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VASCULAR ANOMALIES

VASCULAR TUMORS

- Benign
- Borderline
- Malignant

VASCULAR MALFORMATIONS

Fast-Flow

- Isolated
- Multifocal
- Syndromic

Slow-Flow

Capillary

- Nevus simplex, Salmon Patch
- Port wine CM
- Reticulate/telangiectatic CM
- Geographic Pattern CM
- Low-resistance CM/CM with faster flow
- Cutis marmorata telangiectatica congenita
- Telangiectasias and Spider Angiomas

Lymphatic

- Isolated
- Complex
- Lymphedemas

Venous

- Isolated
- Multifocal
- Syndromic

Combined

- Isolated
- Syndromic

PUVA
(Potentially Unique Vascular Anomaly)

Developmental Anomalies of Named Vessels

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VASCULAR TUMORS

Benign*

- Infantile hemangioma
- Congenital hemangioma
- Tufted angioma
- Cherry angioma
- Epithelioid hemangioma
- Cutaneous epithelioid angiomatous nodule
- Pyogenic granuloma (lobular capillary hemangioma)
- Spindle-cell hemangioma
- Hobnail hemangioma
- Microvenular hemangioma
- Anastomosing hemangioma
- Glomeruloid hemangioma
- Papillary hemangioma
- Acquired elastotic hemangioma
- Intravascular papillary endothelial hyperplasia (Masson tumor)
- Littoral cell hemangioma of the spleen
- Placental chorioangioma
- Eccrine angiomatous hamartoma
- Reactive angioendotheliomatosis
- Bacillary angiomatosis

Borderline

- Kaposiform hemangioendothelioma
- Retiform hemangioendothelioma
- Papillary intralymphatic angioendothelioma (PILA), Dabska tumor
- Pseudomyogenic hemangioendothelioma
- Polymorphous hemangioendothelioma
- Kaposi’s sarcoma
- Composite hemangioendothelioma
- Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT)

Malignant

- Angiosarcoma
- Epithelioid hemangioendothelioma

*Reactive proliferative vascular lesions are listed with benign vascular tumors

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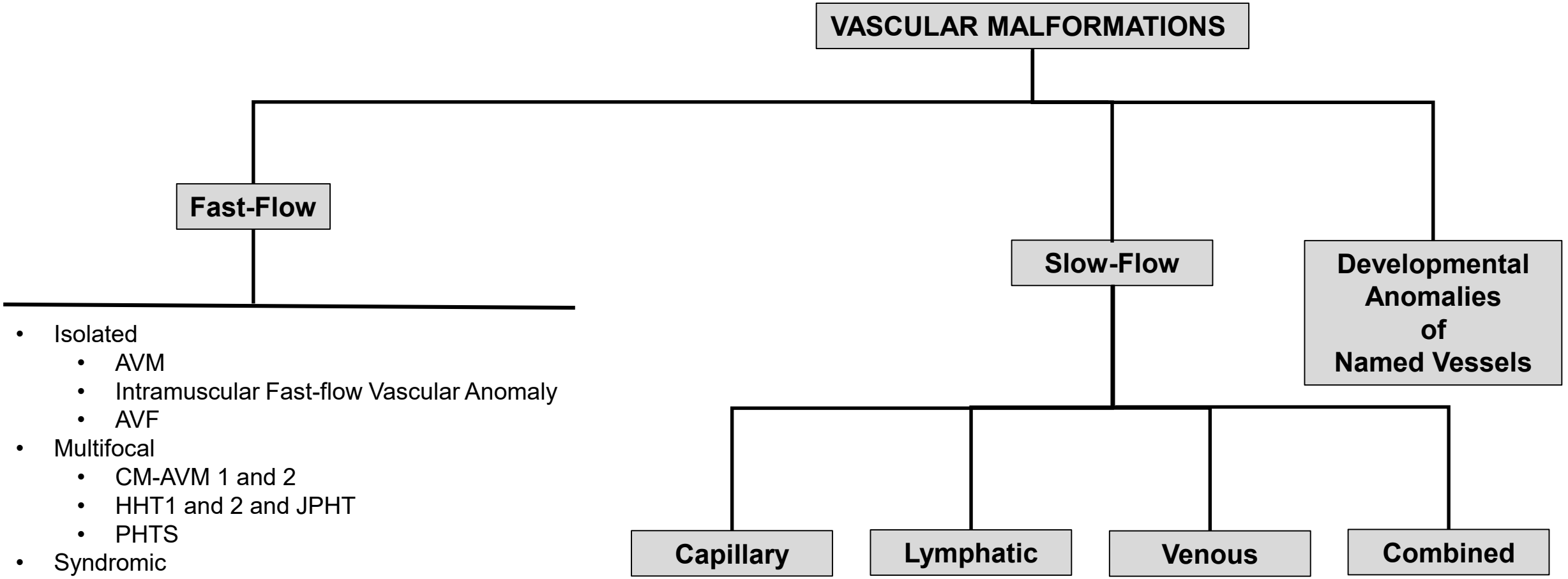

- Isolated
  - AVM
  - Intramuscular Fast-flow Vascular Anomaly
  - AVF
- Multifocal
  - CM-AVM 1 and 2
  - HHT1 and 2 and JPHT
  - PHTS
- Syndromic
  - PHOST (PHTS)
  - Parkes-Weber Syndrome
  - SAMS
  - CAMS

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VASCULAR MALFORMATIONS

SLOW-FLOW

Capillary

- Nevus simplex, Salmon Patch
- Port wine CM (Port wine Birthmark, Nevus flammeus)
  - Isolated (includes Phacomatosis Pigmentovascularis)
  - Syndromic
    - With hypertrophy or extracutaneous disease
    - Sturge-Weber Syndrome
    - DCMO
- Reticulate/telangiectatic CM
  - Isolated
  - Syndromic
    - M-CM
    - MIC-CAP
    - DCMO
- Geographic Pattern CM
  - Isolated
  - Syndromic
    - KTS
    - Associated with CLOVES/Disorders of PROS
- Low-resistance CM/CM with faster flow
  - Isolated
  - Syndromic
    - CM-AVM 1 and 2
    - Parkes-Weber Syndrome
- Cutis marmorata Telangiectatic Congenita
- Telangiectasias and Spider Angiomas
  - Isolated
  - Syndromic
    - CM-AVM 1 and 2
    - HHT 1 and 2 and JPHT (see AVM category)

Lymphatic

- Isolated
  - LM
    - Macrocystic
    - Microcystic
    - Mixed Macro-microcystic
  - Angiokeratoma
- Complex
  - GLA
  - KLA
  - GSD
  - CCLA
    - Isolated
    - Syndromic (RASopathy)
  - GLD
- Lymphedemas
  - Primary
    - Isolated
    - Syndromic
  - Secondary

Venous

- Isolated
  - VM
    - Phlebectatic
    - Spongiform
  - VVM
  - FAVA
- Multifocal
  - VMCM
  - MSVM
  - BRBNS
  - GVM
  - HCCVM/CCM
  - VMOS
- Syndromic
  - PHTS
  - CLOVES
  - Mafucci Syndrome
  - Sinus Pericranii

Combined

- Isolated
  - CLVM
  - LVM
  - CLM
  - CVM
  - HCCVM/VVM
- Syndromic
  - PROS
  - KTS (CLVM with hypertrophy)
  - CLOVES
  - CLAPO
  - Proteus Syndrome

Developmental Anomalies of Named Vessels

- Vena cava
- Aorta
- Vein of Galen
- Others

GLOSSARY

At the end of each item, use Key: [a] = acronym; [e] = eponym; [g] = gene; [s] = syndrome description; [t] = technical term

Abernethy malformation: a very rare vascular anomaly of the portal venous system, also known as congenital portosystemic shunts. It is commonly associated with multiple congenital anomalies and results from persistence of the embryonic vessels. [e][s]

Abortive Infantile Hemangioma (also known as "Infantile Hemangioma with Minimal or Arrested Growth" (IH-MAG): defined as IH where proliferation is seen in 25% or less of IH precursor patch. [t]

Acral Arteriovenous Tumor: superficial, lobulated, benign vascular lesion of the skin, predominantly located in fingers and toes. The combination of three different elements: arterial, venous, and transitional vascular channels make up the predominant histologic features of this lesion. [t]

Acquired Elastotic Hemangioma: a specific type of benign Vascular Tumor. A distinctive clinicopathologic variant of hemangioma that should be differentiated from other cutaneous vascular proliferations. On histopathologic examination, it is characterized by capillary proliferation involving the dermis [t]

Acquired Progressive Lymphatic Anomaly: a specific type of LM. [t]

***ACVRL1*:** gene, related to vascular malformations. Variants in *ACVRL1* are found in Telangiectasia, AVM and AVF of HHT2. [g]

ADAMTS3: gene related to vascular malformations. Pathogenic variants in *ADAMTS3* are found in Primary Generalized lymphatic anomaly type 3 (Hennekam lymphangiectasia-lymphedema syndrome 3). [g]

***AKT1*:** gene. Genetic variants in *AKT1* are found in Proteus Syndrome. [g]

Aplasia: failure of an organ or tissue to develop. [t]

Anastomosing Hemangioma: a specific type of benign Vascular Tumor. [t]

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Aneurysm: excessive localized enlargement of an artery caused by a weakening of the artery wall. [t]

Angel Kiss: a descriptive term used which is synonymous with nevus simplex . [e]

Angiogarchitecture: the analysis of the structure and organization of blood vessels including arteries, capillary bed and draining veins

