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Updated Classification of Vascular Anomalies

A living document from the International Society for the Study of Vascular Anomalies Classification Group

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Abstract

Introduction: The International Society for the Study of Vascular Anomalies developed in 1996 a classification of vascular anomalies that became internationally accepted. The main feature was the division of vascular anomalies into 2 categories: vascular tumors and malformations. Major revisions occurred in 2014 and 2018, for updates and inclusion of newly described lesions. Major advances occurred in recent years, with improved understanding of genetic basis of vascular anomalies and its relevance in therapeutics. It created a demand for a new revision of the International Society for the Study of Vascular Anomalies (ISSVA) classification, and the process is presented in this study.

Methods: A group was created in 2019, joining experts from different specialties and coordinated by the ISSVA Scientific Committee, to reevaluate the 2018 Classification on each subtype of vascular anomaly, considering the clinical presentation, histological subtypes, flow velocity, and genetic aspects. After several multidisciplinary online discussions and in-person meetings at ISSVA Congresses (2022, 2023, and 2024) the proposal for the new classification was presented for ISSVA members ratification, after an opening window for comments and suggestions. A new tool was created, named "Glossary of Vascular Anomalies," along the contours of a medical dictionary.

Results: A new layout of the classification was designed. The visualization begins with a general "Landing Page" where the basic division into vascular tumors and malformations is specified. For vascular tumors, the subdivision was kept between benign, borderline, and malignant tumors. For vascular malformations, the divisions were presented as fast-flow lesions, slow-flow lesions, and developmental anomalies of named vessels. A full classification table page with all updated modifications followed the landing page. All changes and new terms are described in detail and summarized in a table. The glossary lists and explains, in alphabetic order, all technical terms, abbreviations, acronyms, eponyms, genes, and syndromes related to vascular anomalies.

Conclusions: The presented updated ISSVA classification of vascular anomalies reflects our evolving understanding of vascular anomalies, which will be continuously updated by a dedicated committee of ISSVA.

Keywords: angioma, classification, hemangioma, update, vascular anomaly, vascular tumor, vascular malformation

Introduction

Diagnosis and classification of diseases underlie all aspects of medical practice. A satisfactory classification is necessary for correct diagnosis and is an important cornerstone in conducting research. By providing a structure and standardizing nomenclature, communication between practitioners is also facilitated. This is of particular importance in a multidisciplinary field like vascular anomalies. For this reason, the International Society for the Study of Vascular Anomalies (ISSVA) brought together experts from multiple disciplines in 1996 to create the ISSVA classification of vascular anomalies. The most important feature of this classification was

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its fundamental division of vascular lesions into tumors and malformations. The ISSVA classification has since become accepted and utilized internationally. In a field where knowledge is evolving, a classification must be constantly updated to keep pace with the latest research. Indeed, the classification has undergone major revisions in 2014 and 2018. These revisions dealt primarily with newly described lesions, but also with a number of conditions that resisted classification into categories of tumor or malformation.[1]

In recent years there have been major advances in understanding the genetic basis of vascular anomalies and of vascular malformations in particular.[2] The discovery that many vascular malformations are caused by somatic genetic mutations has led to a more nuanced understanding of the difference between tumors and malformations. Some tumors have properties that are generally associated with malformations, and many vascular malformations retain some proliferative potential. While this potential has always been recognized, the successful application of targeted therapies to vascular malformations suggests that it may be of more importance than was previously recognized. Taken together, these considerations have created a demand for a more substantial revision of the previous ISSVA classifications.[3]

This article provides background to the process of how the classification was revised, and presents an updated classification,[4] highlighting the most significant changes.

Methods

Creation of working groups and revision process

Revising the current (2018) ISSVA classification[1] began in 2019 and developed through multiple meetings, both in-person and virtual. A working group was created by the ISSVA Board to study aspects of the classification requiring revision and to generate an updated classification.

Working subgroups were created to reevaluate each subtype of vascular anomaly; hence, 5 subgroups were organized based on the main divisions of the classification (vascular tumors, capillary, venous, lymphatic, and arteriovenous malformations [AVMs]). In each subgroup, experts from different specialties, invited by the ISSVA Board and the Scientific Committee, analyzed the 2018 classification with the aim of making improvements that would allow the use of the classification by any medical specialty. The subgroups, subdivided into those related to vascular tumors and vascular malformations discussed the best way to classify their section diseases, considering the histological subtypes, genetics, clinical behavior, and flow velocity. Combined and syndromic malformations were evaluated by the various groups, and consensus meetings were held to unite impressions and opinions. Therefore, the main objective of this updated classification is to keep the mission of allowing cases to be classified not only on the clinical aspect but also according to imaging findings, angiographic studies, and results of genetic and anatomopathological examinations. In other words, the classification could be used at any stage of the diagnostic process, starting with the initial evaluation of the patient. Of note, the classification is intended to be lesional. Uncommonly, an individual could have more than one type of vascular anomaly at different anatomic sites.

