

The VASCERN-VASCA Working Group Diagnostic and Management Pathways for Capillary Malformations

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Abstract

Objective: VASCERN (<https://vascern.eu/>) is the European Reference Network for Rare Multisystemic Vascular Diseases. VASCERN-VASCA is the working group within VASCERN that focuses on the study of vascular anomalies. One of the objectives of this group is to establish patient pathways to guide physicians toward efficient diagnostic and management measures. The patient pathway presented here is focused on capillary malformations (CMs).

Methods: The Nominal Group Technique, a structured variation of small group discussion was used. Two facilitators were identified: one to propose initial discussion points and draw the pathway and another to chair the discussion. A dermatologist (E. Baselga) was chosen as the first facilitator due to her specific clinical and research expertise. The draft was subsequently discussed within VASCERN-VASCA monthly virtual meetings and biannual face-to-face meetings.

Results: The pathway starts from the clinical recognition of a vascular red stain, describing clinical characteristics and location. Depending on the clinical features, a subsequent workup for associated manifestations or complications is suggested. These steps should enable the establishment of 6 subtypes of CMs: (1) nevus simplex; (2) isolated CM, syndromic or nonsyndromic; (3) CM of microcephaly CM syndrome; (4) CM of CM-arteriovenous malformation syndromes; (5) “pseudo” CM of arteriovenous malformation; (6) cutis marmorata telangiectatica congenita. Management according to the recognized phenotype is detailed in subsequent pages of the pathway. A color code is used to differentiate (1) clinical evaluations, (2) investigations, (3) associated genes, and (4) treatments. Actions relevant to all types are marked in separate boxes, for example, when to perform specific imaging.

Conclusion: The collaborative efforts of VASCERN-VASCA, a European network of the 14 Expert Centers for Vascular Anomalies, have led to a consensus pathway for CMs. This pathway may help clinicians to guide in the diagnosis and management of CMs, as well as to emphasize the crucial role of multidisciplinary expert centers in the management of these patients. This pathway is available on the VASCERN website (<http://vascern.eu/>).

Keywords: algorithm, capillary malformation, cutis marmorata telangiectatica congenita, diagnosis, management, nevus simplex, port wine stain, syndrome

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Introduction

The European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN), is dedicated to gathering experts in Europe for patients with rare vascular diseases. These include large- and medium-sized arterial diseases, lymphedema, hereditary hemorrhagic telangiectasia, neurovascular diseases, and vascular anomalies, including vascular tumors and vascular malformations. Today, VASCERN membership is composed of 39 highly specialized multidisciplinary healthcare providers (HCPs) from 14 EU Member States and of various European Patient Organizations. It is coordinated from Paris, France.

The Vascular Anomalies working group in VASCERN (VASCERN-VASCA) has developed different diagnostic and management pathways based on a group of expert

interactions to share their experience for the diagnosis and management of different vascular anomalies.^{1–3} The VASCERN-VASCA diagnostic and management pathways may help support decision-making for physicians suspecting a vascular anomaly, including severe/rare infantile hemangiomas, lymphatic malformations, and vascular malformations.

Capillary malformations (CMs) are a clinically and genetically heterogeneous group of vascular malformations composed of dysplastic capillaries that are abnormal in number and/or size. They are already present at birth and manifest clinically as a vascular stain that varies in color from pink to dark purple. The appearance/color of the vascular lesion may vary in patients with different skin tones. There are many recognizable phenotypes and, in recent years, a number of somatic and germline variants have been detected in different causative genes.^{4–10}

Many CMs are an isolated phenomenon, and others are part of syndromic clinical presentations. In the latter case, these CMs may represent the only visible lesion that prompts further investigations. In some cases, the initial appearance/phenotype is not always predictive of problematic associations and a careful examination at baseline looking for more subtle findings is essential as is re-evaluation over time since associated features may evolve over time. Therefore, it is important to recognize the different phenotypic subtypes of CMs, as these will direct further specific evaluations and follow-up.

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Patients and methods

VASCERN-VASCA is composed of a multidisciplinary panel of experts (including dermatologists, plastic surgeons, vascular surgeons, pediatric surgeons, interventional radiologist, geneticists, otorhinolaryngologists, head and neck surgeons, and pediatric oncologists) and patient representatives. They represent HCPs endorsed by their national governments as board members of VASCERN-VASCA or affiliated members of VASCA research groups. Based on the principle that decisions from a group of experts are better than those from a single expert, VASCERN-VASCA decided to draw a patient pathway for CMs with a Nominal Group Technique, a well-established, structured, multistep, facilitated group meeting technique used to generate consensus statements.¹¹

The pathway was drawn within 2 face-to-face meetings between March 2018 and October 2018, as well as in multiple online meetings during 2018 to facilitate discussion. It was further developed by e-mail to avoid group dynamics, that is, influence from most authoritative group members. Two facilitators were identified: one to propose initial discussion points and draw the pathway and another to chair the discussion. A dermatologist (E. Baselga) was chosen as the first facilitator due to her particular expertise in CM. Further decision points were proposed by the group, and the best choices were discussed within the panel of experts. Conflicting points were further discussed until the multidisciplinary team reached and agreed on a conclusion unanimously. The chair of the group promoted inputs from all members and summarized the opinions and the reasons for the choices, identifying common ground. No time limits were set to reach a consensus. After the first meeting, the document was circulated by e-mail to all the group members to collect further peer comments. A final face-to-face meeting was organized in order to definitely validate the pathway. The pathway was presented as a poster at the International Society for the Study of Vascular Anomalies May 12–15, 2020 virtual meeting for international expert discussion and as an oral presentation at the 30th European Academy of Dermatology and Venereology Congress (virtual congress, September 29–October 2, 2021).