Angiokeratoma: a lesion characterized by capillary ectasia in the papillary dermis associated to variable epidermal hyperplasia and elongation of the rete ridges enclosing the vascular channels. Lesions present as asymptomatic blue-red hyperkeratotic papules or plaques anywhere on the skin. It is a morphological diagnosis with several etiologies, both genomically and clinically. [t]

Angiomatosis: theterm 'Angiomatosis' in the absence of a qualifier is not a useful diagnosis. The term, in the absence of an adjective should be avoided. The term 'angiomatosis' was introduced in the early twentieth century to describe cases with multiple vascular lesions, in keeping with the way the "-osis" suffix is used elsewhere in medicine (e.g. Fibroma v fibromatosis). An example of this use was 'Goldstein's angiomatosis' an anachronistic term for what is now known as Hereditary Hemorrhagic Telangiectasia. Subsequent developments have similarly made this use of the term redundant as well as imprecise. [t] Specific uses of 'Angiomatosis' persist and can be useful in well-recognized contexts as follows: **Leptomeningeal angiomatosis** most often refers to central nervous system brain involvement in Sturge-Weber. **Angiomatosis of soft tissue**: in 1992 Rao and Wiess described a series of 51 lesions which they termed 'angiomatosis of soft tissue'. Diagnoses in these cases were primarily pathological, and clinical details in the published series were too limited to determine whether a distinct rare entity was being described, or the described cases were examples of other vascular anomalies with unusual but recognized pathological features of those conditions. The name "angiomatosis of soft tissue" after Rao and Weiss, is currently used by some pathologists and clinicians as a histological diagnosis corresponding generally to the clinicopathological entities FAVA and PHOST. [t]

Angiosarcoma: a specific type of malignant Vascular Tumor. [t]

***ANGPT2*:** a gene related to vascular malformations. Pathogenic variants in *ANGPT2* are found in dominant and recessive primary lymphedema. [g]

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Arteriovenous Fistula (AVF): a direct communication between an artery and one or a few veins. This lesion may be congenital (a fast-flow vascular malformation) or acquired, induced by trauma, or iatrogenic. [t]

Arteriovenous Malformation (AVM): a fast-flow vascular malformation in which multiple direct connections between the arterial and venous system result in low resistance flow, with consequent enlargement of adjacent arteries and veins (sometimes referred to as 'feeding vessels'). Approximately one-third of AVMs are evident at birth, but they can present at any age. AVMs tend to gradually enlarge over time, but this is highly variable. Some remain stable in size for long periods. Some AVMs enlarge at puberty and during pregnancy. The genomic causes of AVMs are heterogeneous. Some are due to germline genetic variants, as seen in Hereditary Hemorrhagic Telangiectasia (HHT), Capillary Malformation AVM (CM-AVM)1 or Capillary Malformation AVM (CM-AVM) syndrome 2 (CM-AVM1, CM-AVM2) or Cowden syndrome due to germline *PTEN* genetic variants. However, most AVMs are sporadic and are caused by somatic genetic variants which tend to occur in the RAS/MEK/ERK pathway, the best documented genetic variants being gain of function genetic variants in genes *MAP2K1* and *HRAS*, and less often in *BRAF*. A minority of AVMs occur as part of a syndrome: Capillary Malformation AVM (CM-AVM) syndrome; Hereditary Hemorrhagic Telangiectasia (HHT); and *PTEN* hamartoma syndrome. AVMs are also sometimes seen in Neurofibromatosis Type 1.

AVMs which occur in the brain have traditionally been managed by separate specialists from those occurring elsewhere in the body and therefore tended to be regarded as distinct lesions. With growing evidence that these lesions are caused by the same genetic variants as those elsewhere in the body, it has become clear that differences are likely due to anatomic location rather than intrinsic differences. AVMs in the brain most often remain unrecognized until an episode of bleeding. "AVMs" in the lung and liver are particularly associated with HHT and generally correspond to arteriovenous fistulas. [t]

AST: Angiomatosis of soft tissue. See Angiomatosis [a]

AVF: Arteriovenous fistula [a]

AVF in CM – AVM: Arteriovenous fistulas found in Capillary Malformation-Arteriovenous malformation syndrome. The fistular component of the combined CM-

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AVM vascular malformation. Associated to *RASA1* (CM-AVM1) and *EPHB4* (CM-AVM2) gene pathogenic variants. [a][t]

AVM: see Arteriovenous malformation. [a]

AVM in CM – AVM: Arteriovenous malformation of Capillary Malformation-Arteriovenous malformation. The arteriovenous component of the combined CM-AVM vascular malformation. Associated to *RASA1* and *EPHB4* gene pathogenic variants. [a][t]

AVF in HHT: Arteriovenous fistula in Hereditary Hemorrhagic Telangiectasia (HHT). Specific pathogenic variants were described in different types of HHT. *ENG* variants were found in HHT1 and *ACVRL1* variants in HHT2 and *SMAD4* in HHT3 and JPHT. [t]

AVM in HHT: Arteriovenous malformation in Hereditary Hemorrhagic Telangiectasia (HHT). Specific pathogenic variants are associated with subtypes of HHT. *ENG* variants with HHT1, *ACVRL1* variants with HHT2 and *SMAD4* variants with HHT3 and JPHT. [t]

Bannayan-Riley-Ruvalcaba Syndrome: association of macrocephaly with skin papules, hamartomas, tumors, and vascular malformations. This syndrome is now known to be caused by germline pathogenic variants in *PTEN* and has overlapping manifestations with other clinical conditions with the same pathogenic variants e.g. Cowden Syndrome. These are now considered subtypes of **PTEN Hamartoma Tumor Syndrome (PHTS)**, which is the preferred diagnostic term. [e][s]

Bacillary Angiomatosis: a specific type of benign vascular tumor-like proliferative lesion. [s]

Bier spots: small, light macules usually found in arms and legs. They are associated with CM-AVM but can also occur independently.

Blue Rubber Bleb Nevus Syndrome (BRBNS): this is a rare syndrome caused by somatic genetic variants in the *TEK(TIE2)* gene most of which are double-cis pathogenic variants. Most patients have one large congenital venous malformation, typically present at birth, as well as characteristic small, dome shaped blue lesions of the skin, with a predilection for the palms and soles but they can be present on any skin site. Patients may also have venous malformations affecting the gastrointestinal tract, muscle, viscera, and central nervous system. The term BRBNS is sometimes incorrectly used to refer to any venous malformation found in the

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gastrointestinal tract. Many purported cases of BRBNS in the literature, are in fact cases of multiple venous malformations, or VMCM. One of the main clinical findings is severe anemia. [a][s]

Borderline Vascular Tumor: one of the main categories of vascular tumors, related to lesions that cause systemic involvement or present aggressive behavior, but without histological and clinical characterization of malignant disease. Some of these tumors are associated with platelet sequestration leading to the Kasabach-Merrit phenomenon [t]

***BRAF*:** gene. Pathogenic variants in *BRAF* are often found in Pyogenic Granuloma but occasionally in other vascular anomalies. [g]

BRBNS see Blue Rubber Bleb Nevus Syndrome

CAMS: see Cerebrofacial arteriovenous metameric syndrome

Cerebrofacial Arteriovenous Metameric Syndrome (CAMS): subtype of syndromic fast-flow vascular malformation. Cerebrofacial arteriovenous metameric syndrome (CAMS) is a recent classification of vascular malformations that encompasses a spectrum of phenotypic expression involving arteriovenous malformations (AVMs) of the cerebral, orbital, and facial region [s]

***CAMTA1*:** gene. Pathogenic variants in *CAMTA1* are found in Epithelioid hemangioendothelioma. [g]

Capillary Malformation: in previous ISSVA classifications this term has been attached to both a **specific diagnosis** of an isolated red cutaneous stain, usually caused by a somatic pathogenic variant in the gene GNAQ, and to **a general category** of congenital cutaneous vascular malformations characterized by small vessels on pathology. In the current classification the specific lesion has been renamed as 'Port wine Capillary Malformation'; the term 'capillary malformation' is now a subcategory of slow-flow malformations, and may sometimes be applied non-specifically in the process of seeking a specific diagnosis. [t]

Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM syndrome): an autosomal dominant genetic syndrome characterized by variants in the genes *RASA1* (CM-AVM1) or *EPHB4* (CM-AVM2). Features include cutaneous AVM (previously considered as a type of capillary malformation), and AVM affecting the central nervous system or musculature. [s]

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CAT: see cutaneovisceral angiomatosis with thrombocytopenia. [a]

Cavernoma: see also cerebral cavernous malformation. This term is used for lesions in the brain which are somewhat similar to venous malformations seen elsewhere in the body. Especially when multifocal they occur as a feature of an inherited disorder (Cerebral Cavernous Malformation (CCM) 1,2 and 3) in which case they can be associated with vascular skin lesions of various types, but rarely extracutaneous venous malformations elsewhere in the body. [t]

Cavernous Hemangioma: this historical term dating back to Virchow, is still used by some clinicians as well as in some pathology and radiology reports and is ***highly problematic***. In the past it has been used as a diagnostic term to variably refer to Venous Malformations and to deep Infantile Hemangiomas. As such, use of this term ***is strongly discouraged*** because these two distinct meanings can generate diagnostic confusion. [t]

***CCBE1*:** gene. Pathogenic variants in *CCBE1* are found in Primary Generalized lymphatic anomaly (Hennekam lymphangiectasia-lymphedema syndrome). [g]

CCLA: see Central Conducting Lymphatic Anomaly

CCM: see Cerebral Cavernous Malformation [a]

***CELSR1*:** gene. Pathogenic variants in *CELSR1* are found in Primary lymphedema sometimes associated with renal anomalies. [g]

