INTERNATIONAL ANGIOLOGY
EDIZIONI MINERVA MEDICA

ISVI-IUA Consensus Document - Diagnostic Guidelines on Vascular Anomalies: Vascular Malformations and Hemangiomas

B.B. Lee, P.L. Antignani, V. Baraldini, I. Baumgartner, P. Berlien, F. Blei, G.P. Carrafiello, R. Grantzow, A. Ianniello, J. Laredo, D. Loose, J.C. Lopez Gutierrez, J. Markovic, R. Mattassi, K. Parsi, E. Rabe, K. Roztocil, C. Shortell, M. Vaghi

Int Angiol 2014 May 22 [Epub ahead of print]

INTERNATIONAL ANGIOLOGY
Rivista di Angiologia

pISSN 0392-9590 - eISSN 1827-1839
Article type: Guidelines

The online version of this article is located at http://www.minervamedica.it

ISVI-IUA Consensus Document

Diagnostic Guidelines of Vascular Anomalies: Vascular Malformations and Hemangiomas

Lee BB, Antignani PL, Baraldini V, Baumgartner I, Berlien P, Blei F, Carrafiello GP, Grantzow R, Ianniello A, Laredo J, Loose D, Lopez Gutierrez JC, Markovic J, Mattassi R, Parsi K, Rabe E, Roztocil K, Shortell C, Vaghi M

Corresponding Author:
Byung-Boong (B.B.) Lee, M.D., PhD, F.A.C.S.
Professor of Surgery & Director, Center for Lymphedema and Vascular Malformation, George Washington University School of Medicine
Address: Division of Vascular Surgery, Department of Surgery, George Washington University Medical Center, 22nd and I Street, NW, 6th Floor, Washington, DC 20037, USA

Associate Professor of Radiology, Director of Research Centre in Interventional Radiology,
Chief of Interventional Radiology Unit
University of Insubria Varese, Italy

Rainer Grantzow, MD
Professor of Pediatric Surgery
Kinderchirurgische Klinik der Ludwig-Maximilians Universität, Munich, Germany

Andrea Ianniello, MD
Radiologist, Department of Radiology
Hospital G. Salvini, Garbagnate Milanese (Mi), Italy

James Laredo, MD, PhD, FACS
Associate Professor of Surgery, Division of Vascular Surgery, Department of Surgery
George Washington University School of Medicine, Washington DC, USA

Dirk A. Loose, MD
Professor and Chairman of the Department for Angiology and Vascular Surgery,
European Centre for the Diagnosis and Treatment of Vascular Malformations,
Die Facharztklinik Hamburg, Martinistr 78, Hamburg, Germany

Juan Carlos Lopez Gutierrez, MD
Director of the Vascular Anomalies Center, Department of Surgery
Hospital Infantil La Paz, Madrid, Spain

Jovan Markovic, MD
Vasular Surgery Fellow, Department of Surgery, Division of Vascular Surgery,
Duke University Medical Center, Durham, NC, USA

Raul Mattassi, MD
Professor of Vascular Surgery and Director, Center for Vascular Malformations "Stefan Belov", Clinical Institute Humanitas "Mater Domini", Castellanza (Varese), Italy

Kurosh Parsi, MBBS, MSc(Med), PhD, FACD, FACP
Professor and Head of Department of Dermatology, St. Vincent's Hospital, Sydney, Australia
Head, Dermatology, Phlebology and Fluid Mechanics Research Program, St. Vincent's Centre for Applied Medical Research, University of New South Wales, Sydney, Australia

Eberhard Rabe, MD
Professor of Dermatology, Phlebology and Dermatologic Angiology, Department of Dermatology,
University of Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany

Karel Roztocil, MD, PhD
Angiologist, Institute of Clinical and Experimental Medicine, Prague, Czech Republic

Cynthia Shortell, MD
Professor and Chief, Division of Vascular Surgery
Program Director, Vascular Residency, Vice Chair of Faculty Affairs, Department of Surgery
Duke University Medical Center, Durham, NC, USA

Massimo Vaghi, MD

Vascular Surgeon, Department of Vascular Surgery,
Hospital G. Salvini, Garbagnate Milanese, Italy

Abstract

The diagnostic approach to vascular anomalies should include the distinction between vascular tumors (i.e. hemangiomas) and congential vascular malformations (CVMs). This step is based more on history and clinical examination rather than on instrumental evaluation. In children Duplex ultrasound and histology can be helpful to separate hypervasularized tumors from CVMs.

Appropriate record of objective measures as size or flow volume is required in order to evaluate the progress of the pathology and/or to assess the results of adopted therapeutic interventions. The anatomic, pathological and hemodynamic characteristics, the secondary effects on the surrounding tissues and the systemic manifestations should be defined. Basic diagnostic tools are Duplex sonography followed by MRI or CT scanning.

The definition of the vascular anomaly should be according to the Hamburg classification and should separate vascular tumors from vacular malformations followed by separation of high flow from low flow CVMs. Diagnostic investigations are best undertaken at centers where subsequent therapeutic interventions will be performed.

Key Words: vascular anomalies, vascular tumors, vascular malformations, Hamburg classification, ISSVA classification, truncular and extratruncular lesions, hemangiomas of infancy, arterio-venous malformation, venous malformations, lymphatic malformations, Duplex ultrasonography, MRI, angiography, genetic testing

Prologue

Abnormal development of the vasculature during embryogenesis leads to more or less clinically apparent symptoms, which in some cases may be associated with anatomic deformities, severe life-threating conditions, a significant decrease in daily functional capacity and quality of life and can negatively affect patietn's emotional and social well-beeing. The management of these lesions is often complex and can be frustrating for patients, their families as well as for most vascular specialists. The relatively low incidence of vascular anomalies among general population combined with the fact that their management often falls within the purview of several different medical and surgical specialties has traditionaly resulted in insufficier expertise in the management of these conditions. Nevertheless, in recent years we observed an increased interest to improve the treatment of these patients with a truly multidisciplinary approach to this health problem. At this time, it is neccessary to acknowledge the outstanding activity of the group of experts who have gathered with the aim to share their experiences and to provide guidelines for the diagnosis of vascular anomalies.

One of the leading experts in this process is Professor B.B. Lee, the main author and coordinator of the Consensus. Professor B.B. Lee began his career as a founding member of the transplant and vascular surgery program at Georgetown University in Washington, DC and has made very important achievements in the development of transplant surgery in the USA and Korea. Simultaneously he has also made a tremendous contribution to the field of lymphedema and vascular malformations. His list of publications includes more than 600 items most of them dedicated to the topic of vascular malformations and lymphedema. In recognition of his contributions, in the USA he obtained the title Distinguished Fellow of the Society for Vascular Surgery.

I would also like to emphasize the contribution of Professor P.L. Antignani, a co-chair of the Consensus faculty. His professional career has been associated with a permanent interest in the non-invasive investigation of vascular diseases, which is reflected by his presidency of the Italian Society of Vascular Investigation.

There are multiple reasons why guidelines or consensual documents are created - to transfer new knowledge, to improve the quality of standard management, to reduce the possibility of inadequate care, and to reduce the costs of treatment. The impact of these documents may sometimes be limited if they are followed with insufficient adherence. However, I am convinced that this will not be the case with these newly prepared recommendations. Thanks to their scientific standard and usefullness in daily clinical practice, the recommendations provided in this Consensus will be welcomed and fully applicable.

Karel Roztocil
President of International Union of Angiology

Introduction

Vascular malformations and hemangiomas altogether as vascular anomalies remain one of the enigmas in modern medicine. Given the paucity of knowledge in this field, employing an appropriate diagnostic approach to vascular anomalies is a major challenge for most physicians. Furthermore, achieving a precise diagnosis of a vascular anomaly is a complex task requiring in-depth knowledge of embryology, pathophysiology and appropriate acknowledgement of the clinical, hemodynamic and morphologic features.

As a joint initiative, the International Union of Angiology (IUA) and the Italian Society for Vascular Investigation (ISVI) established an expert Panel under the auspices of the International Union of Phlebology (IUP) to formulate guidelines for physicians and vascular technicians/sonographers on the evaluation of vascular anomalies. The aim of these guidelines is to provide recommendations for the diagnosis of vascular anomalies based on the best currently available scientific evidence. When scientific evidence was lacking or weak, a consensus of opinions amongst expert members of the Panel was reached to support the recommendations.

The guidelines in this document are broad ranged and incorporate proven concepts, expert driven recommendations and new discoveries. In the last decade, progress in both diagnostic techniques and minimally invasive technologies in this difficult and challenging field has been significant. Imaging studies, radionuclide scans, duplex ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) technologies have largely improved.

Recommendations in this document are graded according to the available scientific evidence. The Panel adopted the system used by Guyatt et al[1, 2, 3] and the document has two grades of recommendations: Grade 1 (strong) recommendation, which is reserved for those investigations, where the benefits clearly outweigh the associated risks and Grade 2 (weak) recommendations, reserved for those diagnostic investigations where the benefits do not significantly outweigh the associated risks. The quality of evidence can be high (A), moderate (B), low or very low (C) (Appendix A).

It is the sincere hope of the Panel that these guidelines will serve their purpose: general guidelines based on scientific evidence to assist clinicians in the diagnosis of vascular anomalies. The Panel recognizes that some guidelines may be impractical in certain parts of the world with limited access to advanced technology or special expertise. To this end, the Panel has incorporated the most important advances in this field to

formulate the state-of-the-art and the best-practice guidelines based on the scientific evidence available in year 2014.

Definitions and Classification

Attempts at the diagnosis and classification of vascular anomalies have a long history starting with the indiscriminate use of eponyms and descriptive terms such as “port-wine stain”, “strawberry hemangioma”, “cherry angioma” and others.

With the rapid proliferation of descriptive terms and eponyms, the need to develop a meaningful classification of vascular anomalies became evident. Subsequently, two comprehensive classifications were introduced in the last 30 years. The first attempt was a milestone approach that differentiated vascular anomalies into vascular tumors and vascular malformations. This classification was introduced by John Mulliken et al. in 1982 [4] and formed the basis of the subsequent International Society for the Study of Vascular Anomalies (ISSVA) Classification.[5-7]

The second milestone was the development of the Hamburg classification in 1988 proposed by Dr.Stefan Belov who classified the vascular malformations based on the morphology of the lesions/vessels involved. This classification was soon modified to incorporate the newly discovered embryological findings.[8-10]

In the Hamburg classification, vascular malformations were further subclassified to 'extratruncular' and 'truncular' forms based on the embryological stage of the emergence of the pathology. The term 'extratruncular' was initially re-introduced to replace the popular misnomer 'angioma'. The use of the term ‘angioma’ when referring to vascular malformations created significant confusion as it implied a neoplastic pathology and lead itself to confusion with 'hemangioma' which represents a true vascular tumor with an entirely different nature.[11-13]

Clinically, extratruncular lesions are masses of abnormal small/mid-sized vessels infiltrating various tissues. These lesions result from the defective development during the earlier stages of embryogenesis while the vascular structure is still in the status of plexiform primordial network.[14-16] By contrast, truncular lesions originate from fetal vessel trunks and develop during the later stages of vascular trunk formation. Clinically, truncular malformations present as defects of fully formed and often named vessels.[17-19] (Table 1) Truncular lesions are predominantly hemodynamic disorders while extratruncular lesions are predominantly organic diseases with a great tendency to progress/recur due to their unique embryological characteristics originated from the mesenchymal cells/angioblasts.[20-22]

Table 1. Modified Hamburg Classification of Congenital Vascular Malformation (CVM)

Main classification based on its predominant vascular malformation component:

- Arterial malformation
- Venous malformation
- Arterio-Venous malformation
- Lymphatic malformation
- Capillary/ microvascular malformation
- Combined vascular malformation

* Original classification was based on the consensus on the CVM through the international workshop held in Hamburg, Germany, 1988, and subsequently modified based on the predominant lesion.

Subclassification based on its embryological stage of the defect:

— Extratruncular forms

- Infiltrating, diffuse
- Limited, localized

— Truncular forms

- Obstruction or Stenosis
  - Aplasia; Hypoplasia; Hyperplasia
  - Stenosis; Membrane; Congenital spur
- Dilatation
  - Localized (aneurysm)
  - Diffuse (ectasia)

* Represents the developmental arrest at the different stages of embryonic life: Earlier stage – Extratruncular form; Later stage – Truncular form.

*Both forms may exist together; may be combined with other various malformations (e.g. capillary, arterial, AV shunting, venous, hemolymphatic and/or lymphatic; and/or may exist with hemangioma).

This classification was in part adopted by ISSVA in 1996 in Rome with the maintenance of the subgroups according to the vessels involved. In the ISSVA classification system of vascular anomalies, hemangiomas are considered to be separate from the vascular malformations as true vascular tumors with an often benign nature and the additional differentiation into high flow and low flow malformations based on the hemodynamic flow characteristics. In this classification, some of the eponymic syndromes were maintained (Table 2).

The ongoing use of eponyms in this field is controversial. Undoubtedly descriptive terms can be misleading and not helpful in conveying the correct anatomico-pathological nature of vascular anomalies. Nevertheless, certain eponyms may be useful to highlight non-vascular complications of some conditions, for example, seizure in Sturge-Weber syndrome and kidney tumors in Von Hippel-Lindau and Maffucci syndromes.[23-25]

Table 2. ISSVA classification of CVM and Vascular Tumors

VASCULAR MALFORMATIONS:
— Fast-flow
    — Arterial malformation (AM)
    — Arteriovenous malformation (AVM)
    — Arteriovenous fistula (AVF)
— Slow-flow lesions:
    — Capillary malformation CM (port wine stain, telangiectasia, angiokeratoma)
    — Venous malformation (VM)
    — Lymphatic malformation (LM)
— Combined vascular malformation (CVM, CLM, CLVM, CAVM, CLAVM)

VASCULAR TUMORS:
— Infantile Hemangioma
— Congenital Hemangioma
— Other

The future of the knowledge in this field will be based on new genetic and proteinomic findings.[26-28] Genetic defects have been identified in hereditary hemorrhagic teleangiectasia (HHT), glomovenous malformations (GVM), cerebral cavernous malformations, some primary lymphedemas, some cutaneo-mucosal venous malformations (VMs), capillary malformations (CMs), arteriovenous malformations (AVMs) and PTEN (phosphatase and tensin homologue) related syndrome. [29-31]

Based on the previous consensus publications of the IUA on arterio-venous malformations and the IUP on venous malformations [6, 7, 20] the Panel decided to adopt the modified Hamburg Classification as basis for the diagnostic work up of vascular anomalies. This was based on the anatomical and embryological foundation of this classification and the firm belief that the differentiation of malformations into truncular an extratruncular provides the useful practical tool in the diagnosis and management of these conditions. [31-33]

An updated ISSVA classification which incorporates new genetic and histologic information, new diagnoses and syndromes, and takes into account truncular vs. non-truncular forms, was recently approved by the ISSVA and will be available for citation from the ISSVA website http://www.issva.org.[34]

Clinical Evaluation

Patients with vascular anomalies usually seek help because of pain, disfiguration and/or functional impairment. Patients of any age may be referred for evaluation and hence the physician and vascular technologist must be comfortable dealing with a diverse group of patients that may include the pediatric as well as the neonatal age groups. Age is considered a determinant factor in the clinical evaluation of vascular anomalies since the fetus, newborn, infant, child and adult can present with different signs and symptoms closely related to their lifetime period.

