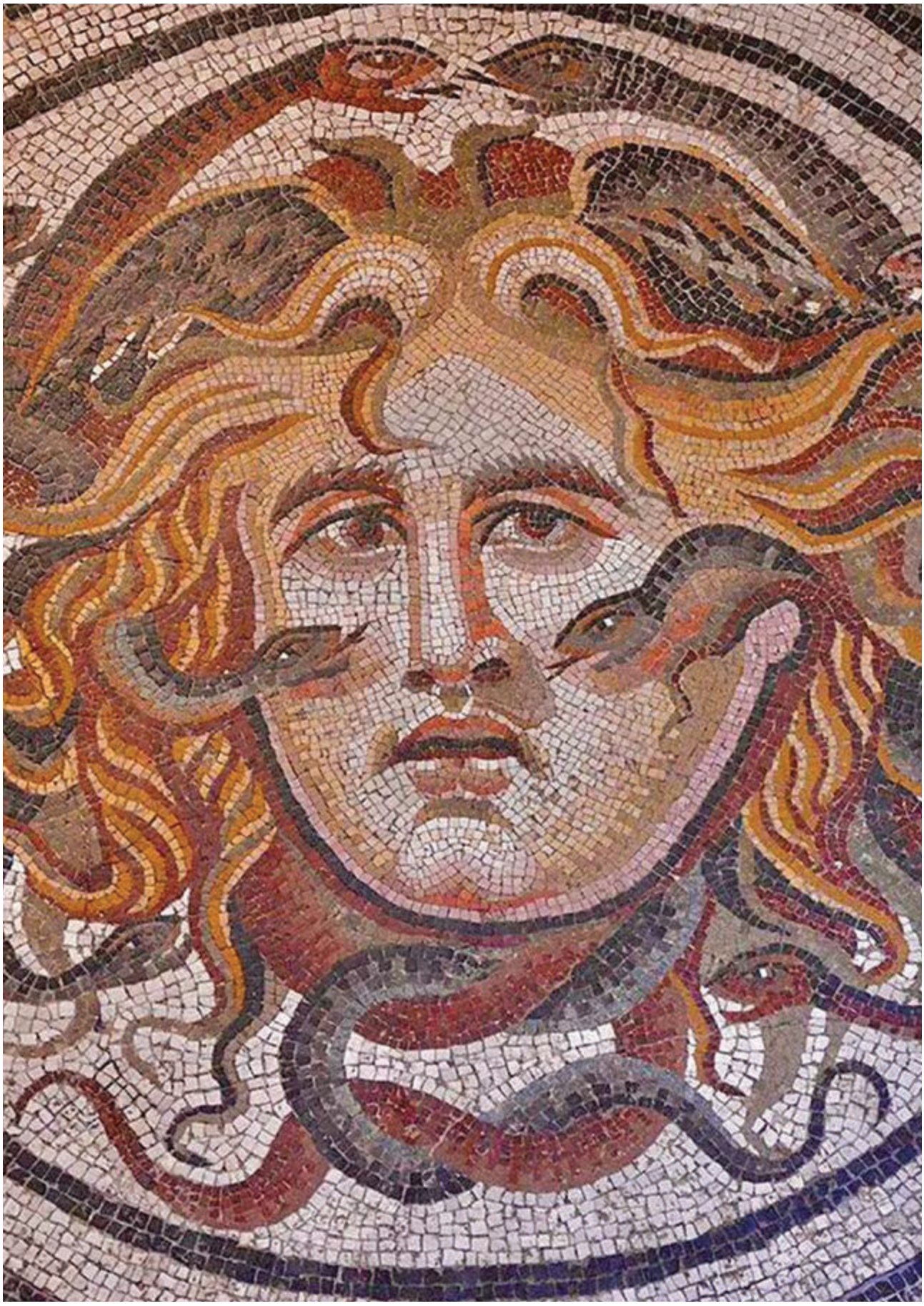
De volgende stap van het ontwikkelen van een COS was het bereiken van consensus over hoe de domeinen en uitkomstmaten gemeten behoren te worden. Hiervoor hebben wij uitgezocht welke meetinstrumenten gebruikt werden voor CMN en hebben wij de methodologische

kwaliteit van deze instrumenten geëvalueerd. **Hoofdstuk 8** presenteert twee systematische literatuuronderzoeken in twee stappen. stap 1) een update van het onderzoek in hoofdstuk 5, waarin alle uitkomstmaten van de CMN-COS en de bijbehorende meetinstrumenten werden geïdentificeerd; en stap 2) het evalueren van de kwaliteit van de meeteigenschappen van de instrumenten die de uitkomstmaten van de COS meten.