Central Conducting Lymphatic Anomaly (CCLA): Central conducting lymphatic anomaly (CCLA) encompasses disorders that are caused by dysfunction of the thoracic duct and/or cisternae chylae with subsequent reflux and leakage of lymphatic fluid, most commonly into the lungs and/or abdomen. Pleural and pericardial effusions, ascites, and generalized edema are common and can result in organ dysfunction, protein loss, and infections. [s]

Cerebral Cavernous Malformation (CCM): see also cavernoma. This refers to a genetically heterogeneous group of disorders including CCM1, CCM2 and CCM 3, which have germline pathogenic variants in genes (*KRIT1, Malcavernin and PDCD10* respectively) resulting in CNS vascular malformations termed "cavernous angiomas". CCM1,2 and 3 can be associated with vascular skin lesions of various types (CM, HCCVM, and nodular VM), but rarely extracutaneous venous malformations elsewhere in the body. Non-

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familial cases often have somatic pathogenic variants in the CCMs genes associated with a pathogenic somatic *PIK3CA* variant. [s] [t]

Channel Type Vascular Malformation: also known as truncal vascular malformations. Correspond to Developmental anomalies of major named vessels in the ISSVA classification. Affects arteries, lymphatics, or veins. [t]

Cherry Angioma: benign vascular tumor, affecting adults, mainly between 30-50 years old, preferentially in the trunk and limbs [e][t]

Chronic Consumptive Coagulopathy (CCC): see LIC.

CLA: Complex lymphatic anomalies, includes lymphatic malformations that present structural complexity, multisystem involvement and functional impairment [a][t]

CLAPO Syndrome (Capillary malformation of the lower lip, Lymphatic malformations of the head and neck, Asymmetry and Partial or generalized Overgrowth): Pathognomonic lower lip capillary malformation associated to intraoral and neck lymphatic and venous malformations. Somatic activating pathogenic variants in *PIK3CA* are associated with CLAPO syndrome and it is now considered by many to be a part of *PIK3CA*-related overgrowth (PROS) spectrum. [a][s]

CLM: Capillary-lymphatic malformation. A type of combined vascular malformations. [a]

CLOVES syndrome: see Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, and Skeletal anomalies. Now considered by many to be a part of PIK3CA-related overgrowth (PROS) spectrum [a]

CLVM: Capillary-lymphatic-venous malformation. A type of combined vascular malformations. CLVM with hypertrophy is designated as Klippel-Trenaunay Syndrome [a]

CM: Capillary malformation. [a]

CM of CM-AVM: Capillary malformation-arteriovenous malformation. In the updated Classification it is considered a specific type of Low-resistance CM, the capillary component of the combined CM-AVM vascular malformation. Also is classified in Multifocal fast-flow Vascular malformations due to the fast-flow component. CM-AVM is associated to *RASA1* and *EPHB4* pathogenic variants. [a][t]

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CM of MCAP: Simple capillary malformation from Reticulate Capillary Malformation subgroup. CM of MCAP is the capillary component of malformation found in megalencephaly-capillary malformation-polymicrogyria, associated to *PIK3CA* gene pathogenic variants. [a][t]

CM of MIC-CAP: Simple capillary malformation from Reticulate Capillary Malformation subgroup. CM of MIC-CAP the capillary component found in microcephaly-capillary malformation, associated to *STAMBP* gene variants. [a][t]

CMTC see Cutis Marmorata Telangiectatica Congenita

CNS: central nervous system. [t]

Cobb Syndrome: metameric-origin fast-flow malformations involving the spinal cord, bone, and skin. [s]. See also Spinal arteriovenous metameric syndrome (SAMS).

Combined Vascular Malformation: this term appeared in earlier iterations of the ISSVA classification and are subdivided in isolated and Syndromic. The terms 'simple' and 'combined' are not designations in the updated classification. Fast-flow and Slow-flow malformations are now considered distinct entities and so terms such as "Capillary lymphatic AVM" which is rarely if ever seen, should not be used. Of note, some slow-flow malformations can have features of both lymphatic and venous differentiation. Where possible the malformation should be named according to the predominant vessel type, though information about other elements can be in more detailed descriptors. Where neither vessel type predominates the term 'mixed' slow-flow malformation or VLM may be appropriate. genetic testing of the affected tissue can help to better classify these ambiguous cases. [t]

Common (CYSTIC) LM: Lymphatic malformation. The prefix 'common' was included in the previous classification but the term 'Isolated LM' is now preferred where it is necessary to distinguish from LM with other features. Lesions are subdivided in macrocystic, microcystic and mixed. [t]

Common VM: Venous Malformation. The prefix 'common' was included in the previous classification but the term 'Isolated VM' is now preferred to distinguish VM found in isolation, especially from those in inherited syndromes. VMs are associated with *TEK (TIE2)* and *PIK3CA* gene pathogenic variants. [a][t]

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Composite Hemangioendothelioma: a specific type of locally aggressive or borderline Vascular Tumor. [t]

Congenital Hemangioma: a group of vascular tumors which develop in utero and are fully developed at birth. Clinical trajectory may vary from those that involute spontaneously (rapidly involuting congenital hemangioma; "RICH"), those which do not involute (non-involuting congenital hemangioma; "NICH") or show partial involution (partially involuting congenital hemangioma; "PICH") A component of large vessels (arteries and veins) and lymphatics, resembling a vascular malformation is often present, associated with the capillary proliferation. Congenital hemangioma is GLUT-1 negative, which distinguishes it from infantile hemangioma, which is GLUT-1 positive. Most lesions are caused by somatic pathogenic variants in GNAQ or GNA11 at position glutamine 209, which differ from those found in Port wine CM. [t]

Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Skeletal anomalies) (CLOVES syndrome). CLOVES **is** now considered to be **a** part of the *PIK3CA*-related overgrowth spectrum. It is a rare, sporadic disorder characterized by tissue overgrowth and complex vascular anomalies. The manifestations are variable ranging from mild to severe anomalies. These abnormalities are typically present at birth, however some, such as fatty overgrowth, progress with age. [a][s]

Connexin47: gene. Pathogenic variants in *Connexin47* are found in Primary Hereditary Lymphedema. [g]

Cowden Syndrome: association of macrocephaly with skin papules, hamartomas, tumors, and vascular malformations, now known to be caused by pathogenic variants in the gene *PTEN*, and therefore a subtype of *PTEN*-Hamartoma Tumor Syndrome (PHTS), which is the preferred diagnostic term. [e][s]

Cutaneous and or Mucosal CM: cutaneous and mucosal capillary malformation, the preferred term is now Port wine Capillary Malformation (Port wine CM). The most common type of Capillary malformation. Port wine CM is associated with *GNAQ* and *GNA11* pathogenic variants. [t]

Cutaneous Epithelioid Angiomatous Nodule: a specific type of benign Vascular Tumor. [t]

Cutaneous Elastotic Hemangioma: a specific type of benign Vascular Tumor. See also Acquired elastotic hemangioma [t]

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Cutaneovisceral angiomatosis with thrombocytopenia (CAT): a vascular anomaly classified in the group of unclassified lesions. The same condition has also been called Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT). ISSVA classification favors the name MLT. Thrombocytopenia is unstable with gastrointestinal tract bleeding or pulmonary hemorrhage. [t]

Cutis Marmorata Telangiectasia Congenita: A congenital vascular anomaly characterized by a fixed, coarse, livedo-like cutaneous vascular network, virtually always present at birth, most often in association with underlying atrophy and/or ulceration. Unlike physiological cutis marmorata, the marks do not fade with warming. CMTC is a heterogeneous group with some cases seen in association with Adams-Oliver syndrome, some due to *AKT3* pathogenic variants, but other causative somatic pathogenic variants have also been reported. CMTC may be associated with aplasia cutis, hemihypertrophy, hemiatrophy or undergrowth of the affected limb. Most lesions fade somewhat during the first years of life, sometimes leaving hyperpigmented net-like patches and often some degree of scarring. [a][s]

CVM: CM+ VM. Capillary-venous malformation. A type of combined vascular malformations. [a]

Cystic Hygroma: this term was used in the past as a synonym for macrocystic lymphatic malformation, most often of the head and neck. It is no longer a preferred term for such lesions. The term may be used, however, in fetal medicine for fluid swelling involving the neck. Many of these, especially those seen in association with Turner and other syndromes are not true lymphatic malformations. [t]

Dabska tumor: a specific type of Locally aggressive or borderline Vascular Tumor. Related, if not identical, to papillary intralymphatic angioendothelioma (PILA)". [e][t]

Deep Infantile Hemangioma: a specific denomination for cutaneous hemangiomas. Deep IH are those that affect soft tissues, preserving the cutaneous layer. Do not consider in this group visceral IH. [t]

Developmental Anomalies of Named Vessels: this category of the Updated Classification was inserted to include in the classification vascular anomalies of specific major arteries and veins, such as anomalies of the vena cava, aorta and vein of Galen. This category is open to the inclusion of new anomalies

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described in the future and aims to improve the ISSVA classification so that it can encompass any and all vascular anomalies. [t]

DCMO: see Diffuse Capillary Malformation with Overgrowth. [a]

DIC: disseminated intravascular coagulopathy. [t]

Diffuse Capillary Malformation with Overgrowth (DCMO): this term was introduced in 2013 to describe patients with extensive blotchy or reticular vascular stains associated with overgrowth. It specifically refers to cases where widespread areas of the skin are affected, with overgrowth being relatively mild and proportionate with somatic growth, and not necessarily in areas with the vascular stain. Somatic pathogenic variants in the gene *GNAQ/GNA11* exon 183 and *PIK3CA* have been reported. [s] [t]