The progress of discussions between the components of each subgroup was evaluated in several multidisciplinary meetings and finally reviewed in person at the ISSVA international meeting in Vancouver in 2022. Based on the comments received, further revisions were made to the classification that was represented for discussion at the following meeting in Boston in 2023. The development was subsequently continued by the ISSVA Scientific Committee during virtual meetings, and the final updated classification was presented at the ISSVA 2024 Scientific Congress in Madrid, Spain, for ratification, after an open comment period for ISSVA members to send suggestions for evaluation and discussion.

Particularities of each type of vascular anomaly for a classification subsystem and creation of a glossary

The new classification considers the individual characteristics of each vascular anomaly, grouping together lesions with similar key features. This approach subdivides each subtype of vascular tumors and vascular malformations into distinct, nonoverlapping categories, making the classification more meaningful and applicable within each specific group of anomalies. In some anomalies, specific diagnoses and syndromic diagnoses were included, considering specific vascular disease syndromes as well as vascular anomalies existing in syndromes in general.

Due to the major research findings in recent years, allowing for more precise diagnosis based on genetic studies, the genetic component was considered and incorporated. It was expanded in the current update and included in detail in the ISSVA Glossary. These changes in nomenclature, based on anatomopathological, immunohistochemical, and genetic studies, led to the emergence of new disease entities that are often unknown to most of the medical profession.

A new tool was created to resolve doubts and allow the appropriate use of terms in the assessment, diagnosis, and treatment of vascular anomalies. The ISSVA Scientific Committee added to the current classification a new document called "Glossary of Vascular Anomalies," where all terms related to vascular anomalies are defined, followed by a brief updated explanation, along the contours of a medical dictionary. The glossary is also a dynamic document that can be updated and refined as needed.

Results

Summary of changes

A new layout of the classification was designed. The visualization begins with a general page (landing page) (Figure 1), displaying the main categories of vascular anomalies. This landing page maintains the basic division of vascular anomalies into vascular tumors and vascular malformations, with enhanced features. Also, a category named potentially unique vascular anomalies was included, replacing "provisionally unclassified vascular anomalies" present in the previous classification. The main changes and new terms added in this updated classification are summarized in Table 1.

For vascular tumors, subdivisions between benign, borderline, and malignant tumors were retained. Reactive proliferative vascular lesions were listed with benign tumors. Specific diseases and diagnoses are listed. For vascular malformations, the divisions were presented as fast-flow lesions, slow-flow lesions, and developmental anomalies of named vessels. Fast-flow malformations are further divided

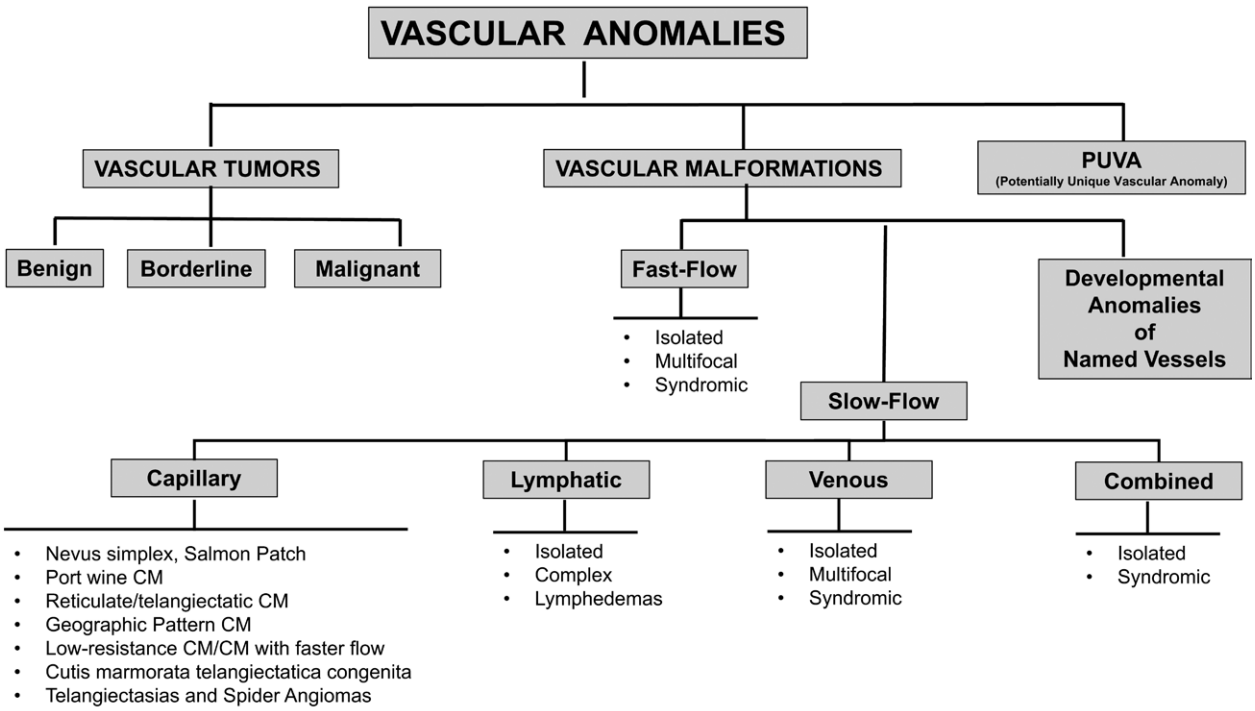

Figure 1. Landing page of updated ISSVA Classification. CLA indicates complex lymphatic anomaly; CM, capillary malformation; CMTC, cutis marmorata telangiectatic congenita. Reproduced with permission from the International Society for the Study of Vascular Anomalies.[4]