Results

Initial pattern recognition of vascular stain and diagnostic workup (Figures 1–3)

CMs are almost always present at birth and appear as pink to red or magenta macules or patches that at least partially blanch on diascopy. The initial step in their evaluation is to identify their clinical characteristics such as the presence of multiple small lesions, whether they are surrounded by a pale halo, whether the CM is linear, confluent, or reticulated, and whether the lesion feels warm to palpation or have a rapid capillary refill (Figure 1).

Multiple small capillary malformations (Figure 1). Multiple, small CMs may be seen in 2 settings: capillary malformation-arteriovenous-malformation syndrome (CM-AVM) and microcephaly capillary malformation syndrome (MIC-CAP).

- CM-AVM is an autosomal dominant condition due to *RASA1* (60%) or *EPHB4* (20%) variants. In up to 20%

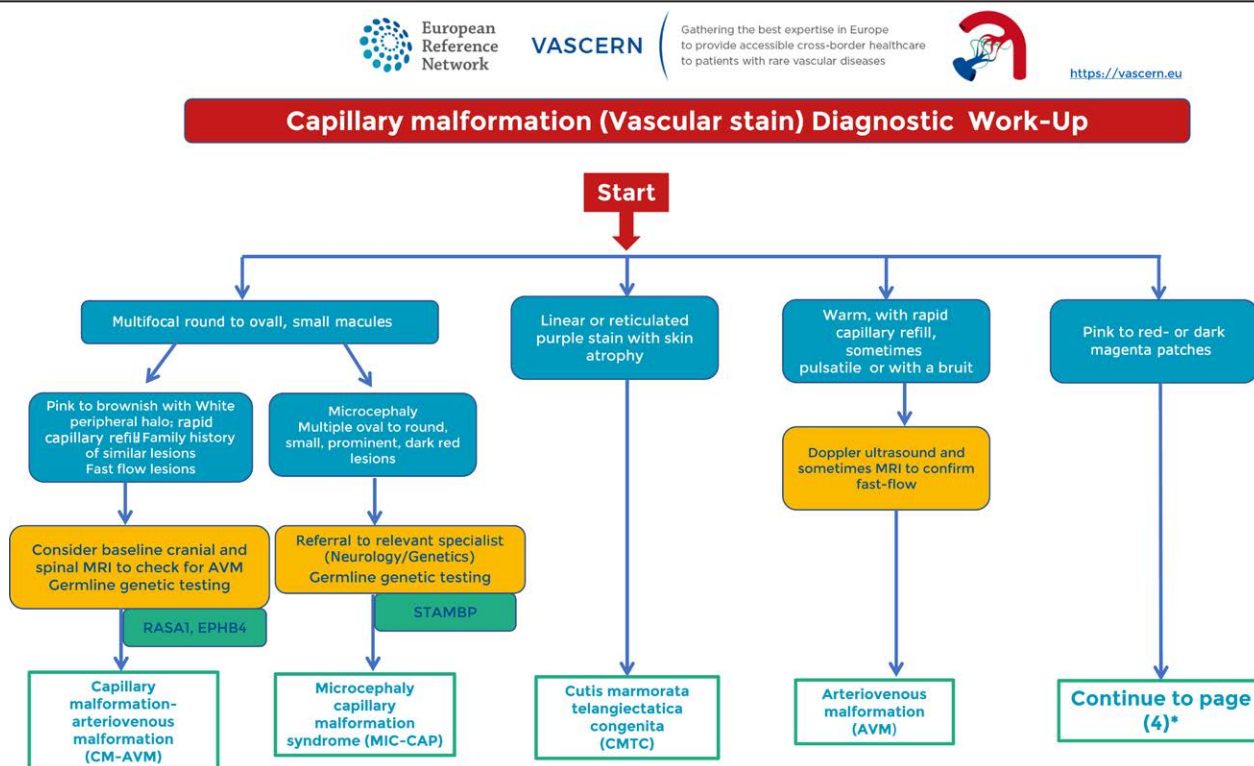


Figure 1. Diagnostic workup for CM (vascular stain). CM indicates capillary malformation. Reprinted with permission of the European Reference Network, VASCERN.