Distichiasis – double set of eyelashes – seen in some lymphedema syndromes (see *FOXC2*)

DMEG: see Dysplastic Megalencephaly. [a]

Dysplastic Megalencephaly (DMEG): one of the diseases of the PIK3CA-related overgrowth spectrum (PROS), due to somatic activating pathogenic variants in the gene PIK3CA. It is a rare cerebral malformation defined by overgrowth and extensive cortical dysplasia of the cerebral hemispheres, usually due to mTOR signaling pathway pathogenic variants. [t]

Eccrine Angiomatous Hamartoma: a specific type of benign Vascular Tumor. [t]

Ectasia: distension or dilation of a vessel. [t]

***ELMO2*:** gene. Pathogenic variants in *ELMO2* are found in Familial intraosseous vascular malformation (VMOS). [g]

***ENG*:** gene, related to vascular malformations. Pathogenic variants in *ENG* are found in telangiectasia, AVM and AVF of HHT1. [g]

EPHB4: gene, related to vascular malformations. Pathogenic variants in *EPHB4* are found in CM-AVM2, but also in hydrops fetalis and CCLA. [g]

Epithelioid Hemangioma: a benign tumor of well-formed blood vessels lined by epithelioid endothelial cells with abundant cytoplasm and a variable eosinophilic infiltrate. Rearrangements of *FOS* or *FOSB* are seen in approximately half of cases, particularly those seated in deep soft tissues and bones. [t]

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Epithelioid Hemangioendothelioma: a specific type of malignant Vascular Tumor. Epithelioid hemangioendothelioma, or EHE, is a rare malignant vascular neoplasm. Most common affected are liver, lungs, and bone. It usually occurs in adult patients (between 30 and 50 years old) but can also occur in children and the elderly. EHE is very rare, with only one in every 1 million people diagnosed worldwide. Because EHE can be hard to diagnose, the actual number of people with EHE may be higher. Pathogenic variants in CAMTA1 are found in Epithelioid hemangioendothelioma. [t]

Facial Infiltrative Lipomatosis (FIL): although not a vascular malformation per se, this condition is often managed in the context of a vascular anomalies team. Most cases are known to be caused by somatic pathogenic variants in *PIK3CA*. The term Facial Infiltrative Lipomatosis is inaccurate in that many lesions involve overgrowth of tissues other than adipose tissue, including bone, muscle, and nerve. Usually presents adipose tissue infiltration in all tissue layers, bone deformities and macrodontia. Thus, PIK3CA related overgrowth syndrome (PROS), i.e., 'PROS of the face' is an alternative diagnostic label. [s][t]

Familial Intraosseous Vascular Malformation (VMOS): a rare hereditary and aggressive intraosseous venous malformation affecting the craniofacial bones and related to *ELMO-2* pathogenic variants. [t]

Familial VM Cutaneo-Mucosal (VMCM): cutaneous and mucosal VM related to germline *TEK (TIE2)* pathogenic variants. [t]

FAO: see Fibroadipose Hyperplasia with Overgrowth (FAO) [a]

Fast-Flow Vascular Malformation: one of the main subdivisions included in the Updated version of the classification for vascular malformations. It is differentiated from Slow-flow lesions and Developmental Anomalies of Named Vessels lesions. Fast-flow vascular malformations can be subdivided into isolated, multifocal and syndromic lesions. The main change was to use flow velocity as a determinant between lesions with arterial components (fast-flow) and lesions with slow-flow components such as venous, lymphatic and capillary. [t]

FAT4: gene related to vascular malformations. Pathogenic variants in *FAT4* are found in Primary Generalized lymphatic anomaly type 2 (Hennekam lymphangiectasia-lymphedema syndrome 2). [g]

FAVA: see Fibroadipose Vascular Anomaly

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Fibroadipose Hyperplasia with Overgrowth (FAO): one of the diseases of the *PIK3CA*-related overgrowth spectrum (PROS), due to somatic activating pathogenic variants. [t]

Fibroadipose Infiltrating Lipomatosis: one of the diseases of the *PIK3CA*-related overgrowth spectrum (PROS), due to somatic activating pathogenic variants. In the face is named Facial infiltrative Lipomatosis (FIL). [t]

Fibroadipose Vascular Anomaly (FAVA): a vascular malformation generally caused by somatic mosaic variants of *PIK3CA*. It is characterized by a mix of malformed venous and lymphatic elements together with fibrofatty infiltration of muscle. Pain and contracture may be observed. [a][t]

FLT4: gene. Also named VEGFR3. Pathogenic variants in *FLT4* are found in Nonne- Milroy Disease. [g]

Focal Infantile hemangioma: a localized IH with small dimensions, not affecting an entire limb, body region or anatomic unit. [t]

FOS: gene. Pathogenic variants in *FOS* are found in Epithelioid Hemangioma. [g]

***FOSB*:** gene. Pathogenic variants in *FOSB* are found in Pseudomyogenic hemangioendothelioma. [g]

***FOXC2*:** gene. Pathogenic variants in *FOXC2* are found in Lymphedema-Distichiasis. [g]

GATA2: gene. Pathogenic variants in *GATA2* are found in Primary Lymphedema with myelodysplasia. [g]

Generalized Lymphatic Anomaly (GLA): a rare multisystem congenital disease, part of the complex lymphatic anomalies (CLA). There is some overlap with Kaposiform lymphangiomatosis (KLA). GLA is characterized by diffuse proliferation of lymphatic channels in osseous and extraosseous tissues. The pathogenesis includes somatic pathogenic variants in RAS/PI3K/mTOR signaling pathway. Patients with GLA have bone and visceral involvement, but in contrast with Gorham Stout Disease, cortical bone is not affected. [s]

Generalized Lymphatic Dysplasia (GLD): is caused by germline pathogenic variants in *PIEZO1*, *MDFIC* and likely other genes. It is characterized by hydrops fetalis and generalized lymphatic dysplasia [s]

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Geographic Pattern CM: new item in the classification of capillary vascular malformations that is characterized by well-demarcated vascular patches with distinctive contours and clinical appearance resembling a map-like distribution. Seen distinctively in Klippel-Trenaunay Syndrome and most often due to somatic mutations in *PIK3CA* hotspots or *PIK3R1*. Many geographic pattern CM have associated superficial blebs due to presence of associated lymphatic malformations. [t]

GLA: see Generalized Lymphatic Anomaly. [a]

GJC2: gene. Pathogenic variants in *GJC2* are found in Primary Hereditary Lymphedema. [g]

Glomangioma: this is a synonym for Glomuvenous malformation (GVM). GVM is the preferred term. [t]

Glomeruloid Hemangioma: a specific type of benign Vascular Tumor. [t]

***Glomulin*:** gene. Pathogenic variants in *Glomulin* are found in Glomuvenous Malformation (GVM). [g]

Glomuvenous malformation (GVM): GVM is a type of slow-flow venous malformation which on histopathology demonstrates glomus cells in the vascular wall. Lesions may be tender or painful and less compressible compared to other venous malformations. The so-called plaque-like variant is more rare. GVMs are mainly found in the skin, and only rarely in the underlying muscle or deeper tissues. GVM may occur as sporadic lesions or as a feature of an autosomal dominant genetic condition caused by variants in the *Glomulin* gene. GVM are clinically and genetically distinct from glomus tumors. [t]

GNA11: gene. Pathogenic variants in *GNA11* are found in congenital hemangioma, CM with bone and/or soft tissue overgrowth, Diffuse CM with overgrowth (DCMO), Limb CM + congenital non-progressive limb overgrowth and some cases of Sturge-Weber Syndrome. [g]

***GNA14*:** gene. Pathogenic variants in *GNA14* are found in Tufted Angioma, Pyogenic Granuloma and Kaposiform Hemangioendothelioma. [g]

GNAQ: gene. Pathogenic variants in *GNAQ* are found in congenital hemangioma, Port wine CM, Sturge-Weber Syndrome. [g]

Gorham Stout Disease (GSD) (also 'Gorham disease'): a rare multisystem congenital disease, part of the complex lymphatic anomalies (CLA). Aggressive

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osteolysis with loss of cortical bone in the context of a lymphatic anomaly, also known as “vanishing bone disease”. [s]

GSD: see Gorham Stout Disease. [a]

GVM: see Glomuvenous malformation. [a]

HCCVM: Hyperkeratotic Cutaneous Capillary-Venous malformations: family history of a dark red or black CM, which becomes hyperkeratotic, and can be associated with cerebral cavernous malformations (CCM), most often CCM1 and so associated with KRIT *1* germline pathogenic variant [a]

Hemangioendothelioma: group of vascular tumors with varying degrees of aggressive behavior ranging from kaposiform hemangioendothelioma with associated consumptive coagulopathy (Kasabach–Merritt phenomenon) to life-threatening epithelioid hemangioendothelioma. "Hemangioendothelioma" alone is not a specific diagnosis. It should always be completed by a qualifier (kaposiform, retiform, composite, polymorphous, epithelioid). [t]

Hemangioma: this term by itself without an adjective or qualifier is not a specific diagnosis, but a term which implies that the lesion described is a tumor rather than a vascular malformation. For diagnostic accuracy, it should always have an accompanying adjective, such as ‘infantile hemangioma’, “lobular capillary hemangioma”, “congenital hemangioma”, etc. [t]

Hemangioma of Infancy: see Infantile Hemangioma. [t]