into isolated, multifocal, and syndromic. Slow-flow malformations are divided into venous (isolated, multifocal, and syndromic), lymphatic (isolated, complex lymphatic anomalies, and lymphedemas), capillary (listing clinical presentations and cutaneous patterns, such as nevus simplex, salmon patch, port wine capillary malformation [PWCM], etc.) and combined (isolated or syndromic).

After the landing page, a full classification page describes in detail each subtype of vascular anomaly (Figures 2–4). Benign vascular tumors were described in detail with the inclusion of diagnoses according to clinical, genetic, and histological aspects. For this reason, diagnoses that are anatomopathological differential diagnoses were included in the list of vascular tumors. Tumors with borderline behavior were listed and new terms were added, including the diagnoses that present aggressive behavior, differentiated by histological type or by the occurrence of clinical-specific problems, such as those associated with the Kasabach-Merritt phenomenon. Malignant tumors include the same list as the previous 2018 classification (Figure 2).

The group of vascular malformations underwent the greatest number of modifications (Figures 3 and 4). In the previous iteration of the classification, the primary division within vascular malformations was between "simple" and "combined" malformations. In the revision process, there was a recognition that this does not reflect fundamental differences in etiology but existed to accommodate a classification based on vessel type. In the present updated classification, vessel type is no longer the primary organizing criteria. The subclassification is now based on flow velocity, in addition to the subgroup of anomalies of named vessels.

Vascular malformations are now primarily divided into the clinically and radiologically distinguished categories of "fast-flow" and "slow-flow."

Fast-flow lesions contain a significant component of low-resistance flow (Figure 3). Isolated fast-flow vascular malformations include AVMs, intramuscular fast-flow vascular anomalies, and arteriovenous fistulas. Multifocal AVMs include those seen in CM-arteriovenous malformation (CM-AVM), hereditary hemorrhagic telangiectasia, and *PTEN* hamartoma tumor syndrome (PHTS). Syndromic fast-flow malformations include syndromes such as PHTS, Parkes-Weber syndrome, spinal arteriovenous metameric syndrome, and cerebrofacial arteriovenous metameric syndrome.

Each slow-flow malformation had its subtypes specified, describing the isolated, multifocal, and syndromic clinical types, with the new descriptions included (Figure 4).

In the group of CMs, priority was given to the inclusion of descriptive terms that facilitate the grouping of lesions according to the cutaneous pattern of the malformation and the presence of genetic and syndromic components. CM were classified into nevus simplex/salmon patch, PWCM, reticulate/telangiectatic CM, geographic pattern CM, low-resistance CM/CM with faster flow, cutis marmorata telangiectasia congenita, telangiectasias, and spider angiomas. PWCM category was divided into isolated (including phacomatosis pigmentovascularis) and syndromic. The syndromic PWCM included PWCM with hypertrophy or extracutaneous disease, Sturge-Weber syndrome, and diffuse CM with overgrowth (DCMO). Syndromic reticulate/telangiectatic CM included megalencephaly-CM (M-CM), Microcephaly-CM, and DCMO. Low-resistance CM/CM with faster flow can be isolated or part of a syndromic form in CM-AVM 1 and 2, and Parkes Weber Syndrome. Finally, syndromic telangiectasias and spider angiomas include CM-AVM 1 and 2, hereditary hemorrhagic telangiectasia 1 and 2, and juvenile polyposis hemorrhagic telangiectasia (JPHT).

Table 1.

Summary of Main Changes in the Updated Classification

Vascular Anomaly	Main Changes	New Terms and Diagnosis
Main division	VAs are divided into tumors, malformations, and PUVA. The term "provisionally unclassified vascular Anomalies" no longer exists. Some terms were moved to the Glossary, making classification simpler. Genetic correlation is also available in the Glossary.	PUVA
Tumors	Inclusion of all histopathologic variants of benign tumors in the same list (removal of terms "other" and "related lesions")	Inclusion in Borderline tumors -Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT)
Vascular malformations	Main division is between fast-flow, slow-flow, and developmental anomalies of named vessels removal of term "simple vascular malformation" The category "vascular malformations associated with other anomalies" is suppressed and the diagnosis incorporated into the VM subtypes	Developmental anomalies of named vessels Fast-flow vascular malformation slow-flow Vascular malformation
Fast-flow vascular malformations	Subtypes are isolated, multifocal, and syndromic. Removal of terms "sporadic," "in HHT" and "CM-AVM"	CAMS CM-AVM 1 and 2 Intramuscular fast-flow vascular anomaly PHTS/PHOST SAMS
Slow-flow vascular malformations	VM are divided into vascular type (capillary, lymphatic, venous or combined)	
Venous malformations	Are divided into isolated, multifocal, and syndromic	CLOVES FAVA HCCVM/CCM Mafucci Syndrome MSVM Phlebectatic VM PHTS Sinus pericranii Spongiform VM
Lymphatic malformations	Are divided into isolated, CLA, and lymphedemas Terms were relocated into these categories	Angiokeratoma CCLA Mixed macro-microcystic Primary and secondary Lymphedemas
Capillary malformations	Inclusion of terms that facilitate grouping of lesions according to cutaneous pattern, the presence of genetic and syndromic components. CM were divided into nevus simplex/Salmon patch type, port wine CM, reticulate/telangiectatic CM, geographic pattern CM, low-resistance CM/CM with faster flow, cutis marmorata telangiectatic congenita, and telangiectasias and spider angiomas	CM in CLOVES CM in disorders of the PROS spectrum CM-AVM 1 and 2 Geographic pattern CM Port wine CM
Combined VM	Divided into isolated and syndromic	CLAPO CLM CLOVES
Developmental anomalies of named vessels	Simplified by naming vessels	Aorta vena cava Vein of galen