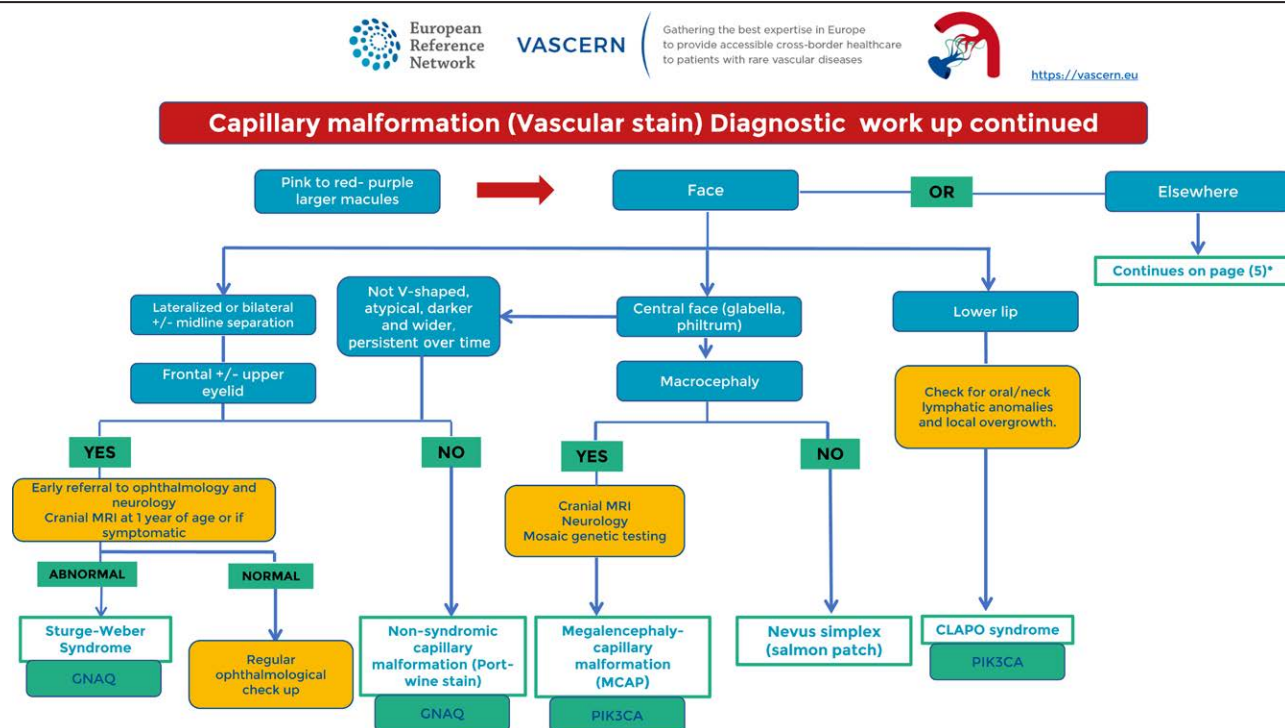


Figure 2. Diagnostic workup for CM (vascular stain), continuation of Figure 1. CM indicates capillary malformation. Reprinted with permission of the European Reference Network, VASCERN.

of patients, no disease-causing variant is found.^{12–14} Affected children present with multiple, small, round-to-oval stains of pale pink to brownish color, from birth or early infancy. They are most commonly located on the trunk, limbs, head, and neck, and rarely on the palms, soles, and oral or nasal mucosa. A characteristic

small halo often surrounds some of the stains and they show a rapid capillary refill to touch. As the child grows, new lesions may develop. Sometimes there is a larger lesion (a “dominant lesion”) already present at birth. An increase in local temperature and blood flow detected using Doppler ultrasonography (US) is also