Stap 1 omvatte een literatuuronderzoek in EMBASE (Ovid), MEDLINE (PubMed), en de Cochrane Library, om uitkomstmaten van de COS en bijbehorende meetinstrumenten te identificeren die eerder werden gebruikt in studies naar CMN. Stap 2 omvatte een systematische zoekactie naar studies over de meeteigenschappen van instrumenten die, ofwel ontwikkeld, ofwel gevalideerd waren voor CMN. De kwaliteit van deze studies werd beoordeeld volgens de COSMIN-methodologie. Stap 1 leverde 29 studies op, welke een overzicht gaven van de uitkomstmaten van de COS en de bijbehorende instrumenten. Er werden slechts twee studies gevonden door de zoekactie van stap 2, waarin twee meetinstrumenten met betrekking tot kwaliteit van leven werden onderzocht. Dit onderzoek laat zien dat er meer onderzoek naar meeteigenschappen nodig is om te beoordelen welke instrumenten gebruikt kunnen worden voor de COS van CMN. Deze studie geeft informatie over de instrumentenselectie voor de COS of en/of de eventuele noodzaak om nieuwe instrumenten te ontwikkelen voor CMN-patiënten.

Uniformiteit en gestandaardiseerde rapportage in zorg en onderzoek is essentieel om behandelrichtlijnen voor CMN te optimaliseren. Dit proefschrift heeft de eerste stap gezet naar de COS-ontwikkeling voor CMN-zorg en -onderzoek.

ADDENDUM



Head of Medusa, National Museum of Rome

100-200 years AD

The most popular version of her story describes Medusa as a beautiful young girl, that was taken and ravished by the sea god Poseidon, in the temple of the goddess Athena. Athena punished Medusa by transforming her into a Gorgon, a horrible creature with claws of brass, tusks instead of teeth and snakes for hair. Those who gazed into her eyes would turn into stone. I always wondered why Medusa was the one who was punished, and not Poseidon. But I suppose that Gods do not punish each other, only humans. She is usually portrayed as an angry woman, but Bernini knew her story and showed her despair in his marble sculpture of her. The most famous myth about Medusa is her beheading by Perseus. Perseus was able to slay her while looking at her reflection from the mirrored shield he received from Athena, while Medusa was pregnant by Poseidon. When Perseus beheaded her, Pegasus, a winged horse, and Chrysaor, "he who has a golden sword", sprang from her body. In the 20th century, feminists reassessed Medusa's appearances in literature and modern culture, including the use of Medusa as a logo by fashion company Versace. On top of that, she became the cover of the thesis of the scientific wonder dr. Lokhorst.

Reference: Wikipedia, Heroes by Stephen Fry

11

PORTFOLIO

PhD student: Anne Clarice Fledderus
PhD period: 2019-2021
PhD supervisors: Prof. dr. C.M.A.M. van der Horst, Prof. dr. P.I. Spuls, Prof. dr. S.G.M.A. Pasmans, dr. O. Lapid

	ORAL PRESENTATIONS	ECTS
2019	Core outcome set for congenital melanocytic naevi Naevus Global congress, Brussel, Belgium	0.25
2019	Core outcome set for congenital melanocytic naevi Cochrane Skin Core Outcome Set Initiative, Paris, France	0.5
2019	Core outcome set for congenital melanocytic naevi Nevus Netwerk Nederland, Alphen aan de Rijn, The Netherlands	0.25
2020	Core outcome set for congenital melanocytic naevi Naevus Global congress, Online	0.25
2021	How to perform a systematic review Plastische-, Reconstructieve- en Handchirurgie Researchmiddag, Amsterdam UMC, Amsterdam, The Netherlands	0.5
2021	"Kind met huidafwijking, behandeling van congenitale naevi" Cursorisch onderwijs kindergeneeskunde, Amsterdam UMC, Amsterdam, The Netherlands	0.5
	POSTER PRESENTATIONS	
2018	Core outcome set for congenital melanocytic naevi Core Outcome Measures in Effectiveness Trials (COMET) congress, Amsterdam, The Netherlands	0.5
2019	Core outcome set for congenital melanocytic naevi Symposium voor Experimenteel Onderzoek Heelkundige Specialismen, Amsterdam, The Netherlands	0.5
	CONFERENCES	
2018	Naevus international meeting, France, Paris	0.25
2018	Core Outcome Measures in Effectiveness Trials (COMET) congress, Amsterdam, The Netherlands	0.5
2019	Cochrane meeting, Utrecht, The Netherlands	0.25
2018 and 2019	Nederlandse Vereniging voor Plastische Chirurgie dagen, Scholingsdag, Amsterdam, The Netherlands	0.5
2019 and 2020	Wetenschappelijke Koepel Nederlandse Vereniging voor Plastische Chirurgie, Amsterdam, The Netherlands	0.5
2019	Cochrane Skin Core Outcome Set Initiative, Paris, France	0.5
2020	Naevus International meeting, Brussel, Belgium	0.25
	SUPERVISION	
2019-2020	Linn Widdershoven, Bachelor Thesis, University of Amsterdam, Medicine Neurological signs and symptoms and MRI findings in patients with Congenital Melanocytic Naevi	3