CCLA indicates central conducting lymphatic anomaly; CLA, complex lymphatic anomaly; CLAPO, capillary malformation of the lower lip, lymphatic malformations of the head and neck, asymmetry and partial or generalized overgrowth; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies; CM-AVM, capillary malformation-arteriovenous malformation; CM, capillary malformation; FAVA, fibroadipose vascular anomaly; HCCVM/CCM, hyperkeratotic cerebrous cavernous venous malformations/cerebral cavernous malformation; HHT, hereditary hemorrhagic telangiectasia; MSVM, multifocal sporadic venous malformation; PHOST, *PTEN* hamartoma of soft tissue; PHTS, *PTEN* hamartoma tumor syndrome; PROS, *PIK3CA* related overgrowth spectrum; PUVA, potentially unique vascular anomalies; VM, venous malformation.

Lymphatic malformations (LM) were divided into isolated LM, including macrocystic, microcystic, mixed macro-microcystic LMs, and angiokeratoma. Other types of LM included complex lymphatic anomaly, divided into generalized lymphatic anomaly, kaposiform lymphangiomatosis, Gorham-Stout disease, and central conducting lymphatic anomaly (isolated or syndromic). Lymphedemas were classified as primary (isolated or syndromic) and secondary.

Venous malformations (VM) were divided into isolated VM, classified as phlebectatic, spongiform, verrucous-VM, and fibroadipose vascular anomaly. Multifocal VM include VM cutaneo-mucosal (VMCM), multifocal sporadic VM, blue rubber bleb nevus syndrome, glomuvenous malformation, hyperkeratotic cutaneous capillary-venous malformations (CVMs) of cerebral cavernous malformations and familial intraosseous vascular malformation. Syndromic VM include PHTS, congenital lipomatous overgrowth with VMs, epidermal nevi and skeletal anomalies (CLOVES) syndrome, Maffucci syndrome and sinus pericranii.

Combined VMs included isolated capillary-lymphatic-VM, Lymphatic-venous malformation (LVM), CVM, Verrucous VM and hyperkeratotic cutaneous CVMs associated with cerebral cavernous malformations. Syndromic combined VMs include *PIK3CA*-related overgrowth spectrum, Klippel-Trenaunay Syndrome (KTS), CLOVES syndrome, and Proteus Syndrome.