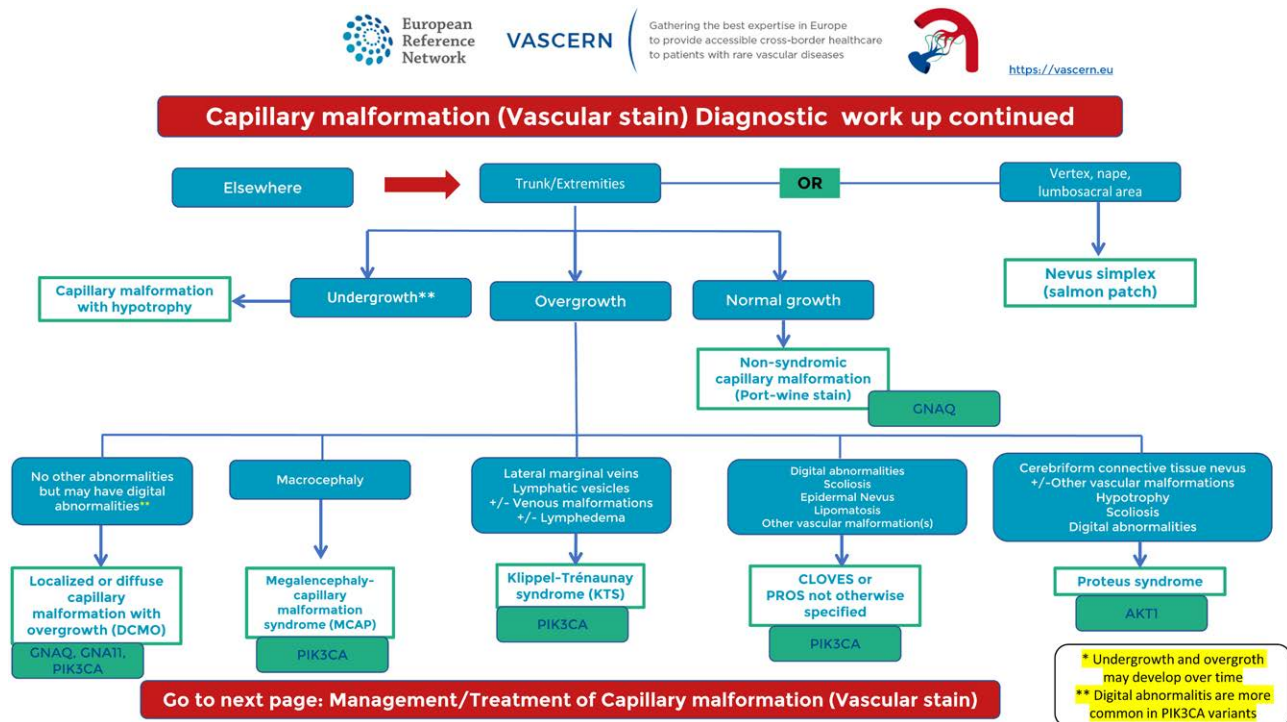


Figure 3. Diagnostic workup for CM (vascular stain), continuation of Figures 1 and 2. CM indicates capillary malformation. Reprinted with permission of the European Reference Network, VASCERN.

a common feature. With time, the stains may become light brown in color and may be confused with *café au lait* macules. Telangiectasias and Bier spots (small white areas of vasoconstriction) may be seen in some patients. Up to one-third of affected patients have an arteriovenous malformation (AVM), and in approximately 10% of cases, the AVM is located in the central nervous system (cranial or spinal).¹⁴ There is limited data on screening for fast-flow vascular anomalies of the central nervous system in patients with CM-AVM. Most centers of VASCERN-VASCA perform imaging of the head and the spine; however, the necessity for treatment or observation of identified lesions cannot be predicted prior to the magnetic resonance imaging (MRI). Thus, screening should be discussed with the patients and their families. It remains uncertain at this point whether follow-up imaging should be obtained and how often after a normal baseline screen.

- MIC-CAP is a rare congenital disorder characterized by severe progressive microcephaly, early-onset refractory epilepsy, profound developmental delay, distal limb abnormalities, and multiple small CMs spread diffusely on the body.^{15–17} CMs in MIC-CAP are multiple round-to-oval, small, red macules. The color is much more intense than the CM in CM-AVM. This rare disease is caused by homozygous or compound heterozygous variants in the *STAMBP* gene.¹⁸ This autosomal recessive condition has only been described in a few families. The facial features and microcephaly should allow the diagnosis to be suspected.

Linear or reticulated purple stain (Figure 1). When evaluating a newborn with a vascular stain that is reticulated, dark purple (resembling livedo reticularis), we should suspect cutis marmorata telangiectatica congenita (CMTC). This is

a sporadic condition. The reticulated, well-defined, purple or blue vascular stain with a marble-like pattern is often unilateral. It involves most commonly the lower extremities, but also the upper extremities and trunk.^{19–22} Skin atrophy or even ulceration at the site of CM is pathognomonic of this condition.²² The affected extremity is usually thinner than the unaffected limb due to atrophy of the underlying dermis or other soft tissues such as subcutaneous fat or muscle. CMs in CMTC usually fade to some extent with years, though underlying atrophic areas will persist in more severely affected cases. There are no consistent associated abnormalities and affected patients do not need further workup unless there is an abnormal physical exam. Only patients with facial CMTC affecting the periocular region may warrant an ocular exam to rule out glaucoma. Generalized CMTC, on the other hand, may be part of Adams–Oliver syndrome. In general, the diagnosis of Adams–Oliver Syndrome is straightforward due to the characteristic aplasia cutis and limb abnormalities.

Warm, pulsatile stain (Figure 1). AVMs may present initially in their quiescent stage (Schobinger stage I) as a macular vascular stain that resembles a CM.²³ These stains are usually solitary and medium to large in size. The exception is CM-AVM disease, where CMs are multiple and often small in size. The most distinctive clinical features of this “pseudo” CM are warmth to the touch, rapid capillary refill when compressed, heterogeneity of stain color saturation, and archipelago-like borders with craggy inlets and outlets. In many cases, there is a peripheral white halo.

When suspected, an initial US, followed by MRI or magnetic resonance angiography are needed to support the diagnosis. Genetic testing may be helpful as most patients present somatic variants in *MAP2K1* or germline variants in *RASA1* or *EPHB4*. Long-term follow-up is recommended, as patients may progress to Schobinger stages II to IV.

Pink to red patches (Figures 2 and 3). Larger solitary or segmental pink to red patches will have different diagnostic workups and implications, depending on whether they are located on the face or elsewhere.