The diagnostic algorithm used in the evaluation of vascular anomalies should be based on an accurate clinical assessment, which includes a thorough history and a detailed physical examination. The most important aspect of history is whether the lesion was present at birth (vascular malformations) and the rate of growth (proportionate or disproportionate to the child's growth). An exception to this is the subtype of hemangiomas termed RICH (rapidly involuting congenital hemangioma) and NICH (non-involuting congenital hemangioma), both of which proliferate in utero. RICH may be highly vascular, occasionally

causing pre-and peri- natal high output states, and/or transient postnatal self-resolved thrombocytopenia.[36-38]

The physical examination should include careful assessment (inspection, palpation, auscultation) of the lesion(s) as well as the arterial, venous and the lymphatic systems. It should also include assessment of blood pressure and peripheral pulses on the affected side and the contralateral limb, making note of visible dilated vessels/varicosities, thrombophlebitis, skin temperature, edema, skin changes including pigmentation, induration or ulcerations and other changes attributed to chronic venous insufficiency (CVI).

Clinical examination of the involved limb should include assessment of the limb size, volume, symmetry, co-existing soft tissue or bony hypertrophy or atrophy.[6, 7, 39-41] Clinical progress should be documented by serial photography.

Hemangiomas vs. Congenital Vascular Malformations

The differentiation between hemangiomas and congenital vascular malformations (CVMs) is critical especially when dealing with pediatric cases. The two entities represent entirely different pathologies although grouped together under the common umbrella of *Vascular Anomalies*.[6, 42-44] CVMs are errors of morphogenesis and structural abnormalities while hemangiomas are vascular tumors. A precise understanding of this critical fact is essential in reaching an accurate diagnosis.

Clinical history can differentiate between most cases of tumors and CVMs although adequate or clear history is not always available.[45-47] In particular, the unique growth pattern of the mass lesion often allows the differentiation. Fundamental differences between hemangiomas and vascular malformations include the timing of their clinical appearance, their growth patterns, the biologic behavior or growth characteristics of their endothelial lining in the cell culture, the stromal cellular and extracellular matrix compositions and the response of the lesions to pharmaco-therapeutic agents.

Hemangioma of Infancy (HOI)
Hemangiomas of Infancy (HOI) are the most common forms of pediatric vascular tumors that have a distinct etiology, genetics, presentation, prognosis and treatment.[42, 43, 48] These lesions are proliferative vascular tumors that are typically NOT present at birth and appear later during infancy. [44, 49, 50] These tumors take on a distinctive course of self-limited growth characterized by a two-stage process of proliferation and regression. HOI grow rapidly and disproportionate to the child's growth, then undergo a plateau phase and finally undergo involution. The majority of HOI have undergone atrophy by the age of 10. HOI possibly stem from placental tissue. Histologically, these lesions stain positive for glucose transporter-1 (GLUT-1) during all stages of growth and involution.[36-38, 51]. HOI during the proliferative phase may be high-flow lesions that may appear as pulsatile masses with increased cutaneous warmth. These clinical signs may be absent or difficult to detect in subcutaneous lesions.

Hemangiomas of Infancy (HOI) vs. Congenital Hemangiomas
HOI should be differentiated from congenital hemangiomas, which form a small group of pediatric vascular tumors. Congenital hemangiomas are fully grown *in utero* and are present at birth and hence do not undergo post-natal proliferation like HOI. Histologically, congenital hemangiomas do not stain with GLUT-1.

Two sub-types of congenital hemangiomas are commonly encountered: Rapidly Involuting Congenital Hemangioma (RICH) and Non-involuting Congenital Hemangioma (NICH). RICH undergo spontaneous involution during the first year of life while NICH persist lifelong.[36-38]
Other (Vascular) Tumors

Infrequently, other tumors such as a Kaposiform Hemangioendothelioma (KHE), angiosarcoma or other tumors may need to be differentiated from a CVM.[52-54]

Congenital Vascular Malformations (CVM)

CVMs are structural abnormalities of the vascular system and NOT tumors. These lesions result from arrested development during various stages of embryogenesis. While HOI are not present at birth, CVMs are always present at birth.

By contrast to HOI, CVMs are always present at birth as inborn errors, even though they may not be apparent. These anomalies grow steadily commensurate with the child's systemic growth. HOI, by contrast, grow disproportionate to the child's growth. CVMs never regress spontaneously and remain present throughout the patient's life as embryologic tissue remnants with 'self-perpetuating' growth.

CVMs may involve any vessel type and can be broadly classified into:

- Arterio-venous Malformation (AVM)
- Venous Malformations (VM)
- Lymphatic Malformations (LM)
- Capillary Malformations (CM)

Arterio-venous Malformations (AVM)

AVMs are high flow structural anomalies that form anomalous interfacial communications between arterial and venous systems. A fully mature AVM may manifest as a warm, enlarged pulsating mass. The enlarged size is due to the increased size of the anomalous vessels as well as an associated soft tissue hypertrophy.[55-57] AVMs may be quite subtle in young children and the initial presenting sign may be pallor of the overlying skin due to a cutaneous 'steal'. Lesions in deeper tissues may not always be clinically recognizable. Hemorrhage can be a presenting sign of an occult AVM. AVMs in neonates may appear as a faint pink stain and may not be readily differentiated from a CM. [58-60]

The associated soft tissue and/or bony hypertrophy may result in the enlargement (in length and circumference) of the affected side. AVMs involving the limbs may present with bony and soft tissue hypertrophy of the affected limb (Parkes-Weber syndrome). The soft tissue hypertrophy involves the subcutaneous fat with a significant number of patients developing severe lymphedema. The muscle is usually hypertrophied, as opposed to VM or Klippel-Trenaunay Syndrome (KTS).[61,62] High-output cardiac failure may be caused by large AVMs involving the shoulders, chest, abdomen, liver, kidneys, pelvis or buttocks.[7, 57-60]

Venous Malformations (VM)

VMs are structural abnormalities of veins and venules. VMs are the most common developmental anomalies of the venous system. These defects are caused by developmental arrest of the venous system during various stages of embryogenesis.[63-65]

VMs can be classified into:

1) Extratruncular VM- lesions may be found in most tissues and may present as clumps of dilated veins or venous lesions.

2) Truncular VM- lesions can present as aplasia, hypoplasia, obstruction, dilation, duplication or aneurysms. A unique group of truncular VMs are the persistent embryonic veins such as the marginal vein of the thigh or the persistent embryonic sciatic vein. These vessels arise when fetal (truncal) vessels fail to undergo normal involution.

Lymphatic Malformations (LM)
Nomenclature of the LMs is still confusing and old terms such as lymphangiomatosis, lymphangiectasia or lymphatic dysplasia are widely used to describe various related entities. Currently, LMs are classified into two groups based on their clinical presentation and morphology:

3) Extratruncular LM- These lesions form cystic masses and typically infiltrate other tissues in a localized or generalized distribution. Such lesions may be macrocystic or microcystic or present as a combination of both forms.

4) Truncular LM- These involve structural abnormalities of the lymphatic trunks and present with lymphedema and thoracic duct disturbances.

When LM involve the skin and subcutaneous tissue only, the prognosis is uniformly good. When the lesions involve the upper airways, viscera or bone, the prognosis is generally poor with a significant mortality rate. [66-68]

Capillary Malformations (CM) [69-71]
CMs are the most common type of CVMs. Descriptive historical terminology referring to CMs has included 'port-wine stain' and 'nevus flammeus'.

As the congenital malformation of the superficial dermal blood vessels, CMs are present at birth and grow in size commensurate with the child. They remain present for life and have no tendency of involution. The clinical progression of CMs is variable and depends on the anatomical location of the lesion.

CMs may be found in association with other CVMs including VMs, AVMs and LMs. A significant number of dysmorphic syndromes have been associated with CMs.

The Panel recommends adequate Clinical History to be obtained and a thorough Physical Examination to be conducted prior to instrumental investigations. Clinical examination should guide the request for further studies. (GRADE 1B)

The genetic basis of an increasing number of vascular anomalies has been identified in recent times [72] (Appendix C and D). Here, we briefly review some of the key syndromic vascular anomalies.

Syndromic Hemangiomas[73-77] (Appendix C)

Approximately 30% of patients with facial segmental hemangiomas may have PHACES Syndrome (OMIM 606519) [**P**osterior fossa or other structural CNS lesions, Segmental **H**emangioma, **A**rterial anomalies, **C**ardiac anomalies, **E**ye anomalies, and **S**ternal or other midline deformities].[73, 74]

Evaluation includes: MRI +/- contrast of the brain, and MRA of the brain, neck and upper chest, ophthalmologic, cardiac and sternal anatomy assessment, and thyroid function tests. Symptomatic airway hemangiomas are seen in increased incidence in patients with "beard" distribution cutaneous hemangiomas (Segment 3).[75]

Segmental hemangiomas on the lower midline back may be associated with congenital renal, sacral, lower spine, or genitourinary anomalies, and should be evaluated radiologically. [76]

LUMBAR Syndrome (**L**ower body hemangioma and other cutaneous defects, **U**rogenital anomalies, **U**lceration, **M**yelopathy, **B**ony deformities, **A**norectal malformations, **A**rterial anomalies, and **R**enal

anomalies) and PELVIS syndrome (**P**erineal hemangioma, **E**xternal genitalia malformations, **L**ipomyelomeningocele, **V**esicorenal abnormalities, **I**mperforate anus, and **S**kin tag) designate a spectrum of clinical features which may be in patients with segmental perineal hemangiomas.[77]

Syndromic Vascular Malformations[28-31, 78-83] (Appendix C)

Syndromic Vascular Malformations include Klippel-Trenaunay (capillary-lymphatic-venous malformation with limb hypertrophy), Parkes-Weber Syndrome (similar to Klippel-Trenaunay with arteriovenous shunting), Sturge-Weber Syndrome (facial capillary malformation in trigeminal distribution, leptomeningeal angiomastosis, glaucoma, and seizures), Blue-Rubber-Bleb-Nevus Syndrome (BRBNS) (generalized small venous malformations), Proteus Syndrome (vascular malformations, truncal lipohypoplasia, scoliosis, cerebriform plantar surfaces, nevi, partial gigantism, and digital anomalies), Ollier Disease/Maffucci Syndrome (hemangioendothelioma, enchondromatosis), HHT (multifocal AVMs), Gorham's Syndrome (lymphangiomatosis with osteolysis), and several lymphatic anomaly/lymphedema syndromes.

PTEN-related vascular anomaly syndromes include Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome and have distinctive clinical and radiologic features. Patients with PTEN syndromes are at increased risk of malignancy (e.g. thyroid, breast, colon, brain, genitourinary), which can present earlier than typically seen in the general population.

Genetic mutations have been identified for many vascular malformation syndromes: familial mucosal VMs: (Tie2 mutation), AVMs with multifocal CMs (CM-AVM; RASA-1 gene), GVM (glomulin), HHT (endoglin, activin A receptor type II-like 1 gene - ACVRL1, SMAD4, one morphogenetic protein 9 BMP9), and Proteus Syndrome (AKT1), CLOVE Syndrome (**c**ongenital **l**ipomatous **o**vergrowth, **v**ascular malformation, **e**pidermal nevus, **s**coliosis), and multiple mutations associated with lymphedema syndromes (including VEGFR3/FLT4, FOXC2, SOX18). [78-80]

Mutations are either germline (in the case of familial vascular malformations, with variable penetrance in some cases) or somatic (e.g. post-zygotic mutations such as mosaic AKT-1 mutations in Proteus Syndrome, PIK3CA in CLOVES and GNAQ in Sturge-Weber Syndrome).[81-83]

Non-invasive Diagnostic Evaluation

Difficulties in the diagnosis are due to the need to have both excellent spatial and temporal resolution in the imaging of the anomalies. This should be tailored to the hemodynamic characteristics of the malformation which may range from the ultra high flow of truncular AVMs to the extreme stagnant flow in venous anomalies or absence of detectable flow in LMs.

Appropriate images of the anomalies should be obtained first with generally available imaging tools like ultrasound, CT scan and MRI.[84-86] Diagnostic algorithm for vascular anomalies should start with an ultrasound investigation first, followed by non-invasive MR or CT scans and finally invasive investigations like angiographies when indicated.[87-89] Additional investigations include nuclear medicine imaging such as radionuclide lymphoscintigraphy, whole body blood pool scintigraphy (WBBPS) and transarterial lung perfusion scintigraphy (TLPS).[90-92]

The Panel recommends the primary diagnostic approach to be based on non-invasive investigations. The basic investigation should include duplex ultrasound integrated with MR examination. (GRADE 1C)

Duplex Ultrasonography (DUS)

Ultrasound is the most essential instrumental examination for vascular anomalies. Ultrasound is widely available and its low cost and lack of radiation exposure makes this modality the primary tool for the study of vascular anomalies.[93-95]

However, ultrasound examination is a procedure that is operator dependent and hence adherence to standard protocols to achieve consistent outcomes is of crucial importance. A dedicated vascular laboratory with expertise in the diagnosis of vascular anomalies should be performing these studies. Sonographers should be trained specifically in this field and should appreciate the complexity and the range of conditions they may encounter.