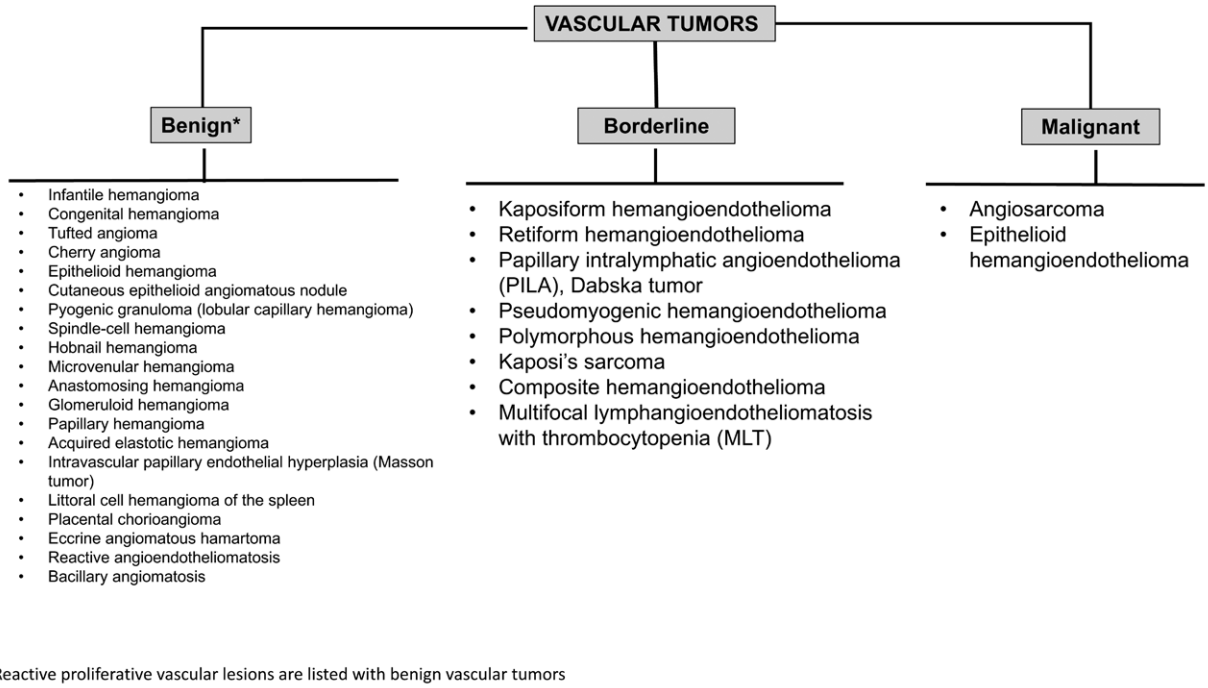

Figure 2. Full classification page. Classification of vascular tumors. Reproduced with permission from the International Society for the Study of Vascular Anomalies.[4]

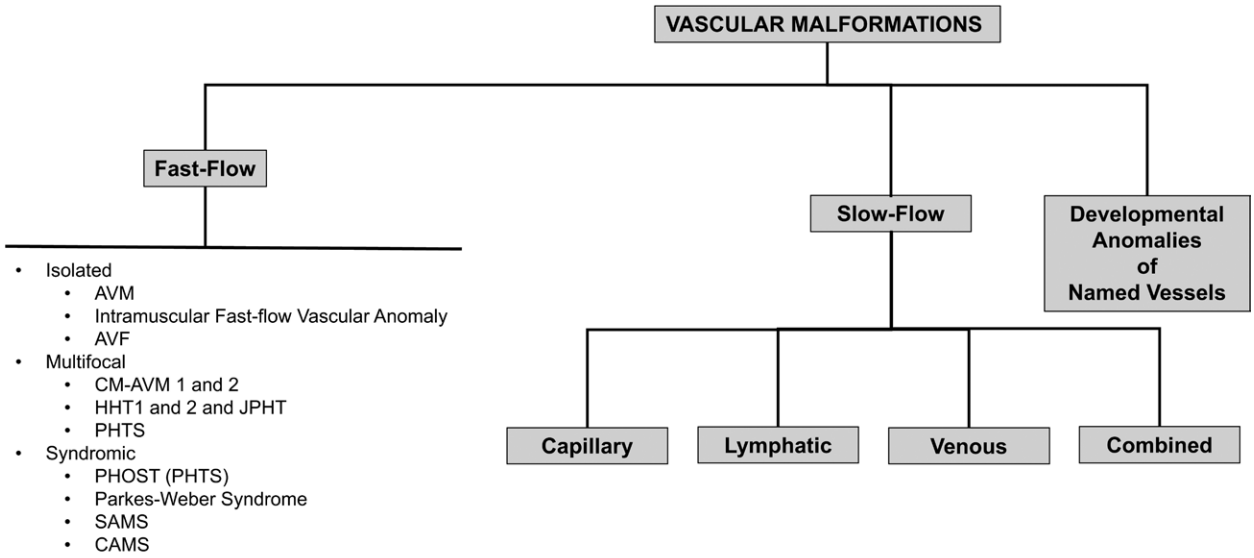

Figure 3. Full classification page. Classification of fast-flow vascular malformations. AVF indicates arteriovenous fistula; AVM, arteriovenous malformation; CAMS, cerebrofacial arteriovenous metameric syndrome; CM-AVM, capillary malformation-arteriovenous malformation; HHT, hereditary hemorrhagic telangiectasia; JPHT, juvenile polyposis hemorrhagic telangiectasia; PHOST, *PTEN* hamartoma of soft tissue; PHTS, *PTEN* hamartoma tumor syndrome; SAMS, spinal arteriovenous metameric syndrome. Reproduced with permission from the International Society for the Study of Vascular Anomalies.[4]

Finally, consideration was given as to whether anomalies of large named vessels should continue to be a category in the ISSVA classification (Figure 4). The Hamburg classification,[5] which preceded the original ISSVA classification, divided vascular malformations into those affecting axial embryological vessels ("truncal" lesions) from those affecting peripheral components of the developing vascular system ("extra truncal" malformations), that is, those we now think of as VMs. Anomalies of named vessels therefore took a natural and logical place in the classification and allowed the entire world of vascular anomalies considered in a unique classification. The category has been retained in the classification.