Facial stains (Figure 2). The first step when evaluating facial CM is to determine if they are centrally located or lateralized to one side. Central stains on the mid-forehead and glabella most often represent nevus simplex (NS), also called salmon patches.²⁴ NS is a very common CM that presents as pale pink to dark pink macules or patches with indistinct borders. They become more visible with crying and temperature changes. On the forehead, they are often present in a V-shaped configuration. They are quite common on the inner part of the upper eyelids, usually bilaterally. Other less frequent locations on the face are the tip of the nose, with a triangular configuration and philtrum. In many patients, facial NS coexists with NS at the vertex, nape of the neck, and more infrequently on the back and lumbosacral area. NS tends to fade in the first year of life and this is also an important feature for diagnosis. NS do not need, even in extensive cases, further workup and they tend to fade in the first 2 years of life. The only exception to this would occur in children with macrocephaly, as NS in the frontal area and philtrum is a characteristic finding in macrocephaly-capillary malformation syndrome (MCAP). However, this entity usually presents with a darker stain. In these cases, cranial MRI is performed to detect megalencephaly or polymicrogyria, and neurology consultation is warranted. Genetic studies for *PIK3CA* variants of the affected tissue could also be offered in this setting. A persistent and larger mid-frontal NS has to raise the suspicion of a median PWS.

Facial CM (port wine stain [PWS]) lateralized to one side, are mostly due to *GNAQ* (p.R183Q) or *GNA11* (p.R183H) variants.^{25–29}

Those CMs located on the forehead have an estimated risk of about 15% of associated glaucoma and/or leptomeningeal angiomatosis.^{25,30} This association, Sturge–Weber Syndrome (SWS), can be explained if one considers the embryologic origin of the face.²⁵ The skin of the forehead and the optic vesicle area are the only parts of the face that are formed by the migration of neural crest cells from the developing prosencephalon (forebrain) and the cortex. The eyes also develop from the forebrain. Therefore, a mutational event during embryogenesis in the developing prosencephalon may lead to SWS. Thus, children with PWS on the forehead warrant ophthalmological follow-up and neurology referral. The risk of SWS is higher in larger PWS (ie, hemifacial PWS) and with bilateral involvement. In a recent study, none of the children with small PWS on the forehead area (involving less than half of the hemi-forehead) had SWS.³¹ Glaucoma may be congenital or develop afterward. The baseline eye examination should include visual acuity measurement, intraocular pressure check, and a full dilated eye examination. Neurologic involvement manifests with seizures, stroke-like episodes, cognitive problems, and headaches. Seizures occur in approximately 75%–80% of patients with SWS.³² Leptomeningeal involvement is better detected using MRI with gadolinium and susceptibility-weighted imaging, which should be obtained in case of neurologic symptoms. The need to perform an MRI in asymptomatic children remains controversial, because of the need of general anesthesia and due to the fact that an early MRI, that is, before 8 weeks of age,

may result in false negatives.³³ On the other hand, a normal MRI in a 1-year-old asymptomatic child can be reassuring.

On rare instances, PWS in SWS may be centrally located on the forehead and it may be difficult to differentiate from NS.³⁰ In these cases, the CM is not V-shaped, it has more distinct borders, its color is more intense than in a NS, and it does not fade over time. In case of doubt, a patient with median PWS may benefit from the same management as those with lateralized forehead PWS. Early-stage arteriovenous malformation also tends to be midline and may mimic a PWS, but they tend to be warmer to touch and show a rapid capillary refill. In case of doubt, a Doppler ultrasound may help in the differential diagnosis.

A CM on the lower lip is a characteristic finding in CLAPO (Capillary Malformation of the Lower Lip, Lymphatic Malformation of the Face/Neck, and Partial or Generalized Overgrowth) syndrome.³⁴ The CM of the lower lip is always midline and symmetrical, it has well-defined borders, and it generally extends to both the adjacent skin and mucosa. Other features of this syndrome that are variably present include lymphatic malformation predominant on the face and neck, facial asymmetry, and partial/generalized overgrowth.³⁵ CLAPO syndrome constitutes a clinical phenotype within *PIK3CA* overgrowth disorders.³⁶

Trunk/extremities CMs (Figure 3). When evaluating a CM on the trunk or limbs, an important feature for diagnostic management is to determine whether there is an associated undergrowth or overgrowth of the affected area.

CM on trunk or extremities without associated undergrowth or overgrowth represents nonsyndromic PWS or CM, and they do not require additional investigations. The finding of somatic variants in *GNAQ*, *GNA11*, or *PIK3CA* point to a key role in the activation of Ras/PI3K pathways in the pathogenesis of CM.³⁷

CMs with associated overgrowth may be part of a more complex syndrome or association. At the initial clinical examination, it is important to check for additional features such as macrocephaly; digital abnormalities; the clinical characteristics of the CM itself; the presence of other vascular anomalies such as lymphatic vesicles, AVMs, or venous anomalies (ie, varicosities or a lateral marginal vein on the extremities); the coexistence of lipomas; epidermal nevi; scoliosis or cerebriiform connective tissue nevi of the soles. A darker sharply demarcated geographic stain points to certain phenotypes.³⁸ Altogether the main clinical phenotypes associated with pink to red patches that may be identified are:

- Diffuse CM with overgrowth is a descriptive term to designate an extensive CM with proportional nonprogressive overgrowth of soft tissues and/or bones.³⁹ In this setting, the CM is usually pale pink and reticulated with a physiologic cutis marmorata-like appearance, although it may be more confluent or solid at distal parts. Overgrowth may affect only one extremity, ipsilateral or contralateral to the stain, or, less frequently, an entire side of the body. Digital anomalies are present in up to a third of patients. They include soft-tissue syndactyly, especially involving the second and third toes; a widened first pedal web space (ie, “sandal gap”); and macrodactyly (fingers or toes). The same type of CM has rarely been described in children with undergrowth of the affected extremity.^{39,40} Patients with diffuse CM with overgrowth do not usually have

other major associated abnormalities, although dilated veins may be seen. *PIK3CA* variants, and most commonly, nonhotspot mutations, may be detected in some patients, as well as *GNAQ* and *GNA11* or even other gene variants. Digital abnormalities are more common in patients with *PIK3CA* variants.⁴¹