Portfolio (continued)

	SUPERVISION	ECTS
2019-2021	Antoine Gout, Research Elective, University of Amsterdam, Medicine Safety and effectiveness of surgical excision of medium, large, and giant congenital melanocytic nevi: a systematic review and meta-analysis	4
2020-2021	Tadzjo Boom, Master Thesis, Utrecht University, Medicine Database of CMN patients in the Amsterdam UMC Systematic review, what outcomes and instruments are reported for CMN	2
2021	Lynn van Mullekom, Research elective, University of Amsterdam, Medicine What are the reasons for people to decide to excide the CMN or wait until the child has an age to decide for him/herself	0.5
2021	Wendy van Gameren, Master Thesis, Utrecht University, Medicine Quality of life and surgical outcomes in CMN patients in South Amerika	1
2020-2021	Ianthe Slegers, Graduation project, University of the Arts, Utrecht How can we help people with CMN accept their appearance	1
	COURSES	
2018	Scientific writing course, Amsterdam UMC, Graduate School, Amsterdam	1.5
2020-2021	Basis Kwalificatie Onderwijs, Amsterdam UMC, University of Amsterdam	2
2020	Evaluation of medical test, Amsterdam UMC, Graduate School, Amsterdam	0.9
2020	Biostatistics, Amsterdam UMC, Graduate School, Amsterdam	1.1
2021	Systematic reviews, Amsterdam UMC, Graduate School, Amsterdam	0.7
2021	Observational Epidemiology, Amsterdam UMC, Graduate School, Amsterdam	0.6
	OTHER	
2019-2020	Teaching physical examination to medical students, Amsterdam UMC, Skills Centrum, Amsterdam	50
2020	Development of a database of patients with congenital melanocytic naevi in the Amsterdam UMC	3
2020-2021	Organisational support of the Congenital Melanocytic Naevi multidisciplinary clinical consultations in the Amsterdam UMC	3
2019-2021	Coordinator of Outcome for Congenital Melanocytic Naevi (OCOMEN) Steering Group	0.5
2020	Development of a database of patients with congenital melanocytic naevi in the Amsterdam UMC	3
2019-2020	Development of the elective 'Evolution and Medicine/One Health' Amsterdam UMC, University of Amsterdam	25
2019-2021	Development of the elective 'Plastic-, Reconstructive- and Handsurgery' Amsterdam UMC, University of Amsterdam	16
2020-2021	Core outcome set focus group, Amsterdam Public Health	1
2021	Scientific and clinical internship in the University Hospital La Paz, Madrid, Spain	7

LIST OF PUBLICATIONS

In this thesis

Fledderus AC, (2021). 'Il nevo melanocitico congenito gigante' Semeraro R. Colorati da natura (pp 101-115). Milano, Blucarminio kiwi. ISBN: 9788898323623

Fledderus AC, Widdershoven AL, Lapid O, Breugem CC, Pasmans SGMA, van der Horst CMAM, Engelen MM, Spuls PI. Neurological symptoms, signs and MRI abnormalities in congenital melanocytic naevi patients and evaluation of routine MRI screening: systematic review with a meta-analysis. Submitted.

Fledderus AC, Gout HA, Lokhorst MM, Pasmans SGMA, Breugem CC, Lapid O, van der Horst CMAM. Safety and effectiveness of surgical excision of medium, large, and giant congenital melanocytic nevi: a systematic review and meta-analysis. Submitted.

Fledderus AC, Oei W, Korfage I, Eggen CAM, van der Horst CMAM, Spuls PI, Brinkmann SJH, Wolkerstorfer A, van Kessel M, Pasmans SGM. Protocol for the development of core set of domains of the core outcome set for patients with congenital melanocytic naevi (OCOMEN project). J Eur Acad Dermatol Venereol. 2020 Feb;34(2):267-273.