Development of ISSVA Glossary

The glossary is an appendix to the classification (additional document 1) and was created to allow wide access and clarification of vascular anomalies terminology. Both the Classification and Glossary have ISSVA copyright. The

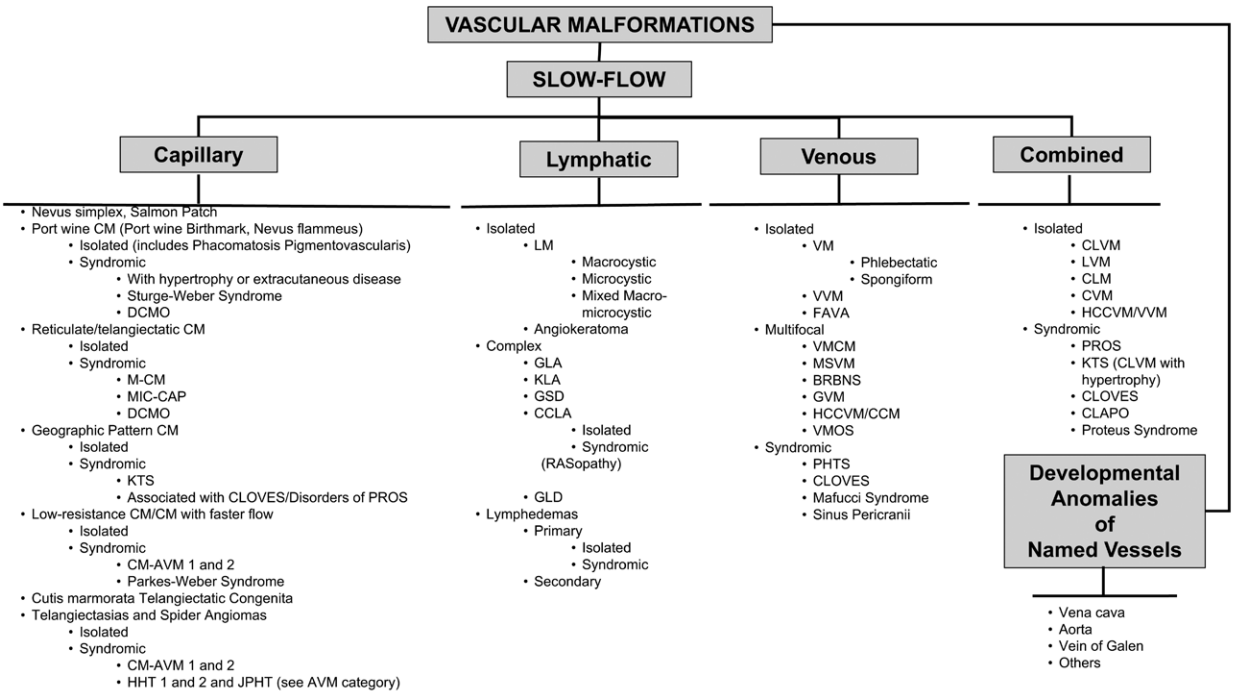

Figure 4. Full classification page. Classification of slow-flow vascular malformations and developmental anomalies of named vessels. BRBNS indicates blue rubber bleb nevus syndrome; CCLA, central conducting lymphatic anomaly; CLA, complex lymphatic anomaly; CLAPO, capillary malformation of the lower lip, lymphatic malformations of the head and neck, asymmetry and partial or generalized overgrowth; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies; CLVM, capillary-lymphatic-venous malformation; CM-AVM, capillary malformation-arteriovenous malformation; CM, capillary malformation; CVM, capillary-venous malformation; DCMO, diffuse capillary malformation with overgrowth; FAVA, fibroadipose vascular anomaly; GLA, generalized lymphatic anomaly; GLD, generalized lymphatic dysplasia; GSD, gorham-stout disease; GVM, glomuvenous malformation; HCCVM/CCM, hyperkeratotic cerebrous cavernous venous malformations/ cerebral cavernous malformation; HHT, hereditary hemorrhagic telangiectasia; JPHT, juvenile polyposis hemorrhagic telangiectasia; KLA, kaposiform lymphangiomatosis; KTS, klippel-trenaunay syndrome; LM, lymphatic malformation; LVM, lymphatic-venous malformation; M-CM, macrocephaly capillary malformation syndrome; MIC-CAP, microcephaly capillary malformation; MSVM, multifocal sporadic venous malformation; PHTS, *PTEN* hamartoma tumor syndrome; PROS, *PIK3CA* related overgrowth spectrum; VM, venous malformation; VMCM, familial vm cutaneo-mucosal; VMOS, familial intraosseous vascular malformation; VVM, verrucous-venous. Reproduced with permission from the International Society for the Study of Vascular Anomalies.[4]

online version is hosted at the ISSVA website (www.issva.org) with hyperlinks within the classification and the glossary, to facilitate cross-referencing and enhanced understanding. The document will be updated periodically.

The glossary lists and explains, in alphabetic order, all technical terms, abbreviations, acronyms, eponyms, genes, and syndromes related to vascular anomalies. After explanation, each term is accompanied by specific codes meaning its definition, that is, whether it is a technical term (t), an eponym (e), an acronym (a) a gene (g), or a syndrome (s). The glossary therefore forms an important part of the classification. Since it is a living document, it is anticipated that glossary entries will also be linked to "atlas" type resources of typical pathology, medical imaging, and clinical images. This should aid not only the proper classification of lesions but also facilitate education and communication for patients and caregivers.