Ultrasound is limited in defining the extent of lesions not located in the extremities and hence ultrasound assessment should be correlated with MRI findings. In case of deep intra-muscular lesions, MRI may help in locating the lesion on ultrasound.

Ultrasound investigations are also limited in presence of air (e.g. lungs) or when anomalies are located within bones. Bony anomalies may be studied using other imaging modalities such as CT or when located within the cranium using transcranial equipment.

Limitations in the hemodynamic evaluation of occlusive venous status by ultrasound can be compensated with intravascular pressure measurement and/or intravascular ultrasound (IVUS). However, IVUS or invasive pressure measurements are not commonly indicated and seldom recommended in routine cases.

In childhood the missing collaboration of patients can be a problem.

Duplex Ultrasound Examination Procedure

General Principles
All ultrasound findings should be interpreted in the context of the clinical presentation and in particular time of onset, family history and rate of progression. In all patients, the contralateral side should be investigated together to assess for possible occult malformations and to compare the morphology, to identify normal size and flow characteristics. In case of unilateral lesions, comparison with the contralateral side to identify normal size and structures should always be performed.

The ultrasound examination of the limbs should be made in the erect and supine positions and the difference in size of the vessels should be recorded.

CW-Doppler Localization
Initial assessment with CW-Doppler is recommended to localize the lesion, determine the basic flow characteristics and to guide the duplex examination.

Patient position
Most vascular anomalies should be investigated in both the supine and the erect/dependent position. Certain CVMs such as VMs and LMs may fill up in one and drain and clinically disappear in the other position. In the evaluation of the limbs, both limbs should be examined in supine/dependent and standing/elevation.

Probe Selection

A high frequency linear transducer is in general suitable to assess most superficial lesions, however the probe can be selected depending on the location and depth of the target lesion. Probe frequency in case of broadband transducers should be optimized to obtain the best image. When assessing facial lesions or anomalies in neonates and small children, a 'hockey-stick' probe may be selected. In case of superficial lesions, minimum pressure should be applied on the probe using a thick layer of ultrasound gel to prevent excessive compression on the lesion.

Key Procedure Outcomes
The ultrasound examination should aim to achieve the following four key procedural outcomes: [96-98]

1) Define the Lesion: diagnosis, classification and measurements

2) Localization and relationship with regional structures

3) Pre-operative mapping

4) Post-operative follow-up studies

1. Define the Lesion: Diagnosis, Classification and Measurements

Aims
To recognize the presence of a vascular anomaly and to differentiate between vascular tumor and malformation. In case of CVMs, the lesion should be classified as a high flow (AVM), low flow (VM) or no flow (LM) lesions. In case of vascular tumors and hemangiomas, the lesion should be classified as *proliferative* demonstrating high flow vs. *involuted*. The dimensions of the lesion and flow characteristics should be accurately documented. This information will be helpful to monitor the progression of the lesion and in the follow-up of the patients.

B-Mode
A thorough B-mode examination should be completed prior to Doppler examination. B-mode can provide a valuable initial description that can narrow down the diagnosis and is essential in differentiating between CVMs and HOI. While CVMs present as a collection of anomalous vessels or cystic spaces (LMs), HOI present as a soft tissue mass. Compressibility on B-mode can further differentiate VM (compressible) from thrombosed or sclerosed VM (non-compressible), LM (non-compressible cystic spaces) and AVMs (partially-compressible). B-mode will help in the evaluation of axial trunks and will determine patency, duplication, presence of valves in venous vessels and aplasia or hypoplasia of the whole vessel length or segments of the affected vessels. Additional information on the structure of the lesion may be echogenicity and separation from surrounding tissue which may be regular or irregular.[99, 100] B-mode examination will also help identify important adjacent structures such as nerve trunks.

Doppler Mode
Doppler assessment should determine whether there is flow within the lesion (active tumors, AVMs, VMs) or no flow (LMs, involuted tumors, thrombosed/sclerosed VMs). If there is flow within the lesion, whether it needs to be induced (VMs) or is spontaneous (active tumors and AVMs). If flow is spontaneous, whether it is a high velocity, low resistance pulsatile flow (AVMs).

Doppler examination should include both Color Doppler and Spectral analysis. For examination in the color mode, the pulse repetition frequency (PRF) should be adjusted to the flow velocity of the investigated vessel. In other words, PRF should be increased for arterial flow and reduced for low flow in VMs. Depending on the ultrasound system used, when assessing high flow malformations, the setting of the color

Doppler may have to be set on real time (no delay and overwriting by the software). Power Doppler is more sensitive than Color Doppler and can be used when detecting flow with low amplitude.

Spectral analysis should include both spontaneous and augmented blood flow and the derived data including the peak velocity and the Resistive Index (RI) in arterial vessels ([peak systolic velocity – end diastolic velocity] / peak systolic velocity) should be documented.

Reflux time in venous vessels should be incorporated in a complete venous incompetence mapping of the lower limb veins.

Diagnosis and Classification
At the conclusion of the B-mode and Doppler study the following information should be obtained:

- The lesion should be classified into a vascular tumor or a CVM or other (e.g. lipoma, hematoma, lymph node, etc.).
- If vascular tumor, the flow characteristics should be used to define whether the lesion is active or involuted.
- If a CVM, then the lesion should be sub-classified into an AVM vs. VM vs. LM.

Measurements
Dimensions of the lesion should be documented and adequate number of B-mode images demonstrating the basic morphology of the lesion should be obtained. Numerical data regarding size, flow and the hemodynamic characteristics of the lesion should be recorded to monitor the progression, the natural evolution and the success or failure of the interventions.[101, 102] In the evaluation of LMs, the size and number of lymphatic cysts should be documented. Adequate number of images should be obtained and stored for future reference.

2. Localization and Relationship with Regional Structures

Aims
To accurately document the relationship of the lesion with the regional blood vessels and the surrounding normal anatomical structures and landmarks. Normal blood vessels should be identified and the affected side should be compared with the contralateral side. Information obtained should be sufficient enough to guide further imaging strategies such as MR or CT.

Localization
Anatomical localization should be obtained relative to regional landmarks recognizable by clinical or ultrasound examination (e.g. intramuscular infiltration).

Relationship with Regional Structures
Regional vascular structures including arterial, venous and lymphatic trunks should be identified and the relationship with the anomaly assessed. All ‘normal’ regional vascular structures should be clearly identified and delineated from the anomaly. This can be achieved by comparing the affected side with the contralateral side looking for differences in size and flow patterns. The architecture in connection with in- and out- flow vessels should be studied and afferent arterial ‘feeders’, efferent ‘draining’ veins and presence of a nidus should be documented.[103, 104]

Flow characteristics in the involved vessels in relationship with major regional vascular trunks should be assessed. The flow pattern in presumably ‘normal’ vessels should be assessed and any findings to suggest AV shunting should be looked for, localized and documented. In case of mixed truncular and extra-truncular lesions (such as those seen in certain VMs), involvement of presumably ‘normal’ vessels should be assessed. In case of VMs involving the lower limbs, a complete venous incompetence study of

lower limb venous system and mapping of the pathway of reflux should be obtained. In this phase, persistent embryological vessels such as a persistent sciatic artery/vein or a persistent marginal vein should be looked for.

Other regional structures should be clearly identified and labeled in images obtained. In particular, in case of intra-muscular CVMs, the muscles involved should be identified and adequate images obtained. Regional nerves, fascia and tendons should be identified. For lesions involving the sole of the feet, the relationship to plantar fascia and tendons should be defined.

Based on ultrasound findings, further investigations such as MRI should be arranged to complete the diagnostic evaluation and to prepare an appropriate management strategy and therapeutic intervention.

3. Pre-operative Mapping

Aims
To define the anatomical location of the lesion in relation to surrounding structures, defining communication with the normal vascular system including any feeding arteries or draining veins and proximity to important nearby structures such as nerves, normal vessels and vital organs in order to guide a surgical or percutaneous approach to the malformation..

Assessment
This investigation is best performed directly prior to the intervention. Prior ultrasound findings, MRI images other investigations and clinical photographs should be reviewed and ideally displayed at the time of the procedure. Any changes (e.g. a new thrombus or occlusion) compared with the prior assessments should be identified and noted.

All target lesion(s) should be identified. It may be useful to add CW-Doppler examination to localize deep seated lesions or Type IIIa AVMs[7] prior to percutaneous sclerotherapy or embolization. Some practitioners utuilze color Doppler with intraoperative hockey-stick head for the same indication. Sonographic assessment should be complemented by skin markings to guide punctures and to plan the optimal approach. Significant near-by structures should be identified and marked on skin. Nerve trunks should be visualized prior to intervention as nerve damage is one of the most serious complications of endovascular or surgical procedures employed to treat CVMs. Nerve damage may be caused by compression secondary to edema/compartment syndrome or direct toxic effect of sclerosing or embolic agents (in particular ethanol).

4. Post-operative Follow-up Studies

Appropriate follow-up ultrasound examination is essential in monitoring complications, success or failure of intervention. Post-operative follow-up studies need to be targeted and timed appropriately depending on the aim of the examination.

Post-operative ultrasound examinations to look for complications such as deep vein thrombosis (DVT) should be done within 7 days of the procedure; otherwise an important silent DVT with potential for embolism may be missed.

Post-operative studies to assess the success of the procedure can be done in two stages: an early follow-up typically within 6 weeks will provide an initial assessment of the treatment outcome and will provide an opportunity for the physician to deal with any concerns the patients may present with. A long-term follow-up typically conducted at one year will provide a meaningful long-term assessment of the treatment outcome.

Ultrasound examinations should follow the same protocol as for the initial assessment, measurements obtained and flow characteristics assessed and any change to the pre-operative values reported. This should include: B-mode images of lesion, measurements of the size and flow, transverse dual image of the lesion to assess for compressibility, color Doppler images of the lesion and sample spectral traces in associated vessels and nidus.

Evaluation of Surgical Treatment of Truncular Anomalies
This assessment should document the residual malformation hemodynamic impairment. Specific anomalies defined in the pre-operative assessment should be followed and reported in the post-operative examination. Restoration of competence or new patterns of reflux should be documented in case of truncular VMs. In case of truncular AV shunts parameters derived from the Doppler curve should be compared with those acquired before the treatment.

Evaluation of Endovascular Interventions
Evaluation of the results of endovascular therapy is more complicated and should follow a set protocol. When assessing treatment success, compressibility of a previously treated (sclerosed/embolized) lesion may not be a reliable marker of success. Sclerosing agents typically induce vessel wall fibrosis despite the presence of a patent lumen. Such non-compressibility is not indicative of complete vessel occlusion and endovascular fibrosis. Color Doppler should be utilized to assess residual flow in otherwise non-compressible lesions.

Hemodynamic consequences and residual venous abnormalities (abnormal Doppler signal, residual marginal vein, residual obstruction or dilatation) should be documented. Reduction of flow or new flow patterns should be documented and appropriately mapped. The effect on the size of the malformations depends on the biological interaction between the embolic agents, vessel wall and blood. This interaction is minimal with mechanical devices and maximal with ethanol and may cause organ enlargements which can last for weeks.

Venous Malformation (VM) - Ultrasound Key Points

General Description[105-107]
VMs are congenital anomalies of the venous system. These malformations may be classified as truncular or extra-truncular. VMs may be found in association with other CVMs such as LMs, CMs and AVMs or part of a generalized syndrome such as KTS.

Truncular malformations may present as agenesis, aplasia, hypoplasia, obstruction, duplication, dilatation, aneurysm or valvular agenesis of mature vessels. A vein may be defined ‘hypoplastic’ when its diameter is smaller than the corresponding artery in the standing position. Extra-truncular VMs present as phlebectatic lesions that infiltrate other tissues.

Ultrasound Evaluation
Ultrasound assessment of VMs should achieve the following key procedural outcomes:

1. Diagnosis, Classification and Measurements

Diagnosis of the anomaly as a VM and sub-classification to truncular vs. extra-truncular. Possible associated CVMs including AVMs or LMs should be identified and documented. Lesion size (depth, length and width) should be documented.

In the evaluation of extra-truncular VMs, B-mode examination is very important to define the size and to localize the lesion. Compressibility to determine patency or incompressibility due to thrombus or a previous treatment should be assessed.

In the evaluation of truncular VMs, aplastic, hypoplastic, obstructed, duplicated, dilated or aneurysmal segments have to be identified and incorporated in a venous incompetence map. Presence, size and competence of valves should be documented. Likewise, a marginal vein can be detected by ultrasonic investigation.

2. Localization and Relationship to Regional Structures
The site of VM and the tissue plane involved (dermal, subcutaneous, intra-muscular, infiltrative, etc.) should be clearly identified. Near-by normal structures such as tendons, nerves and normal vasculature including arteries and veins should be identified.

3. Pre-operative Venous Mapping
Given the intimate relationship of VMs with the normal venous system, a complete venous mapping of both superficial and deep venous systems is required in the evaluation of extremity VMs. Anatomical distribution of the pathological vessels should be incorporated in the broader venous incompetence mapping of the venous system. Site and pathway of reflux should be determined. Relationship with the normal venous structures should be defined. Patency and competence of the deep venous system including variations in diameter compared to the contralateral side should be documented.

4. Post-operative Assessment
Extra-truncular lesions can be treated with sclerotherapy. Successfully treated lesions demonstrate hyperechoic walls and no flow on augmentation. Flow may be difficult to induce and the lesion may not be fully compressible due to vessel wall induration that occurs following sclerotherapy. An anechoic or hypoechoic lumen would suggest patency of the vessel lumen and may indicate the need for further intervention. Treatment should be deemed successful only when the lesion is non-compressible, appears uniformly hyperechoic on B-mode and shows no flow on Doppler examination.

Post-operative assessment of truncular malformations depends on the initial pathology and the initial aims of the surgical procedure. Post-operative venous incompetence studies should be compared with pre-operative evaluations to determine any new pathways of reflux (see below).