Hemihyperplasia Multiple Lipomatosis (HHML): one of the diseases of the *PIK3CA*-related overgrowth spectrum (PROS), due to somatic activating pathogenic variants. [t]

Hennekam Lymphangiectasia-Lymphedema Syndrome also known as Primary Generalized lymphatic anomaly. Characterized by presence of intestinal and renal lymphangiectasia, dysmorphic facial appearance and mental retardation. The facial features include hypertelorism, flat nasal bridge, epicanthic folds, small mouth, and small ears. Associated with *CCBE1, FAT4* and *ADAMTS3* pathogenic variants. [s]

Hereditary Hemorrhagic Telangiectasia (HHT): autosomal dominant disease characterized by multiple arteriovenous malformations affecting mucosa (resulting in epistaxis or bleeding from oral telangiectasia), skin (usually fingers or hands), internal organs (brain, lungs, liver, GI tract, etc.). The

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genetic alterations (pathogenic variants or deletions) usually affect: ENG, *ACVRL1 (Alk1), SMAD4, GDF2*. Clinical presentation sometimes overlaps with CM-AVM caused by *RASA1* or *EPHB4* variants. [s]

***HGF*:** gene related to vascular malformations. Pathogenic variants in *HGF* are found in Primary Hereditary Lymphedema. [g]

HHML: see Hemihyperplasia Multiple Lipomatosis. [a]

HHT: Hereditary Hemorrhagic Telangiectasia. [a]

HHT1: Hereditary Hemorrhagic Telangiectasia type 1. A specific type of telangiectasias, associated to *ENG* gene pathogenic variants. [g]

HHT2: Hereditary Hemorrhagic Telangiectasia type 2. A specific type of telangiectasias, associated with *ACVRL1* gene pathogenic variants. [g]

HHT3: Hereditary Hemorrhagic Telangiectasia type 3. A specific type of telangiectasias, associated with *SMAD4* gene pathogenic variants. [g]

HI: see Infantile hemangioma. [a]

Hobnail Hemangioma: a specific type of benign Vascular Tumor, also known as targetoid hemosiderotic hemangioma. Histologically it is characterized by a pattern of dilated vascular structures in the superficial dermis lined by prominent hobnail endothelial cells, and collagen dissecting, rather narrow neoplastic vessels in deeper parts of the lesion [t]

Hypoplasia: incomplete development or underdevelopment of an organ or tissue. [t]

Hypotrichosis-Lymphedema-Telangiectasia (HLTS): sparse hair (hypotrichosis), lymphedema, and telangiectasia, particularly on the palms of the hands. Associated with *SOX18* gene pathogenic variants. [s]

IDH1: gene. Pathogenic variants in IDH1 are found in spindle-cell hemangioma and Maffucci Syndrome. [g]

***IDH2*:** gene. Pathogenic variants in IDH2 are more rarely found in spindle-cell hemangioma and Maffucci Syndrome than IDH1. [g]

IH: see Infantile hemangioma. [a]

IKBKG(NEMO): a gene related to vascular malformations. Pathogenic variants in *IKBKG* are found in osteopetrosis with lymphedema. [g]

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Infantile hemangioma: the most frequent benign vascular tumor with a characteristic natural history of early proliferation and spontaneous involution. This tumor typically improves with betablocker therapy. On immunohistochemistry, IH endothelial cells typically demonstrate GLUT-1 immunoreactivity. IH subsets include localized and segmental patterns of distribution. While most IH occur in the skin and subcutis, other sites such as the airway and liver can be involved. Some cases are associated with extra-cutaneous diseases such as PHACE and LUMBAR syndrome. [t]

Infantile hemangioma with Minimal/Arrested growth (IH-MAG): sometimes referred to as "abortive hemangiomas", the term describes infantile hemangiomas having a minimal or absent proliferative phase, which differs from the vast majority of IH which grow in early infancy. [t]

INR: international normalized ratio. [a]

Intramuscular Fast-Flow Vascular Anomaly: a new term in the Updated Classification that substitutes for the old term 'Intramuscular capillary-type hemangioma'. Distinguished from AVM by lack of early venous filling on angiography. Associated with somatic pathogenic variants in genes *MAP2K1* and *KRAS* **[t]**

Intramuscular Hemangioma: this term is generally used to describe a slow-flow vascular malformation which is wholly or mostly within skeletal muscle, most often a venous malformation. As such it is not a defined diagnosis but may be used at times to differentiate intramuscular from other slow-flow malformations. The use of the term hemangioma in this situation is not recommended since it is a vascular malformation. Intramuscular venous malformation or intramuscular vascular malformation should be used instead. [t]

Intraosseous Hemangioma: lesions given this label are most often venous malformations and as such should be more correctly referred to as "intraosseous venous malformation". [t]

Intravascular papillary endothelial hyperplasia: a specific type of benign Vascular Tumor. [t]

Isolated (vascular) Lesion: a vascular lesion that is present alone and not in the context of other vascular or other lesions, in contrast to lesions present in syndromes.

JPHT: see Juvenile polyposis hemorrhagic telangiectasia. [a]

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Juvenile Polyposis Hemorrhagic Telangiectasia: a specific type of telangiectasia, associated to *SMAD4* gene pathogenic variants. [t]

Kaposi sarcoma: a specific type of Locally aggressive or borderline Vascular Tumor. [t]

Kaposiform Hemangioendothelioma (KHE): a rare vascular tumor that is typically diagnosed in infancy or early childhood, with some cases present at birth It is an aggressive disease with high potential morbidity, mainly due to associated consumption coagulopathy (the Kasabach–Merritt phenomenon (KMP)), a disorder characterized by severe thrombocytopenia, hypofibrinogenemia and high D-dimers. KHE and tufted angioma are now viewed as part of the same spectrum of disease. [t]

Kaposiform Lymphangiomatosis (KLA): a subtype of complex lymphatic anomaly, with some overlap with generalized lymphatic anomaly. It is a rare aggressive disease characterized microscopically by excessive, dilated and abnormally formed lymphatic channels accompanied by scattered clusters of variably canalized, often hemosiderotic, spindled lymphatic endothelial cells. KLA usually presents during childhood, with respiratory symptoms, bleeding, and subcutaneous mass. Potential complications of KLA include thrombocytopenia and hemorrhage. Somatic pathogenic variants in *NRAS* have been identified in KLA. [s]

Kasabach-Merritt Phenomenon: severe thrombocytopenia and hypofibrinogenemia, often associated with platelet trapping, coagulation factor consumption and elevated D-dimers, occurring generally in infants and children in the context of KHE or tufted angioma. [e][s]

KHE: see Kaposiform Hemangioendothelioma. [b]

KIF11: gene. Pathogenic variants in *KIF11* are found in Microcephaly with or without chorioretinopathy, lymphedema, or mental retardation syndrome. [g]

KLA: see Kaposiform Lymphangiomatosis. [a]

Klippel-Trenaunay Syndrome (KTS): the term KTS has been used to denote a combination of CM+VM +/- LM + Limb overgrowth. It is not a genomically uniform diagnosis. Many severe cases are due to somatic pathogenic variants in *PIK3CA* and are now recognized as part of the PIK3CA-related overgrowth spectrum (PROS). Other cases which mimic the definition of KTS are due to GNAQ/GNA11 somatic pathogenic variants and most often best fit with

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the diagnosis of diffuse capillary malformation with overgrowth (see DCMO). Other cases with overgrowth and vascular birthmarks in association with higher flow vascular anomalies fit best as "Parkes Weber syndrome", a separate diagnostic entity.
Note: The term Klippel-Trenaunay-Weber Syndrome is not correct. It has had moderately widespread use in the pediatric literature, after it appeared in some textbooks, but it is a mixture of two distinct syndromes, Klippel-Trenaunay and Parkes Weber and should not be used. [e][s]

KMP: see Kasabach-Merritt phenomenon. [a]

***KRIT1*:** gene. Pathogenic variants in *KRIT1* are found in Cerebral Cavernous Malformation Type 1 (CCM1). [g]

KTS: see Klippel-Trenaunay Syndrome

LIC: Localized intravascular coagulopathy. A phenomenon seen in large low flow vascular malformations due to localized consumption of coagulation factors. Usually high-levels of D-dimers are observed in conjunction with low levels or fibrinogen. Also called chronic consumptive coagulopathy (CCC). Note that this is a different entity from Kasabach-Merritt phenomenon. [t]

Limb CM + Congenital Non-progressive Limb Overgrowth: capillary malformation in the limbs, associated with overgrowth. *GNA11* pathogenic variants are associated with this disease. [t]

Littoral Cell Hemangioma of the Spleen: a specific type of benign Vascular Tumor. [t]

LM: see lymphatic malformation. [a]

Lobular capillary hemangioma: see Pyogenic granuloma

Low-resistance CM / CM with faster flow: name given to the combination of capillary malformation associated with fast-flow vascular malformations. The flow in the capillary component clinically appears faster than in other capillary malformations, as evidenced by more rapid capillary refill than other CMs. Some cases also show vasoconstriction at the periphery of the stain, a finding rarely seen in other CM subtypes. This is a new category in the updated classification. Many patients with this type of CM have CM-AVM and for this reason, the acronym CM-AVM appears in the subdivision of capillary malformations and fast-flow malformations.