Fledderus AC, Franke CJJ, Eggen CAM, van Etten-Jamaludin FS, van der Horst CMAM, Brinkmann SJH, Spuls PI. Outcomes and measurement instruments used in congenital melanocytic naevi research: A systematic review. J Plast Reconstr Aesthet Surg. 2020 Apr;73(4):703-715.

Oei W, **Fledderus AC**, Spuls PI, Eggen CAM, Kottner J, van der Horst CMAM, Wolkerstorfer A, van Kessel MS, Krengel S, Etchevers HC, Korfage IJ, Pasmans SGM. Development of an international core domain set for medium, large, and giant congenital melanocytic naevi as a first step towards a core outcome set for clinical practice and research. Br J Dermatol. 2020 Nov. doi: 10.1111/bjd.19694.

Fledderus AC, Pasmans SGMA, Wolkerstorfer A, Oei W, Etchevers HC, van Kessel MS, van der Horst CMAM, Spuls PI. Domains and outcomes of the core outcome set of congenital melanocytic naevi for clinical practice and research, part 2 (the OCOMEN project). Br J Dermatol. 2021 May. doi: 10.1111/bjd.20437.

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Not in this thesis

Fledderus AC, Gout HA, Ogilvie AC, van Loenen DKG. Breast malignancy in female-to-male transsexuals: systematic review, case report, and recommendations for screening. Breast. 2020 Oct;53:92-100.

Gorst SL, Barrington H, Brookes S, Chalmers J, Devane D, **Fledderus AC,** Grosskleg S, Hall D, Harman N, Hoffmann C, Katiri R, Maeso R, Saldanha I, Tong A, Williamson PR. Online consensus meetings for COS development: issues to consider. 2021. comet-initiative.org

Khoory BJ, Keuning MW, **Fledderus AC,** Cicchelli R, Fanos V, Khoory J, Deborah N, Elyan E, Vuttipittayamongkol P, Pajkrt D, Mohammed AH, Psychosocial impact of eight weeks COVID-19 quarantine on Italian parents and their children. Submitted.

Becking BE, **Fledderus AC**, Jonkman REG, and van Merkesteyn JP, Profile photo analysis to determine common skeletal malrelationship in children: a diagnostic accuracy study. Submitted.

DANKWOORD

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Special thanks to the stakeholders participating in our research and to the OCOMEN research team, dr. Oei, dr. Eggen, prof. dr. Kottner, dr. Wolkerstorfer, Mrs. van Kessel, dr. Etchevers, dr. Korfage, dr. van Eijsden, and my PhD team, for facilitating the development of a core outcome set for CMN.

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Prof. dr. López Gutiérrez, dear Juan Carlos, thank you for welcoming me to La Paz University Hospital in Madrid and for giving me the opportunity to shadow you in the operating room and the outpatient clinic. I feel very lucky to have learned from your surgical treatment strategies and perspectives on the management of CMN patients. I sincerely hope that this will be the beginning of a long-term collaboration between our centres.

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ABOUT THE AUTHOR

Anne Clarice Fledderus was born on August 16th in 1992 in Chiavari, Italy. Her parents moved to Italy to work as dentists. She enjoyed her childhood in Sestri Levante, growing up together with four other Dutch dentist families as there were scarce job opportunities for dentists in the Netherlands at the time. When she was eight years old, her family moved to Scheveningen, the Netherlands, growing up especially enjoying surfing. In the summer of 2010, she graduated at the Vrije School. That same summer, she received a letter of acceptance to study medicine at the University of Amsterdam.

Early in her studies, she developed interest for natural sciences. In the pursuit of this newfound curiosity, she followed extra electives about natural sciences during her bachelor and went for one semester abroad to study evolutionary biology and marine biology at the University of New South Wales in Sydney, during a year of waiting time between the bachelor's and master's. This waiting time also provided the opportunity to travel and surf in Australia and Indonesia. The professor in Sydney repeatedly mentioned that understanding of evolutionary biology should be implemented in the curriculum of the medical school to allow doctors to understand the origin of human anatomy, physiology and pathology. This inspired her to develop an elective for medical students about this subject together with prof. Roelof-Jan Oostra and prof. Mariska Leeflang, which is now a yearly elective course at the University of Amsterdam about evolution, veterinary medicine and zoonoses (such as the COVID-19 virus).