Infiltrating Extra-truncular Lesions
On B-mode ultrasound, VMs typically present as compressible vascular spaces unless thrombosed or previously sclerosed. Lesions found in the subcutaneous or intra-muscular tissues present as hypoechoic compressible vascular spaces. Spectral and Power Doppler may demonstrate flow on augmentation. Thrombosed or previously sclerosed lesions appear partially- or non-compressible but may still demonstrate flow on Doppler examination. These features allow for differentiation of VMs from LMs that appear as non-compressible cystic spaces or AVMs that demonstrate high flow. Ultrasound assessment should be correlated with MRI findings. In case of deep intra-muscular lesions, MRI may need to be obtained first to aid in locating the lesion on ultrasound.

Truncular Malformations - Contribution to Chronic Venous Insufficiency
Truncular malformations may contribute to CVI due to incompetence or obstruction/aplasia of the affected vessels. Presence of occluded segments (webs, hypoplasia) would result in hemodynamic impacts on their

relevant venous systems depending on the location, extent/severity, and natural compensation through collaterals. CVI develops in the territory drained by such truncular vein. Stenosing truncular lesions produce venous obstruction leading to a reduction in venous drainage. In such cases, a detailed venous incompetence map demonstrating the pathway of reflux in both deep and superficial venous systems needs to be obtained.[108, 109]

Truncular malformations - Venous aneurysms
Jugular vein aneurysm of primary/congenital origin is a rare truncular anomaly and should be differentiated from a false aneurysm for example after a complication of neck abscesses. In 10% of cases, jugular vein aneurysms are bilateral. Only seldom they have a tendency to thrombose but are indicated for intervention when they cause compression of neighboring structures or cause cosmetic concerns.[110-112]

Popliteal vein aneurysms are relatively more frequent and usually detected after an episode of pulmonary embolism. These aneurysms may present alone or together with other VMs. These anomalies may be fusiform or saccular. The minimum size of a popliteal vessel to define an aneurysm is controversial. As proposed by Maleti[113], an aneurysm may be defined when the vessel size has reached three times the size of a normal vein. A diameter greater than 2 cm should be considered pathological. B-mode ultrasound allows the visualization of the aneurysm and provides size, extension and presence of complete or partial thrombosis.[114-116] Unlike jugular venous aneurysm they have a tendency to cause venous thrombosis and consequently increase the risk for pulmonary embolism.

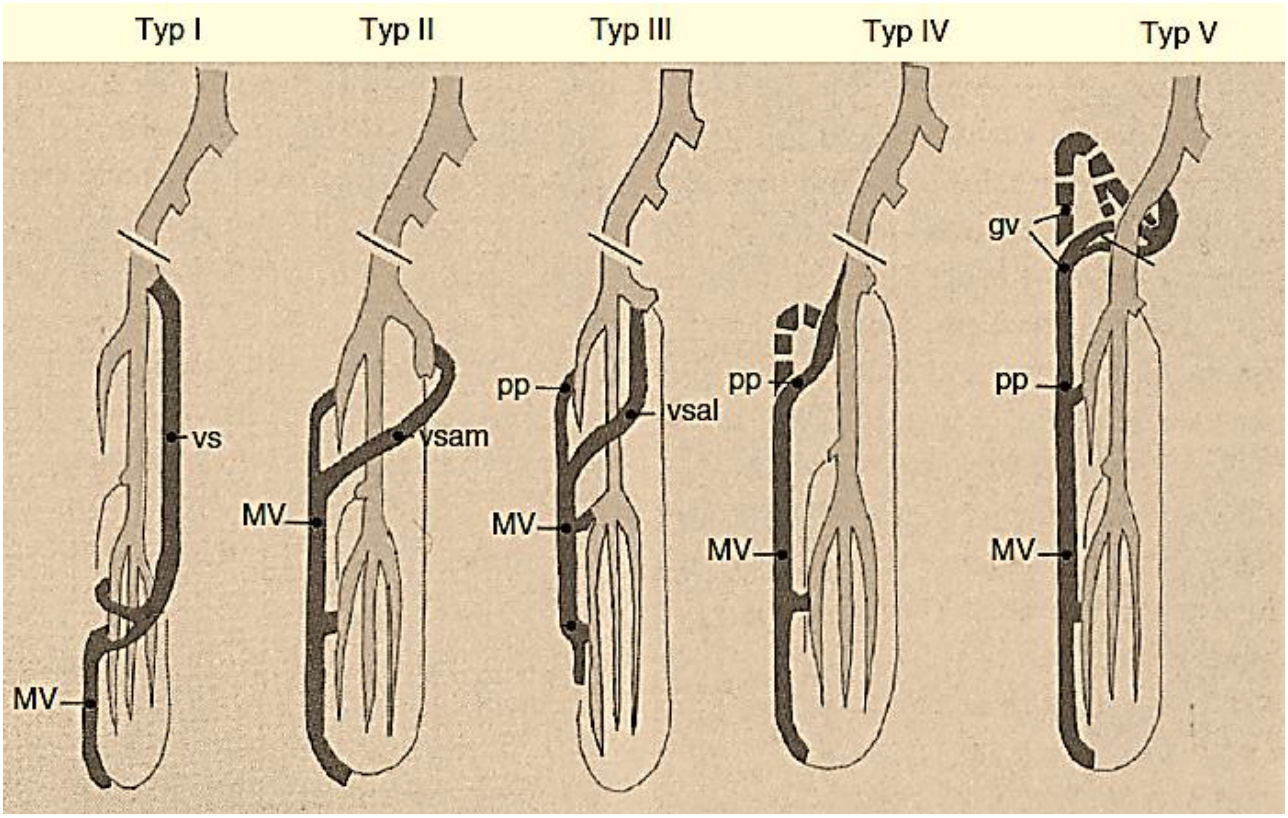
Ultrasound is also useful in the assessment of extracranial cerebral venous outflow.[117-119] In addition to evaluation of aneurysms, stenosis, intraluminal obstructions and valve malformations of the jugular veins at the cervical level can be identified.[120-122]

Truncular malformations – The Marginal Vein
A frequent VM of the lower limbs is the persistence of the marginal vein which is an embryonic vessel which normally involutes and disappears before birth. Marginal vein is also known as lateral embryonic vein which includes sciatic vein as well. The persistence of the marginal vein may exist alone or may be associated with other anomalies of the deep venous system (e.g. hypoplastic femoral vein, absence/agenesis of the femoral vein): in this situation the therapeutic options are absolutely different[123] from those of the free standing marginal vein.[124-126] This malformation may also appear alone or together with CMs and/or changes in soft tissues and bones.

Therefore, the diagnostic evaluation of marginal vein should be extended first to a thorough assessment of the deep venous system since the existence or absence of the deep vein is a most important fact concerning the therapeutic consequences. If a marginal vein is found with the absence of the deep vein, its management is totally different.

Hence, the first step should start with basic investigation of this anomaly including a detailed assessment of the deep veins and their hemodynamics in order to evaluate the risk to remove the vein itself. Because, when the deep venous system is structurally in hypoplastic condition, the blood flow might be re-routed from the deep system through these superficial vessels as natural compensatory mechanism.[127, 128] The second step is to classify the marginal vein in four different types to drain into the normal/deep venous system according to the Weber classification as a road map for subsequent therapeutic strategy (Figure 1).[129] The third and final step is the pre-intervention mapping which should include the most dilated perforators.

Figure 1. Classification of the marginal vein according to Weber*



MV, marginal vein; vs, great saphenous vein; vsam, medial accessory saphenous vein; pp, perforans vein to deep femoral (profunda femoris) vein; vsal, lateral accessory saphenous vein; gv, gluteal veins

*Weber J. Invasive Diagnostik angeborene Gefaessehler (Invasive diagnostic of CVM). In: Loose DA, Weber J, eds. Angeborene Gefaessmissbildungen. Luenburg : Verlag Nordlandddruck Gmbh, 1997;127–63

Truncular malformations – The Sciatic Vein

A persistent sciatic vein is another abnormal/embryonic vessel remnant like marginal vein that should also disappear before birth but has failed to involute. Unlike the marginal vein, this vein is located deep in the thigh and has a course parallel to the sciatic nerve ending at the gluteal veins although incomplete form/ending can result in multiple channels. Sciatic vein may be connected with the popliteal vein or directly with the gemellar veins causing the reflux into the calf muscle veins with various symptoms mimicking sciat pain. However, discomfort requiring treatment is rare.[130-132]

Sciatic vein infrequently exists with the marginal vein together as well as the deep vein aplasia/ hypoplasia so that the increasing risk/probability of all three conditions of marginal vein, sciatic vein, and deep veins aplasia/hypoplasia combined cannot be overemphasized. The diagnostic assessment should be extended to an investigation to exclude/confirm not only the presence of sciatic vein but also marginal vein and deep vein aplasia/hypoplasia, as well.

Lymphatic Malformations (LM) - Ultrasound Key Points

General Description[133-135]

LMs are anomalies of the lymphatic trunks and collectors. LMs may be classified into two categories of truncular malformations and extra-truncular lesions. LMs may exist alone or together with CMs, VMs, and AVMs or part of a generalized syndrome such as KTS.

Truncular LMs are caused by agenesis, aplasia, hypoplasia or hyperplasia/dilatation of the lymphatic vessels and clinically present as primary lymphedema. Extratruncular lesions present as macrocystic or microcystic lesions. Macrocystic lesions are defined as having a dimension greater than 2 cm while microcystic lesions are defined to have a dimension less than 2 cm. A key characteristic of LM is fluid overload to soft tissues: lymphedema in truncular lesions and tissue displacement by infiltrating cystic lesion in extratruncular LMs.[136-138]

Severe forms of LM have to be assessed carefully in order to exclude associated anomalies including bony involvement, presence of spindle cells, development of thrombocytopenia (suggestive of kaposiform lymphangiomatosis) and various syndromes with a significant lymphatic component: Hennekam Syndrome**,** Aagenaes Syndrome (cholestasis-lymphedema syndrome), Lymphedema-dystichiasis syndrome, CLAPO, ODELAID, or Turner Syndrome. (Appendix C & Appendix D)

Ultrasound assessment remains the main diagnostic tool in the assessment of LMs. Ultrasound evaluation should be complemented by lymphoscintigraphy which represents the gold standard in the study of the dynamics of lymphatic circulation in truncular lymphatic malformations. Data obtained by ultrasonography are comparable with the data obtained by MRI. Recent advances in radiological lymphodynamic studies can soon improve our understanding of aberrant lymphatic flows, as well as their evolution and outcome. However, the genetic research to investigate on the aggressive behavior of certain lesions is still underway.

Ultrasound Evaluation
Ultrasound assessment of LMs should achieve the following key procedural outcomes:

1. Diagnosis, Classification and Measurements.
Diagnosis of the anomaly as a LM and sub-classification to truncular vs. extra-truncular. Possible associated CVMs including VMs, CMs and AVMs should be identified and documented. Lesion size (depth, length and width) should be documented.

In the evaluation of extra-truncular LMs, B-mode ultrasound investigation may reveal the presence of anechoic/hypoechoic cysts. Doppler examination will reveal cavities containing fluid but without spontaneous flow. Augmentation and distal compression may cause turbulence in some larger cysts but no directional flow will be induced such as that seen in veins or extra-truncular VMs. Patients may need to be examined in both the sitting and supine position to assess variations in size especially when examining neck lesions. Microcystic lesions generate multiple interfaces and may present as a uniformly diffuse hyperechoic tissue.[139-141] In the evaluation of truncular LMs, assessment should include evaluation of skin, subcutaneous tissue and the associated lymphedema.

Ultrasound evaluation should include morphological assessment of cysts including presence of septae within the cystic cavity, measurement of cystic dimensions and the number of macrocysts. In extensive malformations where large surface areas are affected, it may not be practical to count and measure all lesions.

2. Localization and Relationship with Regional Structures
The site of LM and the tissue plane involved (dermal, subcutaneous, intra-muscular, infiltrative, etc.) should be clearly identified. Ultrasound anatomy of normal skin and deeper layers is generally characterized by the first superficial hyperechogenic layer (the epidermis), the second low-echogenicity layer of "papillary" dermis and hyperechogenicity layer of the deeper reticular dermis, and the third layer of mixed-echogenicity of the subcutaneous layer, which is characterized by connective bands and nodule-like (adipose component) images.

Near-by structures such as tendons, nerves, normal vasculature including arteries and veins and presumably 'normal' lymphatic trunks should be identified.

3. Pre-operative Assessment
Anatomical distribution of the cystic lesions, infiltration in other tissues such as inter-muscular spaces and subcutaneous fat and proximity to vital organs and structures such as airways and major vessels should be determined. Variations compared to the contralateral side should be documented. Pre-operative marking should determine the best pathway of approach for puncture to avoid inadvertent injury to other near-by structures. This is especially important when treating neck lesions.

4. Post-operative Assessment
Extra-truncular lesions can be treated with embolization using agents such as Doxycycline, OK-432 or ethanol. Successfully treated cysts should no longer be visible on ultrasound. Pre-operative images and documentation of the location of the cysts is crucial in guiding the post-operative assessment.

LMs Involving the Neck
Macrocystic lesions predominately localize to the neck and can cause compression of the airways particularly at birth. In these cases, a pre-natal morphological ultrasound can plan an exit procedure for birth.[142, 143] Communication with the thoracic duct or the right lymphatic duct and proximity to major neck vessels should be identified.

Truncular LMs and Lymphedema
In truncular malformations, a high frequency probe > 7.5 MHz can visualize the dermis, the subcutaneous tissue, the presence of dilated lymphatics known as lymphatic lakes and the subfascial space. Flow in these lymphatic vessels cannot be visualized. It is also important to evaluate the echogenicity of the subcutaneous tissue in order to establish the grade of fibrosis.