- MCAP is an overgrowth syndrome characterized by the presence of an extensive reticulated CM of the trunk and limbs, prominent NS (especially involving the glabella or philtrum), and macrocephaly or megalencephaly. Facial dysmorphism and asymmetric overgrowth are usually evident early after birth. Syndactyly and polydactyly are common, as are neonatal hypotonia and mild-to-moderate developmental delay.^{42–44} The macrocephaly may be associated with structural abnormalities such as cerebral asymmetry, ventriculomegaly (usually nonobstructive), Chiari type I malformation, acquired cerebellar tonsillar herniation, cortical dysplasia, and polymicrogyria. These abnormalities can be progressive. Therefore, serial MRI images should be obtained, especially in the first 2 years of life and in case of changing clinical signs.^{45,46} Further recommendations for follow-up are out of the scope of this article and will be the aim of another VASCERN-VASCA patient pathway dedicated to overgrowth syndromes. MCAP is caused by somatic and germline mosaic variants in *PIK3CA*.^{47–49}
- Klippel-Trenaunay syndrome (KTS) is a term that has been applied in the past to CM with overgrowth, and in some cases undergrowth, of the affected limb. However, it is now mostly agreed that KTS consists of a combined capillary-lymphatic malformation; varicosities of unusual distribution (in particular, the lateral venous anomaly); and limb enlargement.⁵⁰ At birth, the capillary-lymphatic malformation presents as a vascular stain with extremely sharply demarcated borders and irregular shape, resembling a continent or a country (geographic stain).³⁸ The color is intense and varies from dark pink to dark magenta. Small hemorrhagic papules or vesicles develop over time and occasionally are present at birth. These stains are most frequently found on the lateral side of the lower limbs, although they may extend to the abdomen. Upper extremities are less frequently affected. Venous abnormalities manifest as large, extensive superficial veins on the lateral aspect of the leg. They often represent persistent embryonic vein remnants, such as the “lateral marginal vein.” They may be noted at birth or in early infancy, but typically become more apparent in adolescence. These venous anomalies can predispose patients to thromboembolic complications.⁵¹ Hypertrophy in KTS is usually obvious at birth and is often progressive. Patients with KTS should be counseled regarding the risk of thromboembolism especially if D-dimers and fibrinogen levels are abnormal. Surgery, radiofrequency, or sclerosis of the malformed veins should be considered in the case of a patent deep venous system.^{52–54} An orthopedic follow-up is also needed to correct the leg length discrepancy. KTS is now considered within the spectrum of PROS (*PIK3CA*-related overgrowth spectrum) since somatic *PIK3CA* variants have been reported in several patients.⁵⁵ This might open opportunities for targeted therapy with *PIK3CA* inhibitors.^{10,56,57}

- Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis (CLOVES) or other PROS diseases. CLOVES syndrome is another overgrowth syndrome with CMs. Usually, the CM in CLOVES syndrome partially involves the skin overlying the lipomatous truncal masses. They are often well-saturated in color, well-demarcated, of variable size, and may have hemorrhagic lymphatic vesicles on the surface, so-called geographic stains.³⁸ Multiple CM may be present.⁵⁸ The most characteristic feature of CLOVES syndrome is the progressive, complex vascular malformation (lymphatic, venolymphatic, or capillary-lymphatic) on the trunk, with dysregulated fat tissue. In addition, AVMs have been recognized as another feature.⁵⁹ Overgrowth is congenital of a “ballooning” nature and grows proportionately with the patient whereas in Proteus syndrome the overgrowth appears later and is disproportionate and very asymmetric. Hands and feet are wide, square-shaped, and often show macrodactyly and a wide sandal gap. Wind-blown hand deformity is often present. Furrowed or wrinkled soles can be observed, but they do not always show the cerebriform connective tissue of Proteus syndrome.⁶⁰ CLOVES syndrome is caused by postzygotic-activating variants in the *PIK3CA* gene, usually but not only at the helical domain, or other hotspot locations. A more detailed description of all the abnormalities and management of complications in CLOVES syndrome is beyond the scope of this patient pathway and will be discussed in another overgrowth pathway.

In clinical practice, there are many patients that present some of the clinical features of CLOVES syndrome but lack other manifestations. These children are classified by most authors as PROS, otherwise unclassified.