Discussion

Classification versus terminology

Jakob[6] draws a distinction in science between "classification," which "involves the clustering of information according to logical rules," and "terminology," which refers to more specific and granular information on specific entities, in this case, particular lesions. In an ideal classification, every observed case would fit into a single category, with no overlap and no gaps between them.

Before the introduction of the ISSVA classification, terminology had been a major barrier to communication. The use of improper and outdated terms caused confusion, and at times, genuine threat to patients. In the past, however, terminological confusion rarely put the patient at high risk, since there were few specific therapeutic alternatives. Improvements in the knowledge of vascular anomalies have allowed the inclusion of various specific targeted therapies on the management of different types of vascular anomalies. These agents have a series of potentially hazardous side effects. Incorrect classification may consequently increase the risk of incorrect therapeutic approach and real harm to the patient.

One of the main objectives of this classification update was to keep a multipurpose classification system so that professionals from different specialties could use the same classification, strengthening communication links between healthcare areas. Instead of having specific classifications for angiographic, anatomopathological, and genetic aspects, ISSVA seeks to unite professionals through a common classification. Science evolves and new ideas emerge all the time, many of them with the potential to change daily practice. It is natural that specific areas or specialties want to detail or elaborate on a particular vascular anomaly and create a subclassification, with specific technical, therapeutic, or prognostic aspects. Even so, it is recommended that these subclassifications or new classification proposals maintain the use, as far as possible, of terms already recognized worldwide and

included in the updated ISSVA classification. This will lead to more uniformity in interdisciplinary communication.

A second important aspect is to have a classification that can be used by professionals with distinct levels of knowledge on vascular anomalies. The "landing page" allows primary care professionals such as general pediatricians and general dermatologists to understand vascular anomalies and categorize them appropriately, facilitating the patient's entry within their investigation and treatment journey.

The "logical rules" by which entities are organized into a classification are dependent on the purposes for which the classification is to be used. Scientific principles, reaching back to Aristotle, dictate that etiological cause should take precedence in grouping entities, but other factors may also influence how lesions are categorized.[7] Medical classifications are used for diagnosis, so it may be desirable that lesions that form typical differential diagnoses are grouped into the same category. The original ISSVA classification closely followed scientific convention in prioritizing etiology as a categorical principle. The primary separation of vascular anomalies into tumors and malformations reflected what was believed at that time: tumors were generally understood to be neoplastic, showing clonal proliferation caused by excess of stimuli or lack of inhibition.[8] Malformations, in contrast, could be best understood as errors in embryologic differentiation and growth, occurring in a precise moment.[9] Recent studies demonstrate that vascular malformations are caused by somatic genetic pathogenic variants, which may affect the potential for cell proliferation. Consequently, vascular malformations, like tumors, could also grow by vascular proliferation.[10,11] Malformations may evolve over time, modifying their clinical behavior and histological appearance.[12] In summary, the continuous development of knowledge raises questions that can stimulate reflection on specific points of the diagnosis. Therefore, the classification tends to be temporally dynamic, requiring periodic reviews.

Classification as a living document

Any classification system should undergo periodic revision, and the way it appears at a particular time is thus a reflection of the state of knowledge in the field at that time. No classification is ever complete and final. A series of initiatives, such as the creation of a permanent working group for classification updates, the maintenance of an online glossary open to receiving active suggestions, and the creation of links to a future image atlas linked to the glossary, have been actively implemented to make the entire classification system interactive and highly updated.

Participation of a broad range of practitioners and scholars in the revision of the ISSVA classification has been important to ensure that the classification continues to perform its vital role, and it will continue to do so in the future. The involvement of multiple disciplines in the development of a classification means that inevitably compromises must be made in drawing boundaries between groups of conditions. Some decisions are made only by consensus and no practitioner is likely to agree with every decision.[13] As an example, one contentious issue was whether "congenital hemangioma" (CH) should still be considered a tumor rather than a malformation. CH shares histological similarities to infantile hemangioma, and they are genetically similar to some malformations. Recently, a new entity caused by a novel mutation in the *GNAQ* gene has been described, which has clinical features somewhere between a congenital hemangioma and a vascular malformation.[14,15]

A resonant point in the group's discussions was the possibility of classifying vascular anomalies more strictly in relation to molecular aspects, and grouping lesions according to their causative genetic variants.[14–16] However, not only can a single genetic variant give rise to widely differing phenotypes, but conversely, several genetic variants may give rise to similar phenotypes. Also, while genes may be conveniently grouped into "pathways" serving well-defined functions in cells, the same gene may have a role in more than one pathway, making classification via grouping of genes challenging. Finally, the sporadically occurring vascular malformations (which form the majority) are caused by somatic mutations that have occurred at different time points of development (stem cell or more differentiated venous, capillary, arterial, or lymphatic endothelial cell). The resulting phenotype not only depends on the gene, its mutation, or pathway but also on the cell type and time point in which the mutation occurred. Thus, the genetic basis needs to be put in the context of the clinical, radiological, histological data, and environmental factors.