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LUMBAR syndrome: acronym used for the association of Lower body infantile hemangiomas (L) and other skin defects; Urogenital anomalies (U) and ulceration; Myelopathy (M); Bony deformities (B); Anorectal malformations and arterial anomalies (A); and Rectal anomalies (R). Synonyms include PELVIS and SACRAL syndromes, describing the same group of anomalies which are seen in association with lower-body segmental infantile hemangiomas. [a][s]

LVM: Lymphatic-venous malformation. Slow-flow vascular malformation with both lymphatic and venous components, where one vessel type or the other is not predominant. [a]

Lymphangioma: historically used as a synonym for Lymphatic Malformation. This term should not be used, 'lymphatic malformation' is the correct diagnostic term. [t]

Lymphatic hypertension: elevated pressure in the lymphatic system can be caused by impaired lymphatic drainage or increased lymph production. This condition results in fluid accumulation, leading to lymphedema and tissue swelling

Lymphatic malformation: slow-flow vascular malformation with lymphatic differentiation, classified as macrocystic, microcystic and mixed. Most lymphatic malformations are associated with a somatic pathogenic variant in *PIK3CA*, more rarely in *BRAF* [t]

Lymphedema-choanal atresia: lower limb lymphedema associated with posterior choanal atresia. Associated with *PTPN14* gene variants. [s]

Lymphedema-Distichiasis: lower limb lymphedema associated with distichiasis of the eyelashes. Associated with *FOXC2* pathogenic variants and is inherited in an autosomal dominant pattern. [s]

M-CM: see Macrocephaly Capillary malformation syndrome. [a]

Macrocephaly Capillary malformation syndrome (M-CM): currently known as M-CM syndrome, it represents the association of capillary malformation of the upper lip, nose or forehead to macrocephaly and diverse intracranial neurovascular disorders. In most cases, caused by somatic pathogenic variants in PIK3CA but similar findings are occasionally seen with germline PIK3CA pathogenic variants. [s]

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Macrocystic LM: Macrocystic lymphatic malformation. LM with predominance of large cystic components. The distinction between Macrocystic and microcystic LM is primarily of importance for responsiveness to sclerotherapy treatment and choice of therapeutic agent. There is no precise definition separating the two types, and many lesions are mixed. [t]

Macrodactyly: one of the diseases of the *PIK3CA*-related overgrowth spectrum (PROS), due to somatic activating pathogenic variants, characterized by digital enlargement. [t]

Maffucci syndrome: non-hereditary congenital condition that affects the skin and skeleton including enchondromas, bone abnormalities, spindle cell hemangiomas and venous anomalies in the context of somatic pathogenic variants in *IDH1* and more rarely in *IDH2*. Malignant transformation may occur. [e][s]

***Malcavernin*:** gene. Pathogenic variants in *Malcavernin* are found in Cerebral Cavernous Malformation type 2 (CCM2). [g]

***MAP2K1*:** gene. Somatic pathogenic variants in MAP2K1 are found in sporadic AVM and AVF. [g]

MAP3K3: gene. Somatic pathogenic variants in *MAP3K3* are found in Verrucous venous malformation. [g]

MCAP: see Megalencephaly-capillary malformation-polymicrogyria. [a]

Megalencephaly-Capillary Malformation-Polymicrogyria (MCAP): part of *PIK3CA*-related overgrowth spectrum, clinically associated to megalencephaly and encephalic abnormalities. [a][t]

MICCAP: see Microcephaly Capillary malformation syndrome. [a]

Microcephaly Capillary malformation syndrome (MICCAP): abnormally small head size (microcephaly) and capillary malformations. Associated with *STAMBP* gene pathogenic variants. [s]

Microcephaly with or without Chorioretinopathy, Lymphedema, or Mental Retardation syndrome: rare autosomal dominant condition associated with *KIF11* gene pathogenic variants. [s]

Microcystic LM: Microcystic lymphatic malformation. LM with predominance of small and multiple cystic components. The distinction between Macrocystic and microcystic LM is primarily of importance for responsiveness to

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sclerotherapy treatment and choice of therapeutic agent. There is no precise definition separating the two types, and many lesions are mixed. [t]

Microvenular hemangioma: a specific type of benign Vascular Tumor. Acquired, slowly enlarging angiomatous lesions histologically characterized by a proliferation of small-sized, irregularly branched, blood vessels throughout the dermis embedded in a desmoplastic stroma, with endothelial cells were surrounded by pericytes. The architectural pattern of microvenular hemangioma make its differentiation possible from other cutaneous benign vascular lesions. [t]

Mixed cystic LM: LM with concurrent large cysts and of minor cystic components. Also related to soft tissue infiltration, and skeletal involvement. [t]

Mixed Infantile Hemangioma: a specific denomination for cutaneous hemangiomas. Mixed IH are those that affect simultaneously the cutaneous and deep soft tissue layers. [t]

Mixed Macro-microcystic Lymphatic malformation: a subtype of LM with presence of mixed large (macro) and small (micro) lymphatic cysts in the same lesion [t]

MLT: see Multifocal lymphangioendotheliomatosis with thrombocytopenia. [a]

MSVM: see Multifocal Sporadic Venous Malformation

mTOR: mammalian target of Rapamycin. Intracellular target in the treatment of some vascular malformations, especially those caused by variants in the PI3Kinase pathway. . [a]

Multifocal Fast-flow Vascular Malformation: category of fast-flow vascular malformations in which multiple lesions are present in the same patient [t]

Multifocal Infantile hemangioma: more than 5 focal IH distributed across the body. Such infants are at higher risk of visceral IH which may warrant further investigation such as liver ultrasound. [t]

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT): a vascular anomaly classified in the group of unclassified lesions. The same condition has also been called Cutaneovisceral angiomatosis with Thrombocytopenia. [s][t]

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Multifocal Sporadic Venous Malformation (MSVM): multifocal, mucosal, cutaneous and muscular VMs, with no family history. MSVM is associated with double pathogenic variants in the TEK (TIE2) gene, where the first one is mosaic and detectable in low frequency in blood DNA, whereas the second one is somatic in the lesion. [t]

Multifocal Vascular Anomaly: vascular anomalies that are simultaneously present in more than one anatomic site in the same patient [t]

Multifocal Venous Malformation: category of venous malformations in which more than one venous malformation is present in the same patient [t]

MYC: gene. Pathogenic variants/amplification in the *MYC* gene are found in post-radiation angiosarcoma. [g]

Nevus Simplex: a descriptive term used for a very common type of superficial capillary malformation with characteristic locations, most commonly the glabella, eyelids, and nape. Nevus simplex is typically pink to red, blanchable, with feathery borders. Except for the nape, nevus simplex has a tendency to fade over time. More extensive anatomic involvement, so-called "nevus simplex complex" can affect the philtrum, nose, occiput, and back and lumbosacral skin. Some cases are inherited in an autosomal dominant fashion. [t]

NICH: Non-Involuting Congenital Hemangioma. See 'Congenital Hemangioma'. [a][t]

Nonne-Milroy disease: a specific type of primary lymphedema. Characterized by lower-limb lymphedema, usually bilateral. Other features include hydrocele, prominent veins, upslanting toenails, papillomatosis, and urethral abnormalities. Cellulitis is frequent. *VEGFR3* gene (encoding *FLT4* receptor) pathogenic variants can be observed. [s]

Overgrowth: increase in volume of a body part often seen in association with vascular malformations, although it may also occur independently, as in macrodactyly and facial infiltrative lipomatosis. When used as a diagnosis, this term implies an increase in volume in proportion of multiple tissue types which normally make up the part, so histological examination is often normal. In a limb, there will usually be increased limb length in addition to girth, although if several structures, such as muscles which are otherwise morphologically normal are enlarged without change in limb length, the term can be used. The term 'overgrowth' should not be used diagnostically to describe an isolated

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vascular malformation, in which the proliferation of vascular structures is out of proportion to other tissues. [t]

Papillary Hemangioma: a specific type of benign Vascular Tumor [t]

Papillary Intralymphatic angioendothelioma (PILA): a specific type of Locally aggressive or borderline Vascular Tumor. [a][t]

Parkes-Weber syndrome: congenital vascular disease characterized by predominant capillary and arterio-venous shunts accompanied by bone and/or soft tissue hypertrophy in the affected area. Usually caused by RASA-1 variants but can also be sporadic. [e][s]

PDCD10: gene. Pathogenic variants in *PDCD10* are found in Cerebral Cavernous Malformation type 3(CCM3). [g]

PELVIS Syndrome: acronym used for the association of Perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag. Synonyms include LUMBAR and SACRAL syndromes, describing the same group of anomalies which are seen in association with lower-body segmental infantile hemangiomas. [a][s]

PHACE syndrome: Posterior fossa malformations (P), hemangioma (H), Arterial anomalies (A), Cardiovascular Anomalies (C), eye anomalies (E), Sternal cleft and/or supraumbilical raphe (S). This acronym as originally described encompasses the following features: describes the association of a segmental infantile hemangioma of the face and/or scalp, arterial anomalies, abnormal posterior fossa development, aortic abnormalities, including coarctation, heart defects and eye anomalies among other symptoms. Most patients with PHACE do not have all the elements described in the acronym. Sometimes also called Pascual-Castroviejo Syndrome type II [a][s]

Phacomatosis Pigmentovascularis: subtype of capillary malformation. Associated with dermal melanosis. Associated with sporadic genetic variants of *GNAQ* and *GNA11* genes. **[s]**

Phlebectactic Venous Malformation: subtype of venous malformation. The clinical and radiological aspect of the lesion is characterized by large venous lakes, dysplastic dilated veins or varicosities which can be isolated or communicate with other affected veins. May be associated with

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consumption of coagulation factors, elevation of d-dimer and consumption coagulopathy. [t]

PHTS: see *PTEN* Hamartoma Tumor syndrome. [a]

PHOST: PTEN Hamartoma of Soft Tissue; see also *PTEN* Hamartoma Tumor syndrome. [a]