In 2016, Anne had an internship at the Red Cross Hospital in Beverwijk during the week of New Year's Eve. Due to the firework use during these days, there were several cases of hand surgery and burn scar treatment. Although her plastic surgery internship was only one week, she witnessed numerous challenging yet fascinating surgeries that sparked her interest for plastic surgery. As she was also interested in paediatrics and dermatology, her supervisor at the Red Cross Hospital advised her to get involved in research on giant birthmarks that would combine these interests. She was therefore thrilled when she received an e-mail two years later from dr. Saskia Brinkmann, proposing a scientific internship about congenital melanocytic naevi. In 2019, under the supervision of prof. Chantal van der Horst, prof. Phyllis Spuls, prof. Suzanne Pasmans and dr. Oren Lapid this subject was developed into a PhD project.

As larger congenital melanocytic naevi are extremely rare, financing this project was a major challenge. Anne worked therefore two days a week teaching medical students how to perform physical examinations, a job she thoroughly enjoyed. Furthermore, she was involved in the development of an elective for medical students about plastic, reconstructive and hand surgery together with dr. Margriet van Doesburg, prof. Corstiaan Breugem and the AUMC department of plastic surgery. With the help of a dedicated research team, international stakeholders, motivated students and financial support of *foundation the Merel*, this thesis completed the first step of harmonizing congenital melanocytic naevi care and research.

The last words of this thesis were written in Madrid, as Anne had the opportunity to do a scientific and clinical internship at the University Hospital la Paz, under the supervision of prof. Juan Carlos López Gutiérrez and dr. Carmen Ceballos Rodríguez. In these final months, she gained new perspectives on congenital melanocytic naevi care and research, about international healthcare systems and how to fully enjoy life according to the Spanish.

CREATING MEANINGFUL NARRATIVES

Ianthe Slegers
Afstudeerproject Hogeschool voor de Kunsten Utrecht

Mijn naam is Ianthe Slegers en dit project is mijn afstudeerproject van de studie Kunst en Economie. In de maatschappij waarin we nu leven is er een schoonheidsideaal. Wanneer je niet in dit perfecte plaatje past, word je al snel anders behandeld en aangekeken. Dit zie ik ook bij mijn beste vriendin, die geboren is met een hand- en voetafwijking, waar het heeft geduurd tot afgelopen jaar dat ze korte jurkjes aan durfde te doen, omdat ze bang was voor reacties. Het hebben van een uiterlijke afwijking heeft impact op zelfvertrouwen en zelfacceptatie. In samenwerking met een PhD studente van het Amsterdam Universitair Medisch Centrum ben ik onderzoek gaan doen naar zelfacceptatie bij dragers van reuzenmoedervlekken.

Ik heb me ingewerkt in de materie aan de hand van Design Thinking en Human Centered Design. In deze methodes is het in kaart brengen van de behoefte van de doelgroep het beoogde doel en een product te creëren wat op deze behoefte aansluit. Door o.a. te spreken met leden van de patiëntenvereniging Nevus Netwerk Nederland (NNN), heb ik onderzoek gedaan naar welke middelen er ingezet kunnen worden om zelfacceptatie te stimuleren. Ik ben gaan ontwerpen aan de hand van de volgende vraag;

"Hoe kan ik reuzenmoedervlek patiënten met een cosmetische aandoening helpen met het stimuleren van meer zelfacceptatie door het delen van informatie en verhalen?"

Gedurende mijn onderzoek zijn er vier pijlers naar voren gekomen die van belang zijn op weg naar zelfacceptatie: informatie, community, herkenning en erkenning. De ontwerpoplossing staat in het teken van het delen van ervaringen. Het doel is om het online platform van NNN uit te breiden met persoonlijke verhalen, om ook in de thuisomgeving een plek te hebben om op terug te vallen. Vanuit storytelling theorieën heb ik een format ontwikkeld voor online posts van persoonlijke verhalen.

Door middel van experience mapping heb ik reacties gepeild en daaruit is gebleken dat de verhalen een belangrijke bijdrage kunnen leveren aan herkenning, erkenning en verbinding met anderen. De testpersonen gaven aan dat het lezen van deze verhalen niet alleen zorgde voor deze drie gevoelens, maar ook voor trots op hun community en zichzelf.

Het delen van verhalen leidt tot het versterken van verbinding met de community en voor het hebben van herkenning, wat in mijn ogen een mooie ontwikkeling is. Ik kijk met een goed gevoel

terug op de afgelopen maanden en hoop dat ik de komende maanden nog meer verhalen mag lezen. De verhalen zijn te vinden op de website van Nevus Netwerk Nederland (nevusnetwerk.nl).