Nevertheless, the current revised classification does represent a step toward a more molecular classification. In the previous iteration of the classification, lesions caused by mutations in *PIK3CA* could be found in the categories of lymphatic, venous, and mixed malformations, where now those same lesions are all grouped under "slow-flow" malformations. Similarly, fast-flow lesions have increasingly been shown to be caused by variants in genes in the *RAS/MEK/ERK* pathway. Thus, genetically similar lesions are now more closely grouped than they were previously. This reflects the fact that while differentiation between fast and slow-flow lesions is primarily clinical and radiological, there is an etiological component. It is expected that this tendency to group lesions will continue to evolve, as knowledge grows concerning genetic causes of vascular anomalies and the interactions and relations between genes and gene products.

Finally, compromise was required concerning entities that are clinically closely related, even clinically indistinguishable, but known to arise in different clinical contexts. For instance, the previous classification listed as separate lesions "sporadic"/common venous malformation and venous malformations that arise as part of a familial syndrome (familial VM, VMCM). The same issue arises with several fast-flow lesions. Once again there is no "correct answer," but in the interests of simplicity, the decision was made that entities that are clinically and especially histologically indistinguishable (only genetic data may be able to differentiate them) should be under a single branch in the classification (i.e. under Fast-flow or Slow-flow), and for the latter subsequently under venous, lymphatic, capillary or combined.

Where an entity can be separately defined by radiologic and/or histological and genetic features, such as the fast-flow lesion "*PTEN* hamartoma of soft tissue," it deserves and receives entry as a separate entity, even though typical AVM and VM can also arise in patients with *PTEN* hamartoma syndrome. Due to the latter, PHTS can be found in the detailed classification under the fast-flow and slow-flow venous branches. This facet of the classification also serves to emphasize another important aspect of the ISSVA classification: it is lesion, not patient-based and it is a classification

system with an inclusive philosophy. Patients occasionally have more than one type of vascular anomaly. This distinction allows for a defined diagnosis on a specific lesion according to the classification and the use of links directing to the glossary to call the clinician's attention to syndromes of which the lesion may be a feature.

Conclusions

The presented updated ISSVA classification of vascular anomalies reflects our evolving understanding of vascular anomalies. It is not a static version of the classification, but one which will continue to be updated by a dedicated Committee of ISSVA.

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References

1. Wassef M, Blei F, Adams D, et al.; ISSVA Board and Scientific Committee. Vascular anomalies classification: recommendations from the international society for the study of vascular anomalies. *Pediatrics*. 2015;136(1):e203–e214.
2. Queisser A, Seront E, Boon LM, Vikkula M. Genetic basis and therapies for vascular anomalies. *Circ Res*. 2021;129(1):155–173.
3. Wassef M, Borsik M, Cerceau P, et al. Classification des tumeurs et malformations vasculaires. Apport de la classification ISSVA 2014/2018 [Classification of vascular tumours and vascular malformations. Contribution of the ISSVA 2014/2018 classification]. *Ann Pathol*. 2021;41(1):58–70.
4. *ISSVA Classification of Vascular Anomalies ©2025 International Society for the Study of Vascular Anomalies*. Available at "issva.org/classification". Accessed March 22, 2025.
5. Loose DA. The hamburg classification. *Gefasschirurgie*. 2005;10(6):388–389.
6. Jakob R. Disease classification. In: Quah SR (editor). *International Encyclopedia of Public Health*. 2 Ed. Academic Press, 2017, p. 332-337.
7. Sokal RR. Classification: purposes, principles, progress, prospects. *Science*. 1974;185(4157):1115–1123.
8. Moolgavkar S, Knudson A. Mutation and cancer - a model for human carcinogenesis. *J Natl Cancer Inst*. 1981;66(6):1037–1052.
9. Jones K. *Smith's Recognizable Patterns of Human Malformation*. Fourth ed. Philadelphia: W. B. Saunders Company; 1988.
10. Couto J, Huang A, Konczyk DJ, et al. Somatic MAP2K1 mutations are associated with extracranial arteriovenous malformation. *Am J Hum Genet*. 2017;100(2):546–554.
11. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr*. 2015;166(4):1048–1054.
12. Sanchez-Carpintero I, Mihm MC, Mizeracki A, Waner M, North PE. Epithelial and mesenchymal hamartomatous changes in a mature port-wine stain: morphologic evidence for a multiple germ layer field defect. *J Am Acad Dermatol*. 2004;50(4):608–612.
13. Iacobas I, Adams DM, Pimpalwar S, et al. Multidisciplinary guidelines for initial evaluation of complicated lymphatic anomalies-expert opinion consensus. *Pediatr Blood Cancer*. 2020;67(1):e28036.
14. Ayturk UM, Couto JA, Hann S, et al. Somatic activating mutations in GNAQ and GNA11 are associated with congenital hemangioma. *Am J Hum Genet*. 2016;98(4):789–795.
15. Ivars M, Frieden IJ, Provini L, et al. Segmental congenital vascular anomaly with atrophy, ulceration, and scarring (SeCVAUS): case series and review of literature. *Pediatr Dermatol*. 2024;41(6):1063–1076.
16. El Sissy FN, Wassef M, Faucon B, et al. Somatic mutational landscape of extracranial arteriovenous malformations and phenotypic correlations. *J Eur Acad Dermatol Venereol*. 2022;36(6):905–912.