PICH: Partially Involuting Congenital Hemangioma. See Congenital Hemangioma. [a]

***PIEZO1*:** gene related to vascular malformations. Germline pathogenic variants in *PIEZO1* are found in Generalized Lymphatic Dysplasia. [g]

***PIK3CA*:** gene. Related to many vascular malformations. Pathogenic variants in *PIK3CA* are found in Lymphatic Malformations, Venous Malformations, Klippel-Trenaunay Syndrome, Megalencephaly-capillary malformation-polymicrogyria, CLOVES Syndrome, CLAPO Syndrome and Fibroadipose vascular anomaly (FAVA). *PIK3CA* related overgrowth spectrum (PROS) is a term which has been coined to cover the many various lesions caused by somatic variants in *PIK3CA*. [a]

***PIK3CA* Related Overgrowth Spectrum (PROS):** this term was introduced by Biesecker in 2014 to refer to a range of conditions characterized by overgrowth of tissues associated with somatic pathogenic variants in the gene *PIK3CA*. 'PROS' has sometimes been used as an inclusive term for all proliferative lesions in which a pathogenic variant in the *PIK3CA* gene is detected (in which case LM would be considered a type of PROS), but the term is more properly used to describe conditions in which 'overgrowth' as defined in this glossary (i.e. growth involving more than one tissue type) is a feature. the list overgrowth disorders caused by PIK3CA somatic mutations has expanded to encompass lymphatic malformation, Klippel-Trenaunay Syndrome (KTS), CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis/skeletal and spinal), FAVA (Fibrodipose vascular anomaly) , Megalencephaly-capillary malformation (MCAP or M-CM), facial infiltrating lipomatosis, regional overgrowth (such as macrodactyly), CLAPO syndrome (capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry of the face and limbs, and partial or generalized overgrowth) and cutaneous lesions (seborrheic There are also some patients who have overgrowth in tissues in association with a gain of function pathogenic variant in PIK3CA, who do not fit any recognized pattern, in which case 'PROS' or 'PROS (unspecified)' may be used as a diagnostic label. [t]

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PILA: see Papillary Intralymphatic angioendothelioma. [a]

Polymorphous Hemangioendothelioma: a specific type of Locally aggressive or borderline Vascular Tumor. [t]

Port Wine CM: new item in the classification of capillary vascular malformations that share the designations of Port wine birthmarks or Nevus flammeus and is dermatologically characterized by homogeneous flat lesions. Many, but not all Port wine CM as due to somatic genetic variants in *GNAQ* or *GNA11* (amino acid arginine at position 183 (R183)). [t]

Port Wine Nevus (also Port wine birthmark, formerly Port wine stain). These terms have been replaced by Port wine CM. The word 'stain' is particularly problematic being associated with connotations of blame and the theory of maternal impressions and must be avoided. [e]

Potentially Unique Vascular Anomaly (PUVA): a term reserved for lesions that present an ambiguous or not precisely defined diagnosis between tumors and malformations. In the Updated classification, this category was included in view of the possibility of new diagnoses based on technological development and precision in genetics and molecular biology [a]

Primary Generalized Lymphatic Anomaly: also known as Hennekam lymphangiectasia-lymphedema syndrome. Characterized by presence of intestinal and renal lymphangiectasia, dysmorphic facial appearance and mental retardation. The facial features include hypertelorism, flat nasal bridge, epicanthic folds, small mouth, and small ears. Associated with *CCBE1* gene genetic variants. This entity should not be confused with Generalized Lymphatic Anomaly (GLA) from which it is entirely separate. [t]

Primary Hereditary Lymphedema: primary lymphedema associated with *VEGFC, GJC2* or *Connexin47* pathogenic variants. [t]

Primary Lymphedema: primary lymphedema is classified under slow-flow malformations, usually is related to hypoplasia of lymphatic vessels, leading to impairment of normal drainage of extracellular fluid. Can be an isolated disease or be part of specific syndromes[t]

Primary Lymphedema with myelodysplasia: primary lymphedema associated with myelodysplasia, is associated with *GATA2* gene pathogenic variants. [t]

PROS: see *PIK3CA* Related Overgrowth Spectrum. [a]

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Proteus Syndrome: a rare progressive multisystem disorder characterized by asymmetric, disproportionate overgrowth of bone, skin, and other tissue types. Overgrowth of the feet is characteristically cerebriform with increased connective tissue; bullous pulmonary lesions may be observed. Molecular pathogenesis has been identified as somatic activating pathogenic variants of the *AKT1* gene. The presentation of Proteus syndrome is exceptionally variable. [e][s]

Pseudomyogenic Hemangioendothelioma: a specific type of Locally aggressive or borderline Vascular Tumor. [t]

***PTEN*:** gene. Germline pathogenic variants in *PTEN* cause syndromes in which vascular anomalies are a feature including Bannayan-Ruvalcava Syndrome and Cowden syndrome, now encompassed within the preferred term *PTEN* Hamartoma Tumor Syndrome (PHTS)which is unique to PHTS. Somatic variants in *PTEN* may also be a cause of vascular malformations. [g]

***PTEN* Hamartoma of Soft Tissue (PHOST):** a fast-flow vascular anomaly which arises uniquely in the syndrome PHTS. Histological features are very similar to those of FAVA, but the etiology and clinical behavior is different.

***PTEN* Hamartoma Tumor Syndrome (PHTS):** is a rare syndrome due to inherited variants in the gene *PTEN*, with a broad phenotypic spectrum, including macrocephaly, autism spectrum disease, slow and high flow vascular anomalies, tissue overgrowth, hamartomas and increased risk of breast, endometrial and thyroid cancer. [s]

***PTPN14*:** gene. Pathogenic variants in *PTPN14* are found in Lymphedema-choanal atresia. [g]

PUVA: see Potentially Unique Vascular Anomaly

Pyogenic Granuloma (Lobular Capillary Hemangioma): an acquired proliferation of benign capillaries in the dermis or in mucous membranes most commonly occurring in childhood or in pregnancy. Can arise spontaneously, or in sites of a minor trauma or at sites of pre-existing vascular malformations. In some cases, somatic *BRAF*/RAS pathogenic variants are present. [t]

***RAF1*:** a gene related to vascular malformations. Germline pathogenic variants in *RAF1* are found in Noonan syndrome 5 (Rasopathy with lymphedema). [g]

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***RAS*:** a family of genes in which genetic variants have been found in multiple vascular malformations. Originally identified as an oncogene (the term is short for 'rat sarcoma') three subtypes were subsequently identified (*HRAS, KRAS* and *NRAS*) variants in all of which have been found in vascular malformations. RAS proteins are small GTPases which signal through the MEK/ERK pathway, but also into the PI3 Kinase pathway. [g]

***RASA1*:** gene. Related to many vascular malformations. Pathogenic variants in *RASA1* are found in CM-AVM1 and Parkes -Weber Syndrome. Some patients have hydrops and/or lymphedema [g]

Rasopathy: a group of conditions, including some vascular anomalies in which the causative mutated gene is RAS related genes. [a]

Reactive Angioendotheliomatosis: rare condition characterized by cutaneous vascular proliferation that usually occurs in patients with diverse types of coexistent systemic disease. Present distinct patterns of vascular proliferation in a wide distribution pattern, and a number of clinical presentations. [t]

Reticular Infantile Hemangioma: variant of infantile hemangioma that has a predilection for the lower extremity and perineum, with feature now often referred to as "abortive IH" or "IH-MAG". It is often associated with recalcitrant ulceration, LUMBAR syndrome, and rarely with cardiac overload. [t]

Reticulate/telangiectatic CM: a subgroup of Capillary malformation often has associated neurological findings. Reticulate-CM are subdivided in CM-of MIC-CAP (microcephaly-capillary malformation) (STAMBP gene pathogenic variants) and CM of *MCAP* (megalencephaly-capillary malformation-polymicrogyria) (*PIK3CA* pathogenic variants). Some Port wine capillary malformations have areas with reticulate morphology, particularly on the extremities, with other areas that are more confluent. Hence reticulate morphology of CM needs correlation with other findings e.g. Other areas of CM if present, macrocephaly or microcephaly, digital anomalies and other features for more specific diagnoses. [t]

Retiform hemangioendothelioma: a specific type of Locally aggressive or borderline Vascular Tumor. [t]

***RIT1*:** gene related to vascular malformations. Germline pathogenic variants in *RAF1* are found in Noonan syndrome 8 (Rasopathy with lymphedema). [g]

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RICH: Rapidly Involuting Congenital Hemangioma. See congenital hemangioma. [a][t]

Salmon patch: a lay term used for nevus simplex, best avoided as a diagnosis because of lack of specificity. [e]

SACRAL Syndrome: acronym used for the association of spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an hemangioma of lumbosacral localization. Synonyms include LUMBAR and PELVIS syndromes, describing the same group of anomalies which are seen in association with lower-body segmental infantile hemangiomas. [a][s]

SAMS: see spinal arteriovenous metameric syndrome [a] [s]

Secondary Lymphedema: acquired lymphedema, leading to impairment of normal drainage of extracellular fluid. Can be caused by infection, radiation, malignancies or surgery [t]

Segmental Infantile hemangioma: large IH compromising an entire anatomic unit or limb. Segmental IH are associated with specific syndromes ((PHACE, LUMBAR, SACRAL, and PELVIS) and more severe evolutional complications. [t]

Servelle-Martorell Syndrome: describes the association of a vascular malformation, usually a venous malformation, with undergrowth of the ipsilateral limb. This phenotype can result from several different genotypes, making it less a specific diagnosis than a descriptive term. [e][s]