The evolution and treatment outcomes may be confirmed by the measurement of skin thickness. Skin elasticity may be assessed by compressing the tissue with the transducer to assess the progression of lymphedema. The ultrasound evaluation of subcutaneous tissue thickness is a useful parameter to evaluate lymphedema and its response to treatment. The suprafascial and the subfascial thickness of the edematous tissue is demonstrable through high resolution echography (and/or CT scan) and tissue compressibility.[144, 145] These are useful measurements that allow periodic assessment of the response to therapy and are useful in monitoring a patient's progress and determining prognosis.[39, 40]

In patients with lymphedema, thickening of the cutaneous, epifascial, and subfascial compartments has been sonographically observed. This contrasts with MRI observations, where the subfascial compartment was shown to be unaffected.[146] High frequency ultrasound (20 MHz) reveals characteristic patterns of cutaneous fluid localization in various types of edema.[39, 40] In lymphedema, there is a distinctively uniform pattern of distribution. Ultrasound imaging has applications both in differential diagnosis and in therapeutic monitoring, although further refinement may become necessary to better characterize the spectrum of subcutaneous fibrosis that can be encountered in lymphedematous skin.[7, 141, 147]

Arterio-venous malformations (AVM) - Ultrasound Key Points

General Description
AVMs are congenital anomalies of the arterial and venous systems. These malformations may be classified as truncular or extra-truncular. AVMs may be found in association with other CVMs such as VMs, LMs and CMs and can be part of a generalized syndrome such as the Parkes-Weber syndrome.

Extra-truncular AVMs present as anomalous communications between the arterial and venous systems. Truncular arterial malformations are discussed below under 'Arterial Malformations'.

Ultrasound Evaluation
Duplex ultrasound remains the first choice investigation amongst various non-invasive modalities in the initi clinical assessment and subsequent follow-up of AVMs. Ultrasound assessment of AVMs should achieve the following key procedural outcomes:

1. Diagnosis, Classification and Measurements
Diagnosis of the anomaly as an AVM and sub-classification based on Do' criteria (see angiography below). Possible associated CVMs including VMs or LMs should be identified and documented. Lesion size (depth, length and width) should be documented. Presence or absence of nidus should be documented.

On B-mode examination, AVMs may present with a honeycomb appearance of multiple non-compressible vascular spaces. The surrounding soft tissue may appear hyperechoic. AV fistulas present with a single afferent artery and draining vein.

Spectral, color and power Doppler are very helpful to further define the flow characteristics in the afferent feeding arteries, within the nidus and in the efferent draining veins. Aliasing is a typical Doppler feature noticed within the nidus and represents turbulent flow.[7] Ultrasonography of AVMs is characterized by multidirectional (high-flow Doppler signal with low-resistance arterial waveforms) blood flow, high amplitude arterial waveform with spectral broadening and arterialized venous outflow.[101, 148] This is in contrast to VMs which demonstrate monophasic, biphasic or no detectable flow in 78%, 6% and 16% of cases, respectively.[149]

Do's classification of AVM is based on the nature of afferent (single or multiple arteries or arterioles) and efferent vessels (single or multiple veins or venules) and the presence or absence of a nidus (see below). Although angiography is the best way to sub-classify AVMs, in superficial lesions, ultrasound can achieve a similarly accurate diagnosis.

Ultrasound examination can readily differentiate an AVM from a VM or LM. VMs (when not thrombosed or sclerosed) are compressible while AVMs (and LMs) are non-compressible. On Doppler examination, AVMs present with a pulsatile, high volume, low resistance flow.[7] By contrast, LMs have no flow while augmentation is required to induce flow in VMs.

In most cases, ultrasound can also differentiate a vascular tumor from an AVM from. Vascular tumors are relatively homogeneous soft tissue masses. Active tumors are highly vascular and contain pulsatile blood flow and varying low flow draining veins. By contrast, AVMs are formed of multiple vascular channels with a honeycomb appearance and monophasic high flow characteristics in afferent feeding arteries.[7]

The differentiation from vascular tumors may not be straightforward in children and a RICH or NICH may be confused with an AVM. In adults, NICH can still be confused with an AVM. Such cases will require histological assessment to make a diagnosis.

Measurements should include measurement of the diameter of the vessels involved in comparison with the contralateral side.

2. Localization and Relationship with Regional Structures
The site of the AVM and the tissue plane involved should be clearly identified. The origin of the afferent vessels in the normal arterial system and the drainage into the normal venous system should be mapped.

The extent of the arterialized flow within the venous system should be identified. Associated tissue hypertrophy or atrophy and in particular hypertrophy of the subcutaneous fat should be documented and reported on. Near-by normal structures such as muscles and nerves should be identified.

3. Pre-operative Assessment
AVMs originate from feeding afferent arterial vessels and efferent draining veins. Given this communication with the normal vascular system, a pre-operative map is required to demonstrate the anatomical position of the anomaly and to map the flow from the arterial system into the venous system. Such ultrasound derived map should be supported and complemented by MR angiographic information. The anatomical distribution of the pathological vessels should be incorporated in the broader arterial and venous mapping of the extremity or the region.

An important pre-operative consideration in the management of AVMs is to select the most suitable catheterization approach. The approach in general may be trans-arterial, trans-venous or trans-cutaneous. Ultrasound can play an important role in the selection process and puncture and catheterization is ultrasound guided. The pre-operative marking should identify the location of the nidus and the direction and location of the afferent and efferent vessels.

4. Post-operative Assessment
AVMs are typically treated with embolization which may be complemented by surgical resection or sclerotherapy of the embolized lesion. The outcome depends on the type of embolic agent used. Ethanol will cause distortion of the tissue and scar formation that will appear hyperechoic on ultrasound. The most important parameter is flow which should be reduced or completely interrupted following the intervention.

Arterial malformations - Ultrasound Key Points

Sciatic artery - truncular lesions
The persistent sciatic artery is an artery which runs parallel to the sciatic nerve and involutes before birth. This artery often degenerates to an aneurysmal dilatation and remains (because of the defective vessel wall structure) as an embryonic vessel remnant.

There are two variants for this malformation. First, the sciatic artery coexists with normal iliac-femoral arteries. Second, it may be accompanied and compensates for an aplasia of the iliac-femoral arteries. This lesion can easily be identified by ultrasound investigation. The symptomatology is related to the compression of the sciatic nerve, distal embolization and acute ischemia secondary to the thrombosis of the aneurysmal sac.[150-154] Therefore, proper investigation should also include the appraisal of these findings.

Visceral Vascular Malformations
This unique anomaly can develop at any splanchnic vascular bed mostly as a truncular malformation. Amongst them, the splenic artery and renal artery aneurysms are well known.

Therefore, the alertness on various lesions as described below is mandated for the ultrasonographic evaluation of the abdomen whenever indicated with suspicion.

Visceral arterial aneurysm - truncular malformation
Arterial aneurysms involving the visceral organs in young patients are usually secondary to congenital defects of the arterial wall. They are usually asymptomatic until rupture and may be easily detected incidentally during routine ultrasound abdominal examination.

Renal vascular malformations

The ultrasound investigation allows detection and measurement of the size of the vessels involved. Doppler will assess the blood flow direction and velocity.[155-157]

Renal AVMs are uncommon.[158] Renal AVMs are classified according to their location as central or peripheral (for the renal hilum) or intra-parenchymal. On B-mode ultrasound, hypoechoic cysts or tubular structures are evident.[159] With the use of color Doppler and pulsated Doppler high flow vessels are evident. The pulsating flow is also evident in the efferent vein. Small AVMs near the hilum might be difficul to visualize as they may be hidden by normal vessels.[160]

Hepatic vascular malformations and vascular tumors

Due to the complexity of vascular structure, the liver is frequently involved by hemangioma as well as vascular malformations, mostly VMs. These lesions may cause important changes of the metabolism resulting in complete liver failure. Therefore, this unique hepatic lesion warrants appropriate knowledge to distinguish hemangiomas from various vascular malformations, especially on their dynamic course with times.

The most important differentiating factor in the evaluation of hepatic vascular anomalies is the age of the patient. The most common involvement in children is a HOI which remains the most common benign liver tumor in pediatric population. VMs, often mistakenly called “hemangiomas”, are most common in adults.[45, 47]

Recently, pediatric liver vascular tumors were reclassified based on the GLUT-1 expression to replace the old confusing term of hepatic infantile hemangioendothelioma. GLUT-1 positive expression is usually demonstrated in multifocal, and diffuse hepatic infantile hemangioma, which shares clinical and morphological features with cutaneous HOI. Multiple cutaneous and hepatic hemangiomas are also involved in 'diffuse neonatal hemangiomatosis'. Since the prognosis of hepatic hemangiomas has become much favorable with propranolol, proper evaluation with the ultrasonography is further mandated for proper management.[161-164]

GLUT-1 negative vascular liver tumors occur in neonates with unique clinical, imaging and pathological features. They differ from diffuse hemangiomas in terms of earlier presentation as solitary masses with central necrosis, rapid involution and pathologic features showing a notable, often prolific, lymphatic component. Following the parallelism with cutaneous anomalies, the term hepatic congenital hemangioma has been suggested comparing their behavior with RICH described in skin and subcutaneous locations. The natural history for focal liver hemangiomas is spontaneous regression in the first year of life. However, shunts embolization or complete surgical excision is required only in case of serious cardiac failure.

VMs are the most common hepatic vascular anomalies in the adult population. Liver hemangiomas do not exist by definition after puberty, and the diagnosis of epithelioid hemangioendothelioma has to be considered in the adult patient with a hepatic vascular tumor.

Blebs, spurs, webs and membranes due to a truncular anomaly may be found in the vena cava at the confluence site of the hepatic veins. These cause inadequate outflow of the hepatic veins resulting in hepatic vein outlet obstruction, known as primary Budd-Chiari syndrome.[165-167]

In HHT (Osler-Rendu-Weber disease), AVM/AV fistula is known as the most common finding among various CVMs. In this case, high velocity profile in the hepatic artery with a pulsatile flow in the portal branch is detected with an inversion of the flow direction. Portal hypertension secondary to splenic AVM lesion can be detected. Porto-systemic shunts, intra- or extra- hepatic, may be detected by color Doppler examination and the shunt fraction may be measured.[168-170]

The Panel recommends (Duplex) Ultrasound examinations as the basic non-invasive test to define the hemodynamic and anatomic features of the malformation. The examination has to be complete and in case of limb involvement both limbs should be investigated. The examination should be performed in orthostatism and clinostatism. (GRADE 1B)

Hemangioma of Infancy (HOI)

The diagnosis of HOI is usually clinical but ultrasound is required to make the precise organ assignment and the precise classification of the stage which is obligatory for the indication if this hemangioma needs a treatment or is a candidate for spontaneous regression, which is the majority.

HOI in the early phase (stage 1 and 2) are characterized by the presence of a highly vascular soft tissue mass demonstrating high velocity flow patterns during the proliferated phase followed by a lesser vessel density and hyperechoic tissue due to the fat degeneration during the regression phase (Table 3). It is normally not hypoechoic but relatively hyperechoic as it contains fat. The vessels are hypo- or anechoic but the bulk of the mass is not.

Congenital hemangiomas may be lobulated and the vessels have a palisading architecture. Ultrasonography is therefore, a non-invasive imaging technique very useful for differentiating hemangiomas and VMs as the first-line imaging study for the children.[97, 171] Clinically, if the mass is deep-seated, located in the subcutaneous tissue or in the muscle layer, a hemangioma may mimic a VM. In these cases, the clinical diagnosis may be impossible and instrumental investigations are necessary to confirm the differentiation between the two entities.[6, 20]

Hemangioma typically appears in the proliferative phase as a well-circumscribed, solid mass consisting of a parenchymal tissue which is intensely hypervascular. Most hemangiomas are hypoechoic, although up to 18% have been reported to be hyperechoic. They show a high-flow Doppler signal with low-resistance arterial waveforms.[6, 20]

Table 3. Correlation of clinical presentation and Color Coded Duplex Sonography (CCDS) characteristics of HOI

Stage	Clinic	CCDS
S I **Prodromal phase**	red/white spot; teleangiectasia blurred swelling	loss of skin structure, structure less, low echo space no signs of pathological vessels
S II **Initial phase**	loss of typical skin structure increasing of thickness and induration	hyposonor center at the edges beginning hypervascularization
S III **Proliferation phase**	cutan bright red infiltration, flat spreading subcutaneous growth of thickness infiltration of surroundings, even organ borders possible early central ulceration	increasing Intratumoral hyperperfusion center vessel density nutrition tumor vessels drainage veins with arterial flow profile
S IV **Maturation phase**	pale and livid color decreasing of growth possible late ulceration over drainage veins	declining central vessel density increasing ectatic drainage veins declining arterialization of the drainage veins central increasing hypersonore
S V **Regression phase**	hypopigmentation, wrinkled skin/teleangiectasias surroundings subcutaneous drainage veins subcutaneous palpable induration	circumscribed hypersonore area loss of typical tissue structure nearly no central tumor vessels residuals of supplying tumor arteries residuals of ectatic drainage veins

The spectral analysis of arterial and venous flow and the measurement of flow velocities is extremely helpfu to identify the Doppler flow characteristics of hemangiomas based on high vessel density and high peak arterial Doppler shift: vessel density in excess of five per cm^2, and peak arterial Doppler shift greater than 2 kHz, taken together are highly specific and give a positive predictive value of 97% for the diagnosis of proliferative hemangioma.[6, 20]

Therefore, an ultrasound study of a child being assessed for a hemangioma should provide the following information:[6, 20]

General Principles

All ultrasound findings should be interpreted in the context of the clinical presentation and in particular time of onset, family history and rate of progression.

B-Mode

- Gross ultrasonographic morphology of the lesion and whether it is primarily composed of a soft tissue solid mass (tumor) or vascular channels with little soft tissue (vascular malformation).
- The lesion measurements in length and cross-sectional diameter.
- Location with respect to known landmarks.
- Location and depth of the lesion in the tissue (sub-cutaneous, intra-muscular, inter-muscular, peri-articular, intra-articular, etc.).
- Compressibility of vascular channels and presence/absence of thrombus within the channels.
- Evidence of previous treatments (hyperechoic walls/segments), sclero-thrombus, and surgical scarring should be identified and commented on.

Flow Characteristics

- Spectral, Color and Power Doppler examinations should confirm the flow characteristics.
- Flow characteristics (no flow, low flow, or high flow) should be determined according to the stage of hemangioma.

Other Observations:

Comments should be made regarding:

- Whether the lesion is unilateral or bilateral.
- If the underlying tissue shows hypertrophy or atrophy.