- Proteus syndrome is a rare condition characterized by distortive and asymmetric postnatal progressive overgrowth of the bones, skin, and other tissues.^{61–66} Newborns with Proteus syndrome have few or no signs of the condition. Overgrowth becomes apparent between the ages of 6 and 18 months and becomes more severe with age. With time, adipose dysregulation including lipomatous overgrowth and lipoatrophy becomes also apparent. Dysmorphic facial features including dolichocephaly, long face, down slanting palpebral fissures, and/or minor ptosis, depressed nasal bridge, wide or anteverted nares, and open mouth at rest are also common. With time, an almost pathognomonic cerebriform connective tissue nevi is seen on plantar soles and rarely elsewhere. Other manifestations include epidermal nevi; pulmonary bullae; specific types of tumors; the possibility of deep vein thrombosis; intellectual disability; and, in some cases, seizures and/or brain malformations. Some of the patients may have a CM, but this is not the cardinal feature that allows suspicion of this syndrome. When present, CMs are well-defined, dark pink or red, and they are located on the trunk or extremities. Prominent veins underlying the CMs may be observed, as well as lymphatic malformations. Diagnostic criteria have been proposed.^{61,63} Proteus syndrome is caused by a distinct activating missense somatic variant in the *AKT1* gene (E17K).^{67–71}

Management/treatment of capillary malformations (Figures 4 and 5)

Management and treatment of CMs will depend on the associated conditions. Indeed, in complex syndromes, CM in itself may be the most innocuous and least worrisome

component. In the case of visible lesions, vascular-selective lasers represent the treatment of choice. Pulse dye laser is the gold standard for the treatment of CMs, although other lasers such as the Neodymium Yag or Alexandrite lasers may be used in therapy-resistant CM lesions. CM thickening may

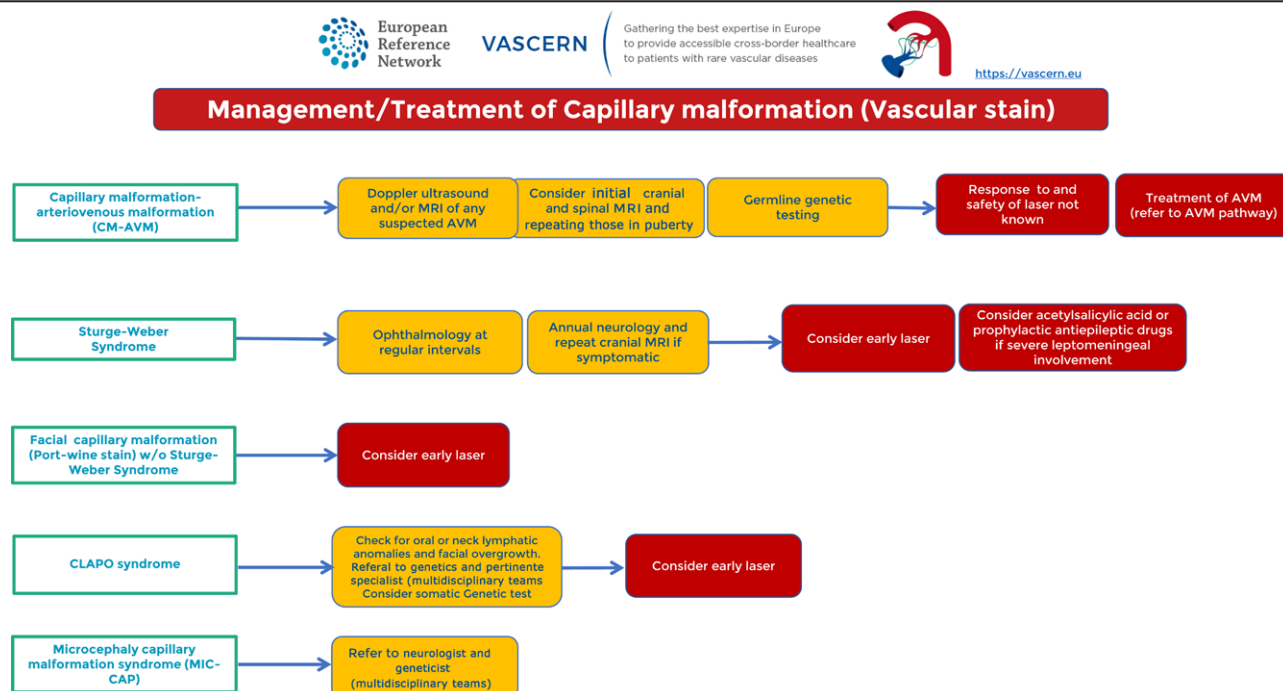


Figure 4. Management and treatment for CM (vascular stain). CM indicates capillary malformation. Reprinted with permission of the European Reference Network, VASCERN.