Simple Vascular malformation: term from the previous classification, distinguishing lesions with a single vessel type from combined malformations, no longer in use. [t]

Sinus pericranii: cranial venous anomaly in which there is an abnormal communication between intracranial dural sinuses and extracranial venous structures, usually via an emissary transosseous vein. [t][e]

Sinusoidal hemangioma: a vascular anomaly classified in the group of unclassified lesions. Histologically show dilated, interconnecting, thin-walled vascular channels, with a pseudopapillary pattern. Vessels had a predominantly lobular architecture and can be confounded with malignant vascular tumors. [t]

Slow-flow Vascular Malformation: one of the main subdivisions of the Updated version of the classification for vascular malformations. The main change was to use flow velocity as a determinant between lesions with arterial

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components (fast-flow) and lesions with slow-flow components such as venous, lymphatic and capillary. It is differentiated from Fast-flow lesions and Developmental Anomalies of Named Vessels lesions. Slow-flow vascular malformations can be subdivided into Venous, Lymphatic, Capillary and Combined**. [t]**

***SMAD4*:** gene. Pathogenic variants in SMAD4 are found in Telangiectasia, AVM and AVF of Juvenile polyposis hemorrhagic telangiectasia (JPHT). [g]

***SOS1*:** gene related to vascular malformations. Germline pathogenic variants in RAF1 are found in Noonan syndrome 4 (Rasopathy with lymphedema). [g]

***SOS2*:** gene related to vascular malformations. Germline pathogenic variants in RAF1 are found in Noonan syndrome 5 (Rasopathy with lymphedema). [g]

SOX18: gene. Pathogenic variants in SOX18 are found in Hypotrichosis-Lymphedema-telangiectasia. [g]

Spider Angioma also Spider Nevus: vascular lesion, considered a CM, characterized by anomalous dilatation of end vasculature found just beneath the skin surface. The lesion contains a central, red spot and reddish extensions which radiate outward like a spider's web. They may appear as multiple or solitary lesions. [t]

Spinal Arteriovenous Metameric Syndrome (SAMS): a subtype of fast-flow vascular malformation. Relatively new and is derived from cerebrofacial arteriovenous metameric syndrome (CAMS),1 which was introduced to designate a rare form of vascular malformation involving both brain and face. SAMS includes all spinal vascular malformations of nonhereditary genetic metameric origin, affecting not only the central nervous system (spinal cord) but other tissues originating from the same metamere. The classic definition of Cobb syndrome is limited to metameric-origin malformations involving the spinal cord, bone, and skin. SAMS is intended to include all forms of metameric malformations, even if lesions are expressed without involving the spinal cord. [s]

Spindle Cell Hemangioma: a benign neoplasm composed of spindled cells, ectactic vascular spaces, and vacuolated endothelial cells. May present as multiple lesions in the same limb. Sporadic lesions and lesions in patients with Maffucci syndrome are associated with *IDH1* (or rarely IDH2) p.R132C hotspot genetic variants. [t]

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Spongiform Venous Malformation: subtype of venous malformation, different from phlebectatic venous malformations. Spongiform refers to the clinical and radiological aspect of the lesion, characterized by small and multiple venous dilations or communicating and divided by small septa. Phleboliths are frequently seen. [t]

Sporadic AVM: the most common type of AVM. Related most commonly to somatic pathogenic variants of gene MAP2K1 and KRAS. [t]

Sporadic AVF: sporadic direct communication between an artery and one or a few veins. This lesion may be congenital (a fast-flow vascular malformation) or acquired, induced by trauma, or iatrogenic. Sporadic AVM can be found in association to MAP2K1 gene pathogenic variants. [t]

***STAMBP*:** gene. Pathogenic variants in STAMBP are found in CM of MIC-CAP. [g]

Stenosis: abnormal narrowing of a vessel. [t]

Stork bite: lay descriptive term used for nevus simplex. [e]

Sturge Weber Syndrome: triad of Capillary malformation (Port Wine Stain) of the face, glaucoma and leptomeningeal angiomatosis. Associated with somatic pathogenic variants of the GNAQ and GNA11 genes. [e][s]

Superficial Infantile Hemangioma: a specific denomination for cutaneous hemangiomas. Superficial IH are those that affect only the cutaneous layer. [t]

Syndromic Fast-flow Vascular Malformation: category of fast-flow vascular malformation in which lesions present in conjunction with other signs and symptoms as part of a specific syndrome. May be associated with other vascular anomalies or other findings not associated with vascular anomalies [t]+

Syndromic Vascular Anomaly: vascular anomaly that occurs with a pattern of signs and symptoms that tend to occur together and suggest a particular disorder. Vascular lesions may be present in conjunction with other non-vascular signs and symptoms as part of a specific syndrome.

Syndromic Venous Malformation: category of venous vascular malformations in which lesions present in conjunction of other signs and symptoms as part of a specific syndrome. May be associated with other vascular anomalies or other findings not associated with vascular anomalies [t]

TA: see Tufted Angioma. [a]

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Telangiectasia: descriptive term which refers dilation of the capillaries, often spidery in appearance, on the skin or the surface of an organ. It is not a diagnostic term per se though historically has been used as a diagnostic component of certain vascular anomalies such as "hereditary hemorrhagic telangiectasia" (though most of these are actually small arteriovenous shunts or AVMs). Telangiectasias (sometimes called telangiectases) can also be seen in other vascular anomalies such as residua of infantile hemangiomas, in CM-AVM2, and several others. They can also be seen in many other conditions which are not vascular anomalies such as scleroderma, mast cell disorders, and certain liver diseases. [t]

TEK (TIE2): gene. Pathogenic variants in *TEK (TIE2*) are found in VM, Sporadic Multifocal VM (MSVM), and Blue-rubber bleb nevus (Bean) syndrome (all due to somatic pathogenic variants), and in Familial VM cutaneo-mucosal (VMCM) due to germline pathogenic variants. [g]

***TFE3*:** gene. Pathogenic variants in *TFE3* are found in Epithelioid hemangioendothelioma. [g]

***THSD1*:** gene related to vascular malformations. Germline pathogenic variants in *THSD1* are found in Hydrops with severe edema. [g]

***TIE1*:** gene related to vascular malformations. Pathogenic variants in *TIE1* are found in late onset primary lymphedema [g]

***TIE2*:** See *TEK*

Truncal Vascular Malformation: also known as channel type vascular malformations. Anomalies of major named vessels. Affects arteries, lymphatics, or veins. [t]

Tufted Angioma: benign vascular tumor characterized by lymphatic infiltration lobules of closely packed capillaries in a cannonball distribution. Now considered part of a disease spectrum with Kaposiform Hemangioendothelioma. [t]

Unifocal Vascular Anomaly: vascular anomaly that is present in only one anatomic site. [t]

Vascular Anomalies: the main category [T] of disease classified according to cellular and clinical behavior in tumors and malformations. [t]

Vascular Malformation: originally this was a non-specific term to describe any congenital anomaly affecting the vascular system, including conditions such as absence or duplication of great vessels (truncal anomalies). Over time the

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term has acquired a more specific meaning in vascular anomalies practice. It is now referred to lesions in which there is an overabundance of specific types of vessels. Vascular malformations are subdivided into fast-flow and slow-flow malformations. Caution is needed when using the term outside this context, and to avoid confusion with the term Vascular Anomaly. [t]

Vascular Tumors: one of the 2 main categories of Vascular Anomalies. Vascular Anomalies are didactically divided in Vascular tumors and Vascular malformations. Vascular Tumors are classified in benign, locally aggressive, or borderline and malignant. [t]

***VEGFC*:** gene. Pathogenic variants in VEGFC are found in Primary Hereditary Lymphedema. [g]

***VEGFR3*:** gene. Also named FLT4. Pathogenic variants in VEGFR3 are found in Nonne- Milroy Syndrome. [g]

Vein of Galen: is the great cerebral vein, also known as the great vein of Galen. It is a short valveless midline venous trunk that drains the deep parts of the brain, brainstem and parts of the posterior cranial fossa. Congenital low resistance shunts into the vein of Galen (Vein of Galen Malformation) are particularly associated with CM-AVM syndrome. [e]

Venous hypertension: elevated pressure in the venous system is commonly caused by venous insufficiency or occlusion. A similar but more severe form occurs with fast-flow anomalies. Swelling, edema, pain, skin changes (hyperpigmentation, stasis dermatitis, lipodermatosclerosis), ulcerations and secondary lymphedema.

Venous Malformation: venous malformations are due to defective assembly of the venous vasculature. Defined subsets are now recognized. Venous malformations are most often due to pathogenic variants in the TEK (Tie2) gene, but also PIK3CA. Lesions due to Glomulin pathogenic variants (GVMs) can mimic venous malformation. Nodular VMs can be seen in KRIT1 mutated CCM patients. [t]

Verrucous Hemangioma: old term still used for Verrucous Venous Malformation. [t]

Verrucous Venous Malformation (VVM): formerly called "verrucous hemangioma," is a non-hereditary, congenital vascular malformation comprised of aberrant clusters of malformed dermal venule-like channels underlying

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hyperkeratotic thick skin in the context of MAP3K3 somatic pathogenic variant. [t]

VM: see Venous Malformation. [a]

VMOS: see Familial intraosseous vascular malformation. [a]

VMCM: see Familial VM Cutaneo-mucosal [a] associated with TIE2/TEK germline pathogenic variants.

VVM: see Verrucous Venous Malformation

Key: [A] = acronym; [E] = eponym; [S] = syndrome description; [T] = technical term

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