Magnetic Resonance Imaging (MRI)

MRI is the procedure of choice after ultrasound evaluation for the assessment of all CVM: MRI has a better spatial resolution/definition and a wider field of view than ultrasound; it also presents an intrinsic capability to visualize blood flow and characteristics of tissues without using ionizing radiation.[172, 173] However, both have the possibility of multiplanar acquisition.

In the investigation of vascular anomalies equipment with high power (at least 1.5 Tesla) should be used in order to have a better contrast and spatial resolution which allows to detect also small anomalies.[174-176]

Disadvantages of MRI are that they may be lengthy, noisy and potentially frightening examination for children, especially in younger age groups where consequent sedation for MRI is required.[173]
Each vascular anomaly has unique MRI feature as summarized in Table 4.
A typical CVM imaging protocol consists of spin echo (SE) or fast spin echo (FSE) T1-weighted sequences axial to the lesion generally with fat suppression in order to highlight the lesion; images obtained

after gadolinium injection are useful to distinguish LMs and VMs which have similar images in normal and i angiographic acquisition. SE sequences can also identify signal voids representing arterial feeders.[172, 173, 177]

T2-weighted images (FSE with fat suppression or in alternative short tau inversion recovery -STIR- images) in at least two planes has been found most sensitive and specific for detection of the extent and depth of the lesion because of a generally bright signal intensity lesion over a low signal intensity fat, muscle and bone background; these sequences can also show the content of the malformation.[172, 177]

Some authors also proposed the use of bright blood gradient recalled echo (GRE) sequences, to identify high flow vessels as rounded and hyperintense signal voids; the use of these sequences, however, is not essential and has been progressively abandoned.[178-180]

The presence of signal voids on T2-weighted images is suggestive for hemosiderin, dystrophic calcification or phleboliths typical for VMs.[172]

Magnetic resonance angiography (MRA) techniques are complementary to the conventional MRI sequences; traditional Time-of-Flight (TOF) and Phase Contrast techniques have now abandoned in the study of CVM, preferring contrast enhanced MRA (CE-MRA).[174] CE-MRA uses 3D T1-weighted sequences with fat suppression: the contrast medium (gadolinium chelates) is injected in a peripheral vein causing a shortening of T1 relaxation times.[172]

Although many techniques have been described for CE-MRA, time resolved 3D-MR digital subtraction angiography is best suited for evaluating vascular anomalies. With this technique a serial acquisition of less than or equal to 10 second duration are performed in rapid succession. At least one acquisition will certainly coincide with the arterial phase and at least one will coincide with the venous phase of enhancement. Of course for optimal visualization, temporal resolution must be maximized: improvement of data processing techniques can generate 3D images every 2 seconds.[172]

Compared with conventional angiography, the CE-MRA has the advantage of being able to perform multiplanar reconstructions, does not use ionizing radiation and is much less invasive. The disadvantages of CE-MRA are related to the fact that spatial resolution and the area of interest are influenced by a high time resolution; MRA also lacks the selectivity that may instead provide a selective catheterization.[181]

The Panel recommends MR imaging as a major non-invasive test together with ultrasonograhic evaluation. MR has a better spatial resolution allowing a wider field of examination. This examination allows to highlight various anatomic components according to the magnetic stimulation of the organs. It gives the best evaluation of organ involvement by the malformation. (GRADE 1B)

Extratruncular Venous malformations (VM)
MRI and MR venography (MRV) are excellent for evaluation of VMs. The test is reliable, it confirms the extent and type of the VM, delineates feeding and draining vessels, distinguishes between different soft tissues (muscle, fat) and the vascular structures. MRI and MRV is therefore, essential imaging modality to provide highly accurate diagnosis before performing interventions on VMs.[6, 20]

MRI findings of the VMs including the typical appearance of VMs as a collection of serpentine structures and its relationships with adjacent tissue/structures were thoroughly described in diagnostic section of the VM. They usually show low to intermediate signal in T1-weighted sequences and high contrast in FSE T2-weighted or STIR sequences, where the vascular malformation is highlight from the surrounding fat. In case of thrombosis or hemorrhage heterogeneous signal are seen in T1-weighted images. VM lesions may be localized or diffuse and have usually lobulated margins.

A slow filling of the malformation is visible with the use of contrast medium.[177] This characteristic of the VMs is important in the differentiation with the LMs and other cystic lesions which do NOT have any contrast enhancement after gadolinium injection.

The morphological features of VMs correlate with the success of the sclerotherapy.[182] Well defined margins and dimensions less than 5 cm are predictive of good results after ethanol therapy.

Extratruncular Lymphatic malformations (LM)
The MRI appearance of LM is variable in relation to the size of the cysts. Microcystic LMs usually appear as diffuse areas with low signal in T1-weighted and high signal intensity on T2-weighted sequences.[181] These cysts are too small to be individually identified on MRI. The microcystic LM may appear completely avascular or show a mild enhancement.

The macrocystic LM instead are characterized for the presence of cysts and septa well defined. The cysts have low signal intensity on T1-weighted sequences and appear markedly hyperintense on T2-weighted images. It is often possible to recognize a fluid-fluid level within the cyst, due to the presence of blood or proteins. The presence of flow voids or areas of intralesional enhancement are not typical of LM.[181]

The septa and the walls of the cyst after injection of contrast present a mild enhancement. The cystic spaces do not show enhancement and this behavior helps to differentiate them from the VMs. Sometimes, however, an enhancement of the cyst can be detected after treatment (both surgical and percutaneous) or in the case of mixed formations (lymphatic-venous).[181] PET scan and/or CT scan is indicated in cases of chylous reflux.

Truncular Lymphatic malformations (LM): Primary Lymphedema
MRI with or without contrast is indicated for further detailed evaluation of tissue overgrowth, pelvic pathology, obstructing lymph drainage or malformations among the patients with a combined form of vascular malformations (e.g. KTS).[183, 184]

In lymphedema, the images reveal a characteristic distribution of edema within the epifascial compartment, disclosing a honeycomb pattern along with thickening of the skin. In venous edema, both the epi- and subfascial compartments are affected, while in lipedema, there is fat accumulation without fluid.[185, 186]

MRI is also helpful in the identification of lymph nodes, enlarged lymphatic trunks, and in the differentiatior of the various causes of lymphatic obstruction in secondary lymphedema. The anatomic information derived from MRI may complement the functional assessment provided by lymphoscintigraphy. At times, these complementary sources of information are necessary to establish the diagnosis and to make the requisite therapeutic decisions.[187]

Extratruncular Arterio-venous malformations (AVMs)

AVMs have a significantly different appearance on MRI than their low-flow counterparts (VMs).[188, 189] On MRI, an AVM appear as ill-defined alteration in the context of soft tissue, of variable signal intensity in both T1- and T2-weighted images, with enlarged blood vessels in the presence of both afferent arteries (feeding artery) and efferent veins dilated without a mass that can be viewed with respect for the distinct

levels.[173, 177]

The blood vessels in AVMs cause linear or rounded signal voids in the T1-weighted SE sequences that correspond to signal hyperintensity in the GRE sequences.[172, 181] The " nidus " is heterogeneous, characterized by a tangle of multiple empty signal in T1-weighted sequences in the presence of dysplastic veins, well highlighted in the T2-weighted sequences.[177] Thickening of the skin, increasing amount of fat tissue and muscle atrophy in proximity to the AVM can also be present.

The AVM can affect bone causing hypoplasia, cortical thinning and demineralization; direct involvement of the bone is identified by the presence of intraosseous high flow vessels.[181,177, 178]
Surrounding tissue signal alterations (representing edema) can be detected with MRI. This aspect can be confused with the presence of a mass: such relief is often found when the AVM is localized in the context the muscle sheath; in this case the differential diagnosis between an AVM and a vascular tumor (rhabdomyosarcoma, hemangiopericytoma, angiosarcoma) can be extremely difficult.

Elements useful in the diagnosis of AVM are therefore represented by the presence of fat within the lesion, muscle atrophy and absence of surrounding edema.[190]

CE-MRA is used to identify a dilation of arteries and veins, an early visualization of the draining veins and to provide details of vascular anatomy useful for the treatment or angiography.[172]

Post treatment evaluation
The effect of a treatment on vascular malformation may be measured according to the size or the flow reduction. In extratruncular flow malformation, the treatment can be the injection of sclerosing agents or surgical excision in low flow malformations and transarterial embolization in high flow malformation. The biological response to sclerotherapy with all agents is long and the scarring process may last some months. In these cases the evaluation of the results and the indication for further treatment is based on the injection of gadolinium which allows detection of the perfused area.[191]

Table 4. MRI Imaging features of vascular anomalies

Vascular pathology	MRI Imaging features
Hemangioma of Infancy (HOI)	In the proliferating phase appearance of a well lobulated mass with low signal intensity on T1W images and high intensity in T2W images; presen of flow voids in SE T1W images, no perilesional edema and early homogeneous enhancement Involuting phase: fat replacement with high signa T1W images and decreased enhancement
Venous malformations (extratruncular)	Lobulated sometimes septated mass with low sign intensity in T1W images, high intensity in T2W images, flow voids in T2W fat saturation images (phleboliths), slow gradual enhancement in delay with contrast media
Lymphatic malformations (extratruncular)	The same characteristics of the venous malformations. No enhancement in microcystic malformations. Septal and rim enhancement in macrocystic malformations
Capillary	Skin thickness lesion

Arterio-venous malformations (extratruncular)	Enlarged feeding arteries and draining veins. Flov voids in T1W SE sequences; early enhancement c arteries nidus and draining veins

Hemangioma of Infancy (HOI)
MRI plays no role in the diagnostic of HOI and may be only required in uncertain and in deep localizations where ultrasound is not possible. But in cases of KHE and NICH, MRI is important to detect soft tissue and bone infiltration and to guide biopsy.

So MRI is the second non-invasive test for differential diagnosis of hemangioma and VM although it is NOT as critical as ultrasound. MRI may be indicated for diagnostic confirmation when the ultrasound findings are not clear. This investigation allows to better define the anatomy and the vascularization of the lesion, so distinguishing hemangiomas and VMs. In many cases, MRI and ultrasound with color flow imaging are complementary.[177, 178,192]

The characteristics of the tissue involved differ according to the biologic phase. In the proliferating phase, HOI appears as lobulated well defined mass, hyperintense in T2-weighted images and intermediate intense in T1-weighted images. Typically, prominent draining veins will be identified along both central and peripheral and some smaller arterial high-flow vessels are seen. There is intense, uniform, diffuse enhancement following intravenous administration of gadolinium chelates. Usually there is no perilesional edema.[100] In the presence of edema it is useful to make a biopsy of the tissue in order to exclude sarcoma.[188]

Involuting hemangiomas presents more varied and heterogeneous appearances with increasing amount of fibrous tissue, fat and an increased signal, evident in T1 sequences with less vascular enhancement.

Congenital Hemangiomas
MRI findings are similar to those of HOI but an increased venous component, vascular aneurysm and arterio-venous shunting may be present[174, 188] For the RICH, ultrasound is sufficient but in progressive NICH and KHE, an additional MRI is beneficial. In case when Kasabach-Merritt-Syndrome (KMS) should develop, the signal becomes much more intense with interstitial edema same as ultrasound. The reduction of these signs correlates with the normalization of the coagulopathy although the thrombocytopenia can remain for long time.[193, 194]

Computed Tomography (CT)

Although MRI is preferred for assessing CVM, CT may replace or complement MRI in some cases: CT is an alternative to MRI in those patients with respiratory or cardiac failure because of the velocity in the images acquisition. Of course it is useful in patients who have contraindications to sedation with MRI and is preferable to MRI in imaging vascular anomalies of bowels and lungs.[173]
In addition, it presents fewer artefacts compared to MRI in patients with embolization coils or metallic clips.
Compared to MRI, CT may better define both alteration in bony architecture and identify phleboliths or other dystrophic calcifications.[177] If there is a CVM (in particular in high flow vascular lesion) bone involvement, CT may provide additional information to MRI.

The adverse effects are represented by the exposure to ionizing radiation and the necessity to use contrast medium to visualize the vessels. The problem of the exposure to ionizing radiation is of particular importance in pediatric age, regarding CT's potential for carcinogenesis.

On CT, VMs often appear hypodense or heterogeneous lesions which enhance slowly from the periphery after the injection of contrast.[191] CT venography has a unique value for evaluation of obstructed, anomalous, atretic, or absent veins and other truncular anomalies of large veins in the chest, abdomen or pelvis. CT accurately identifies the underlying pathology, confirms venous obstruction or extrinsic compression, delineates anatomic variations and extent of venous thrombosis.[195-197]

LMs shows fluid-filled, low-attenuation masses occasionally with fluid-fluid levels and peripheral contrast enhancement of the wall.[191]

Contrast enhanced CT of AVMs, with bolus tracking technique (CT-angiography; CTA) to obtain an optimal study of arterial vessels, reveals numerous enlarged feeding arteries with rapid contrast shunting into enlarged draining veins without significant intervening tissue enhancement that usually would be seen within a normal capillary network. Contrast-enhanced CT of AVMs is significantly more informative than in other vascular malformations because it provides a distinct three-dimensional data set for accurate mapping and measurement of arterial, nidal, and venous structures and assessment of flow patterns for interventional radiologic or surgical planning which is possible especially due to the many post-processing options.[188]

VMs are heterogeneous lesions which enhance slowly from the periphery after the injection of contrast.[172] In AVMs, the afferent artery, the efferent veins and the nidus are well defined.