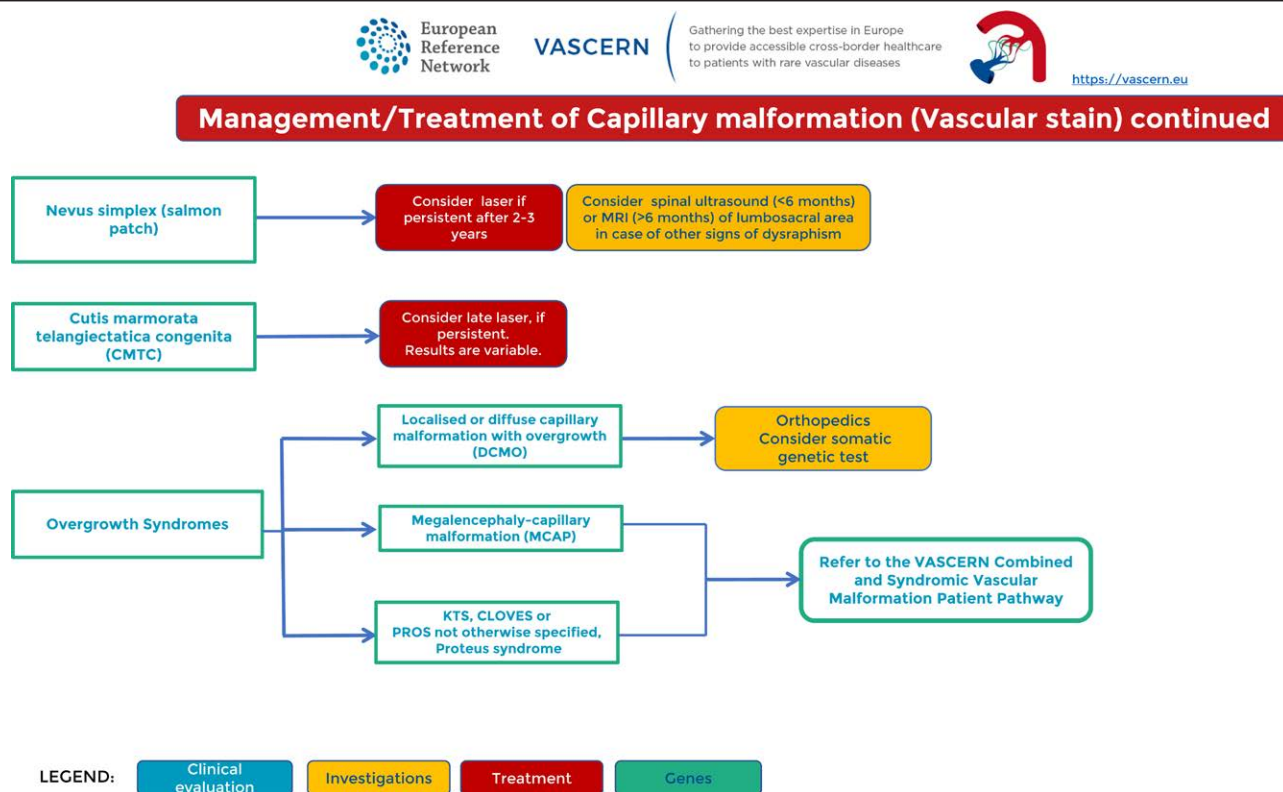


Figure 5. Management and treatment for CM (vascular stain), continuation of Figure 4. CM indicates capillary malformation. Reprinted with permission of the European Reference Network, VASCERN.

occur even if the malformation has been treated very early. Intense pulse light may also be useful.^{72–74} Treatment can be initiated at any age, although most authors recommend starting early during childhood, as CMs may thicken with time and become more difficult to treat. However, it must be noted that there are no studies showing a better response to treatment at a younger age. Several treatments are necessary to obtain significant lightening. Some anatomic sites may respond better than others, with distal and centrofacial sites showing less response. With time, CM may get dark again and further treatments may be necessary.

For patients with an associated limb overgrowth, evaluation by an orthopedic surgeon is advised. Interdisciplinary evaluation is mandatory for more complex syndromes and is beyond the scope of this CM pathway.

Discussion

CM is a broad term used to describe any vascular stain with dysplastic capillaries.⁴¹ CMs belong to a group of rare vascular anomalies and may be an isolated manifestation or part of a complex syndrome. In most cases, the clinical appearance of CM informs the diagnostic evaluation needed. In this article, we present major clinical patterns for CM that facilitate further diagnostic workup. Other CM subtypes are not part of this algorithm (eg, nevus roseus, phacomatosis spilorosea).

In the absence of clinical trial and meta-analysis in the field of rare conditions, expert opinion is the best tool to improve the quality of patients care. The Nominal Group Technique is a consensus technique that involves a group of experts to generate ideas and determine priorities.^{75,76} It has been defined by Van de Ven and Delbecq as “a structured meeting which seeks to provide an orderly procedure for obtaining qualitative information from target groups who are most closely associated with a problem area.”⁷⁷ The structured process allows the participants to decide which topics require further discussion, avoiding the domination of the debate by more authoritative or dominant members. Moreover, equal participation for all group members in conflicting concepts is guaranteed by the facilitator. The limiting factor of this technique is the absence of anonymity, which is guaranteed in the Delphi method. Therefore, we cannot completely avoid the fact that the process may be driven by the authority and personality of some of the experts involved.

The quality of the statements by an expert panel depends on the members' skills. Using the VASCERN network, the group's expertise in the field of vascular anomalies was guaranteed by the selection of national reference centers endorsed by their governments and selected by the European Community's ERN network based on well-defined criteria. These HCPs have representatives who are members of the International Society for the Study of Vascular Anomalies.

In conclusion, VASCERN-VASCA proposes an expert opinion on CMs patient pathways as a useful tool to improve the diagnosis and management of these patients. It focuses on the importance of a careful clinical examination and family history and, in most cases, the need of appropriate investigations, including genetic testing, to confirm whether it is an isolated phenomenon or part of a complex syndrome. The proposed management outlined earlier is currently used in multidisciplinary centers and will be kept up-to-date based on the latest insights.

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