CT venography has a unique value for evaluation of obstructed, anomalous, atretic, or absent veins and other truncular anomalies of large veins in the chest, abdomen or pelvis. CT accurately identifies the underlying pathology, confirms venous obstruction or extrinsic compression, delineates anatomic variations and extent of venous thrombosis.[195-197]

CT with intravenous contrast enhancement has been used for the differential diagnosis of hemangiomas and VMs.[198] Yet CT involves significant exposure to ionizing radiation making it less useful, although CT gives superior resolution for osseous lesions.[6, 20]

Standard MRI is not a good technique for precisely demonstrating the nidus or arterio-venous connection. Instead, CTA provides much better anatomical information, sometimes showing the arterial and venous anatomy in excellent detail, but is inferior in all aspects to the newer technique of CE-MRI.[7]

Even considering that CTA may give more precise anatomical detail than MRI, particularly in small blood vessels, the benefits of clinically justified CT examinations should always outweigh the risks for an individu child, and referral to a center that performs CE-MRI[100, 199] should be considered as well.[7]

MRI should remain as the option of choice in the diagnosis of high flow vascular anomalies for this special group. Only when dealing with a specific AVM in a critical area difficult to treat, CT is indicated, though extremely rare.[7]

We recommend CT scan as useful test especially with the contrast medium presenting excellent spatial and temporal resolution. Its principal indications are thoracic and visceral malformations as well as AVM with bone involvement. (GRADE 1C)

Conventional Radiological Assessment: Plain X-Ray and Bone Scanograms

Scanograms are long bone radiographs that provide accurate measurement of the long bone length of the upper and lower limbs. Scanograms are needed to assess any bone length discrepancy between the limbs. This document would become objective criteria for further management.[6, 20]

Conventional radiologic techniques are addressed to discover bone involvement in CVMs. Bones may be elongated, shortened, deformed, thickened or thinned because of osteolysis.[173, 200] The pathological cause is related to ischemia of the osteoblasts representing a growth stimulation or to compression of the bone by the surrounding structures or vein and lymph stasis.[201-203]

Calcification in the soft tissues is a hallmark of VMs. Multiple encondromas are typical of Maffucci syndrome and they have the tendency to progress to malignancy.

The Panel recommends Plain X-rays as an essential test in detecting bone pathology related to CVMs. Bony changes including lengthening, shortening, enchondromas and vanishing bone syndrome should be identified. These images are also useful in detecting calcifications (phleboliths) in soft tissues as a hallmark of VMs. (GRADE 1B)

Invasive Diagnostic Evaluation

- Ascending, descending, and/or segmental venography/phlebography
- Standard and/or selective arteriography
- Percutaneous direct puncture angiography: arteriography, phlebography, varicography, lymphography

Basic diagnosis of CVMs is generally sufficient with proper combination of the non- to minimally invasive tests and "invasive" tests are seldom needed to establish the diagnosis of the VM and can be deferred until intervention is required. It is required for treatment planning either surgical or endovascular. However, invasive tests may be required for diagnosis when non- to minimally invasive tests (e.g. CT and/or MRI) fail to confirm the diagnosis or to delineate important diagnostic details which are important for options of treatment. [6, 20]

For example, an obstructive truncular VM lesion along the iliac vein often needs more precise anatomic information. Ascending phlebography combined with intravascular ultrasound (IVUS) studies is essential for proper management. Descending phlebography is an indispensable tool to assess deep venous reflux along the pelvic veins and/or sciatic veins. These studies are required before treatment with embolotherapy.[6, 20]

Direct puncture phlebography is also very useful to identify a large efferent vein of extratruncular lesions.[125, 204] These veins can be treated in advance to allow more effective therapy with reduced risk of recurrence, with subsequent embolotherapy or sclerotherapy.[6, 20]

There is no role for diagnostic angiography in the diagnosis or follow-up of low-flow vascular malformations; angiography should be reserved only in AVM as a road map to further define the lesion and plan proper treatment. To minimize radiation exposure, these techniques are usually performed at the time of treatment in young patients.[200, 205]
These studies include:

- Selective and superselective arteriography
- Percutaneous direct puncture phlebography

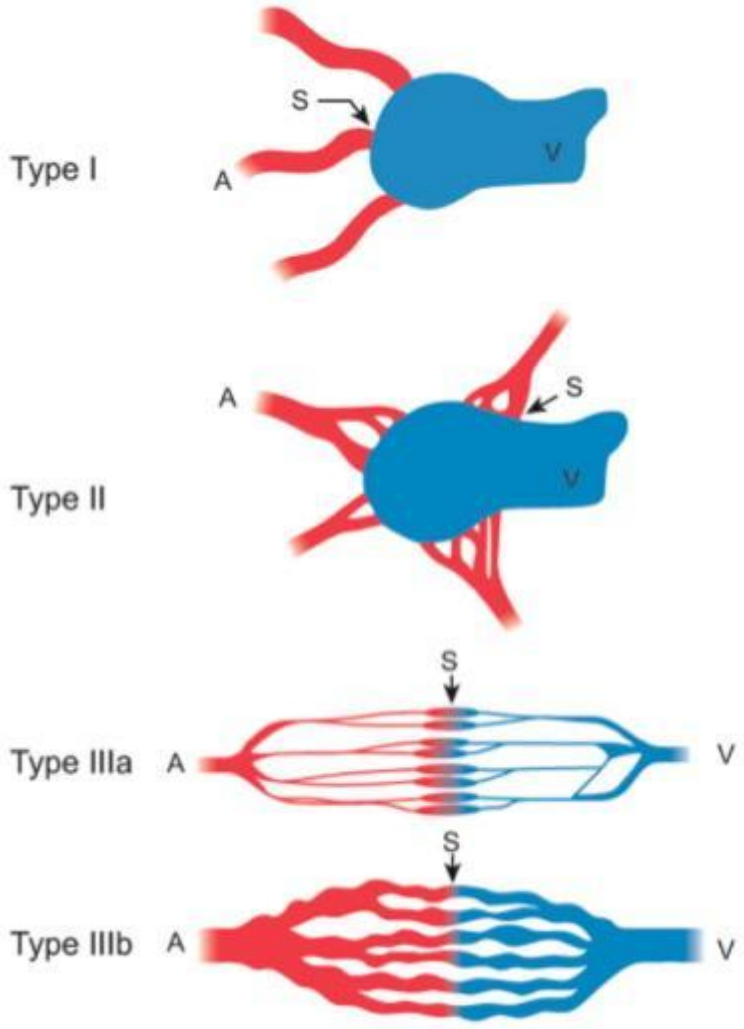
Therefore, once the intervention is decided, the level of propaedeutic to the therapy should be elevated to pre-therapeutic mapping of the lesions including the angiographic classification of extratruncular VMs

(Table 5) and also AVMs (Figure 2) proposed by Puig[103] and YS Do et al,[104] respectively. These classifications have a great importance as predictive measurement for the results of intravascular therapy.

Table 5. Angiographic classification of Venous Malformation

Angiographic classification of Venous Malformation by YS Do et al.	**Description**
Type 1	Isolated malformation without peripheral drainage
Type 2	Malformation that drains into normal veins
Type 3	Malformation that drains into dysplastic veins
Type 4	Malformation that represents a dysplasia

Figure 2. Arteriographic classification of AV Malformation



— Type I (arteriovenous fistulae): at most 3 separate arteries shunted to a single draining vein.
— Type II (arteriolovenous fistulae): multiple arterioles shunted into a single draining vein.
— Type III (arteriolovenulous fistulae): multiple shunts between the arterioles and venules.

Phlebography

Phlebography not only determines hemodynamic characteristics of the lesion but it also allows the classification of the VM based on its anatomy in regards to the communication pattern with the draining venous system. Based on the appearance of the VMs and the draining venous system during phlebography all VMs can be classified into four distinct groups: Type I (isolated VMs without phlebographically appreciable venous drainage), Type II and Type III VMs (demonstrate normal-sized and enlarged venous drainage, respectively) and Type IV VMs (characterized by essentially ectatic dysplastic veins).[97, 103, 206]

From a diagnostic standpoint, phlebographic evaluation of patency and anatomic variations of the deep venous system deserves special consideration in addition to phlebographic classification of the VM. Although above mentioned phlebographic classification does not provide information regarding the location of the VMs or the involvement of surrounding anatomical structures it provides useful data for treatment planning, especially when the sclerotherapy is considered as a treatment option.[6, 20]

Ascending phebography is rarely required for the diagnosis of a vascular malformation. The role of ascending phlebography is limited to the diagnosis of truncular venous disease and in particular of obstructive pathology. It is important to evaluate the patency of the deep veins in presence of dilated

superficial veins and hypoplasia or aplasia of deep veins according to the non-invasive investigations.[125, 204, 207] Technical skills are required to avoid incorrect results of phlebography, as preferred abnormal outflows may sometimes simulate absence or main vein stenosis.

The main advantage of this procedure is that the imaging can be performed in orthostatism. Descending phlebography is indicated to avalvulia and in pelvic, sciatic, and visceral malformations. Direct puncture venography is related to the treatment of extratruncular VM lesions. With this procedure it is possible to visualize the outflow drainage of the malformation and it is possible to distinguish four types according to the drainage veins.

We recommend direct puncture phlebography for the evaluation of the venous outflow of the lesion. It helps in understanding the success probability of a vascular surgical procedure or sclerotherapy. (GRADE 1A) We also recommend retrograde phebography to evaluate deep venous incompetence in the lower limbs, visceral and pelvic malformations. (GRADE 1B)

Arteriography

The use of arteriography has been replaced by MRI and CT scan for the management of the CVM in general but it still remains as the gold standard for the ultimate assessment for the AVMs and warranted for the planning of the treatment of an AVMs which were already studied with non-invasive diagnostic tools.

It is necessary to have panoramic and superselective pictures in order to highlight the feeding arteries to lead to the nidus. It is possible to adopt an arteriographic classification of AV shunts in order to guide the therapy as mentioned in details above.[104]

We recommend arteriographies as pre-operative invasive investigations. They should be reserved for the patients who need a therapy and should be performed by the centers which deliver this therapy. (GRADE 1B)

Lymphography

Invasive tests are seldom needed for the actual diagnosis of LMs but are occasionally needed for differential diagnosis. Further studies with invasive tests such as direct puncture percutaneous lymphangiography can be generally deferred to later stages if there is a need for refining the diagnosis or if surgical or other invasive therapeutic measures are considered. Otherwise, these should be reserved for road-mapping in subsequent therapy if needed.

Conventional oil contrast lymphangiography, especially if coupled with CT scan, is still advantageously employed in selected patients with chylous dysplasia and gravitational reflux disorders in order to define more clearly the extension of the pathologic alterations and sites of lymphatic and chylous leakage. These are the only diagnostic investigations that can clearly demonstrate pathologies of chylous vessels, chylous cyst and thoracic duct in cases of chylothorax, chylous ascites, protein losing enteropathy, etc.[39, 40, 208, 209]

For most instances, lymphography has been replaced by lymphoscintigraphy in the diagnosis of lymphedema. There is a revival in the use of lymphography in case of lymphoceles, and pathology of chylous reflux. In this case a direct puncture of inguinal nodes is made under ultrasound and lipiodol infused. The procedure causes the inflammation of the lymphatic pathways and may be curative.[210, 211]

Nuclear Medicine Evaluation

Whole body blood pool scintigraphy (WBBPS)

WBBPS using Tc99 is a very useful tool to detect the presence of a vascular malformation. With a single examination it is possible to check the presence of a vascular malformation in the whole body. Their strength is the possibility to investigate whole anatomic structures in one examination. It gives some quantitative data on the blood trapping of the lesion and this allows the possibility to assess the results of treatment.[212-214]

WBBPS is an optional test to screen for multiple VM lesions scattered throughout the body. It allows qualitative and quantitative evaluation of the VM lesion especially during the course of multisession sclerotherapy as a cost-effective measure. It is an excellent tool for routine follow up and the evaluation of therapy to assess the progress of treatment and the natural course of the VM lesion with some numerical values.[215-217] It can exclude the LM where the absence of an abnormal blood pool over the lymphatic lesion is the typical finding.[6, 20]

WBBPS is also an excellent optional test for the AVM evaluation as well. But it is rather more useful for the screening of hidden CVM lesions throughout the body and also for a qualitative analysis of the AVM lesion along the course of the multisession therapy as a cost-effective measure. It is an excellent tool for the routine follow-up on the progress of treatment and its natural course as well when TLPS is not feasible/available.[7]

We recommend Whole body blood pool scintigraphy as a very useful tool to detect the presence of a vascular malformation throughout the body. (GRADE 1B)

Transarterial lung perfusion scintigraphy (TLPS)

Scintigraphy is not an essential examination necessary for the diagnosis of AVM and/or CVM in general but remains an option for a secondary investigation only in selected cases. TLPS[7, 57, 91] has a unique role in determining the degree of AV shunting by the AVM lesion within an extremity.[218]

TLPS has a special value to detect and assess a micro-AV shunting lesion, which is often difficult with conventional techniques. Micro-AVMs frequently exist in the combined form of CVM, the hemolymphatic malformation (HLM), and its delayed or overlooked diagnosis with subsequent progress beyond the optimum time for the interception can be avoided with TLPS alone.[7, 57]

TLPS allows not only to quantify the AV shunt present in a malformation[66, 67] but also provides quantitative measurement of the shunting status during therapy. TLPS may replace the substantial role of traditional arteriography as a follow-up assessment tool for extremity AVMs.

TLPS is not indicated for evaluation of the VM lesion but its major function is to rule out the presence of a combined AVM lesions.[7, 57]

The Panel recommends transarterial lung perfusion scintigraphy to quantify the AV shunt in an AVM when indicated. (GRADE 2B)

Radionuclide Lymphoscintigraphy (LSG)

LSG is a functional study that complements the anatomical information provided by lymphangiography. There are no standardizations nor is there a gold standard as of yet.[39, 40, 219-222]

LSG, performed with injection of 99mTc-labeled human serum albumin or 99mTc-labeled Sulphur Colloid subcutaneously into the first and second web-space of the toes or fingers, is the test of choice to confirm or exclude lymph vessel pathology as the cause of chronic limb swelling.[39, 40]

Movement of the colloid from the injection site, transition time to the knee, groins or axilla, absence or presence of major lymphatic collectors, number and size of vessels and nodes (e.g. popliteal nodes), the presence of collaterals and reflux, symmetric activity with the opposite side are recorded and used for interpretation.[223] Semi-quantitative assessment has been reported, and most recently, the technique of quantitative assessment of transit time from the foot to the knee was also validated [224-228]

LSG represents the main examination to evaluate the lymphdynamics of the limbs. This will be recorded in rest, after exercise, and one hour of daily activity. With this examination it is possible to detect the presence of deep and superficial lymphatic vessels and the presence or absence of reflux.[7, 55, 59] In patients with genital and abdominal lymph leakage there is an indication for SPECT examination to visualize the intraabdominal lymph node status.[57]

LSG is essential to rule out lymphatic dysfunction especially due to the presence of a truncular LM known as primary lymphedema, which often exists with the VM lesion (e.g. KTS).[229-231]

LSG remains the gold standard for lymphatic function evaluation since the LSG is the only test that can clearly indicate lymphatic function. Radionuclide lymphoscintigraphic findings provide the proper clinical and/or laboratory staging that may be essential for proper clinical management.
LSG, along with clinical evaluation, is the most essential component for the diagnosis of chronic lymphedema.[39, 40]
LSG is extremely useful for identifying the specific lymphatic abnormality and has largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. LSG can easily be repeated with minimal risk. Data and images obtained from the study identify lymphatic (dys)function, based on visualization of lymphatics, lymph nodes, and dermal backflow as well as semi-quantitative data on radiotracer (lymph) transport.[39, 40]

However, the LSG has not been standardized with regard to the various radiotracers and radioactivity doses, different injection volumes, intracutaneous vs. subcutaneous injection site, epi-or sub-fascial injection, number of injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques.[223]

The Panel recommends lymphoscintigraphy as the most essential non-invasive test for a morphodynamic evaluation of the lymphatic circulation. (GRADE 1B)

Laboratory Tests

Coagulation Studies in Venous Malformations

Coagulation disorders occur at a high frequency in patients with extensive VMs and may result in potentially severe thrombo-embolic events and hemorrhagic complications.[6, 20] Extensive VMs are often associated with a ‘localized intravascular coagulopathy’ (LIC). LIC is due to stagnant flow in extratruncular lesions resulting in a cycle of ongoing intravascular thrombosis and fibrinolysis. Secondary hypofibrinogenemia (von-Willebrand-Juergens-syndrome) may follow resulting in spontaneous hemorrhage.

The pathogenesis of LIC in VMs is different from that of KMS associated with certain vascular tumors[232-234] although both coagulopathies are closely linked.[235, 236] The differentiation between the two coagulopathies is critical as the 'early detection' of KMS is warranted before it progresses to severe coagulopathy with multi-organ failure. KMS never develops in GLUT-1 positive HOI but in KHE or tufted angiomas. Progressive NICH accompanies the highest risk.[36-38, 51-53]

Currently, there are no evidence-based guidelines to advocate screening for coagulopathy in patients with potentially life-threatening VMs. It is important to follow an accurate diagnostic algorithm for coagulopathies associated with especially extensive VMs involving large surface areas, muscle involvement and/or palpable phleboliths.[6, 20]

Assessment of the coagulation profile and D-dimer levels is indicated in patients with extensive VMs. D-dimer (a degradation product of cross-linked fibrin) measured with rapid enzyme linked fluorescent immunoassay is being increasingly utilized in the assessment of VM patients and is considered to be the biochemical gold standard for ruling out an episode of thrombophlebitis or thrombo-embolic events. D-dimer can detect a sign of consumptive coagulopathy which is common among VMs .[235]

Elevated D-dimer among the symptomatic VMs has a unique value for the clinical assessment of the severity of the VM lesions although D-dimer in general is highly non-specific. D-dimer levels may also assist in the diagnosis of occult lesions and help differentiate GVMs and LMs (normal D-dimer levels) from other multifocal venous lesions.[237] Therefore, in addition to imaging studies, plasma D-dimer representing a direct measurement of endogenous fibrinolysis as a biological marker should be evaluated in the diagnosis and follow-up of VMs.
Patients with *extensive* VMs or *high risk* lesions in particular should undergo the following laboratory tests:[6, 20]

- Full blood count including hemoglobin levels and platelet count
- D-dimer- quantitative assay
- Fibrinogen
- PT, APTT
- Thrombophilia screening

The Panel recommends D-dimer measurements to detect elevated values linked to the presence of VMs, platelet count and fibrinogen levels in Kasabach Merritt syndrome often associated with kaposiform hemangioendotheliomas.(GRADE 1B)

Histology

Biopsy should be reserved to make an accurate diagnosis and is mostly required when the lesion is suspected to be a tumor. Biopsy in particular may be required to differentiate between AVMs, NICH and vascular sarcomas. Histologic differentiation between HOI and congenital hemangiomas may be required and can be facilitated by GLUT-1 staining of HOI which persists also after regression. Biopsy may also be required to differentiate between GVM and BRBNS. GVM are lined by cuboidal glomus cells that stain positive for smooth muscle actin and myosin and is histologically differentiable from BRBNS.[82, 83, 161-164]

Recently, immunohistochemistry has been used in the study of hemangiomas and supports a new classification of the pediatric liver vascular tumors based on the expression of GLUT-1 as a substitution of the old and confusing term of hepatic infantile hemangioendothelioma:

GLUT-1 positive expression is usually demonstrated in multifocal, and diffuse hepatic infantile hemangioma which shares clinical and morphological features with cutaneous infantile hemangioma. Diffuse neonatal hemangiomatosis is a disorder characterized by multiple cutaneous and hepatic hemangiomas.

Therefore, timely identification of GLUT-1 expression is crucial for children with hepatic hemangiomas in view of improved management before reaching to the liver transplantation. In the last 5 years propranolol has dramatically changed the scope of children with hepatic hemangiomas. Prognosis is currently considered as favorable and those previously considered as unfortunate patients are not anymore candidates for liver transplantation.[161-164]

The Panel recommends biopsy to be reserved only for unclear cases. (GRADE 1B)

Endoscopic Evaluation

Endoscopic examinations are recommended when vascular anomalies are suspected to involve intra-cavity organs. This is usually performed when investigating causes of occult bleeding.

CVMs located on the face and neck often require early pharyngo-laryngo-tracheoscopy as the possible associated mucosal involvement may result in bleeding, infection or respiratory complications. Conventional imaging techniques may not be precise enough to detect such lesions. Endoscopic identification and destruction of the lesion may be achieved during the same session.

Malformations located in the pelvic cavity and lower extremities often need procto-sigmoidoscopy, urethrocystoscopy, and/or vaginoscopy (colposcopy) for early detection before bleeding occurs. This is especially true in patients with KTS which accompanies a high incidence of gastrointestinal and genitourinary involvement.

Arthroscopy is indicated to assess lesions involving the knee as small lesions are frequently not detected by conventional imaging techniques. Accurate assessment is required for subsequent laser coagulation. Patients with BRBNS need regular esophago-gastro-duodenoscopy and complete colonoscopy due to the high risk of gastrointestinal mucosal involvement that can cause severe bleeding.

HOI with perioral/intraoral localizations may require an early pharyngo-laryngo-tracheoscopic evaluation for an early detection of accompanied subglottic or tracheal hemangioma before clinical symptoms occur. The vulvar lesion often needs a vaginoscopy/colposcopy and urethroscopy, while perianal lesion needs a proctoscopy.

Genetic Testing and Family Screening

Germline and somatic mutations have been identified in a number of vascular anomalies. Germline mutations were identified when practitioners observed a familial occurrence of some vascular lesions, and blood samples from these individuals enabled researchers to identify these mutations. Sporadic syndromes are thought to occur due to mosaic distribution of somatic mutations that are detected from studies of affected tissue.[27-31, 238-242]

Why, how and when to test patients and families for potential genetic mutations?
Why to perform genetic testing: identification of germline mutations may be important for a number of reasons. There may be a strong family history of affected individuals (e.g. HHT).

However, certain vascular anomalies occur with variable penetrance, such that parents of the proband patient may harbor a genetic mutation without overt expression of the disorder (e.g. GVM). If these parents are interested in further offspring (and the genetic mutation has been identified), prenatal genetic testing can be offered.

Options include chorionic villus sampling, amniocentesis, or pre-implantation genetic testing with in vitro fertilization of an unaffected embryo. Identification of the PTEN mutation requires counselling regarding the necessity for early and consistent surveillance for early detection of malignancies. Additionally, affected patients can be educated about their chances of having affected offspring. (Appendix C and D)

Identification of somatic mutations may have implications for new therapies. In many cases, discussion with a specialist in human genetics and/or genetic counsellor is recommended. In the USA, many insurance plans require prior authorization for this testing, which may be costly. Some research laboratories are interested in patient/family blood and/or tissue samples for genetic studies. Updated information regarding available tests and laboratories which perform them is available at the GeneTests website: http://www.genetests.org/

Follow-up Assessment

Follow-up is necessary to evaluate the natural evolution of the pathology and/or the therapy results. The follow-up assessment may be carried based on non-invasive investigations (MRI and ultrasound). A temporary enlargement of the malformation lesion may be normal reaction after intravascular therapy. The results may also be evaluated using WBBPS.

We recommend follow-up evaluation to evaluate the natural evolution of the pathology and/or the therapy results. The follow-up shall be based on non-invasive investigations (MRI and ultrasound). (GRADE 1B)

References:

1. Guyatt GH, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, et al: Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines. *Chest* 2006;129;174-181
2. Guyatt GH, Meade MO, Jaeschke RZ, Cook DJ, et al: Practitioners of evidence based care. BMJ 2000;320:954-955
3. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, et al: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations BMJ 2008;336:924-926
4. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69:412-422.
5. Enjolras O, Wassef M, Chapot R. In: Color atlas of vascular tumors and vascular malformations. New York: Cambridge University Press; 2007. Introduction: ISSVA classification; pp. 1–11.
6. Lee BB, Bergan J. Gloviczki P, Laredo J, Loose DA, Mattassi R, Parsi K, Villavicencio JL, Zamboni P: Diagnosis and treatment of venous malformations - Consensus Document of the International Union of Phlebology (IUP)-2009. International Angiology 2009 December;28(6):434-51.
7. Lee BB, Baumgartner I, Berlien HP, Bianchini G, Burrows P, Do YS, Ivancev K, Kool LS, Laredo J, Loose DA, Lopez-Gutierrez JC, Mattassi R, Parsi K, Rimon U, Rosenblatt M, Shortell C, Simkin R, Stillo F, Villavicencio L, Yakes W. Consensus Document of the International Union of Angiology (IUA)-2013. Current concept on the management of arterio-venous malformation. Int Angiol. 2013 Feb;32(1):9-36
8. Belov St. Classification of congenital vascular defects. Int Angiol 1990;9:141-146.

9. Belov S. Classification, terminology, and nosology of congenital vascular defects. In: Belov S, Loose DA, Weber J, eds. Vascular Malformations. Reinbek, Germany: Einhorn-Presse; 1989:25-30.
10. Belov St. Anatomopathological classification of congenital vascular defects. Seminars in Vascular Surgery 1993;6:219-224.
11. Lee BB, Laredo J, Lee TS, Huh S, Neville R. Terminology and classification of congenital vascular malformations. Phlebology. 2007; 22(6):249-52.
12. Malan, E. (1954) Considerazioni sulle fistole artero-venose congenite degli arti. Boll Soc Priem Chir 24: 297 – 301.
13. Malan, E, Puglionisi A: (1964) Congenital angiodysplasia of the extremities. Note 1: generalities and classification; venous dysplasias. J Cardiovasc Surg (Torino). Mar-Apr; 5:87-130.
14. Bastide G, Lefebvre D. Anatomy and organogenesis and vascular malformations. In: Belov St, Loose DA, Weber J, editors. Vascular Malformations. Reinbek: Einhorn-Presse Verlag GmbH; 1989.p.20-22.
15. Woolard HH. The development of the principal arterial stems in the forelimb of the pig. Contrib Embryol 1922;14:139-154.
16. Vollmar J, Vogt K. Angiodysplasie und Skeletsystem. Der Chirurg. 1976;47:205-213.
17. DeTakats G. Vascular anomalies of the extremities. Surg Gynecol Obstet 1932;55:227-237.
18. Leu HJ. Pathomorphology of vascular malformations: analysis of 310 cases. International Angiology. 1990;9:147-155.
19. Leu HJ. Pathoanatomy of congenital vascular malformations. In: Belov S, Loose DA, Weber J, eds. Vascular Malformations. Vol 16. Reinbek, Germany: Einhorn-Presse Verlag; 1989;37-46.
20. Lee BB, Baumgartner I, Berlien P, Bianchini G, Burrows P, Gloviczki P, Huang, Y, Laredo J, Loose DA, Markovic J, Mattassi R, Parsi K, Rabe E, Rosenblatt M, Shortell C, Stillo F, Vaghi M, Villavicencio L, Zamboni P. Diagnosis and Treatment of Venous Malformation: Consensus Document of the International Union of Phlebology (IUP): Updated-2013. In press on Int. Angiol. 2014
21. Lee BB, Kim HH, Mattassi R, Yakes W, Loose D, Tasnadi G. A new approach to the congenital vascular malformation with new concept -Seoul Consensus. Int. J. Angiol. 12:248-251, 2003.
22. Lee BB, Mattassi R, Loose D, Yakes W, Tasnadi G, Kim HH: Consensus on Controversial Issues in Contemporary Diagnosis and Management of Congenital Vascular Malformation– Seoul Communication – Int J Angiol, 2004; 13(4): 182-192.
23. Lewis RJ, Ketcham AS.Maffucci's syndrome: functional and neoplastic significance.J Bone Joint Surg, 1973; 55A: 1465-1479.
24. Courivaud D, Delerue A, Delerue C, Boon L, Piette F, Modiano P. Familial case of Parkes Weber syndrome Ann Dermatol Venereol. 2006 May;133(5 Pt 1):445-7.
25. Bartels C, Claeys L, Ktenidis K, Horsch S. F.P. Weber syndrome associated with a brachial artery aneurysm. A case report. Angiology. 1995 Nov;46(11):1039-42.
26. Boon LM, Balliuex F, Vikkula M. Pathogenesis of vascular anomalies Clin Plast Surg. 2011:1; 38:7-19
27. Kurek KC, Howard E, Tennant LB, Upton J, Alomari AI, Burrows PE, Chalache K, Harris DJ, Trenor CC 3rd, Eng C, Fishman SJ, Mulliken JB, Perez-Atayde AR, Kozakewich HP. PTEN hamartoma of soft tissue: a distinctive lesion in PTEN syndromes. Am J Surg Pathol. 2012 May;36(5):671-87
28. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. Genetics in medicine : official journal of the American College of Medical Genetics. 2011;13(7):607-16.
29. Tan WH, Baris HN, Burrows PE, Robson CD, Alomari AI, Mulliken JB, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. Journal of medical genetics. 2007;44(9):594-602.
30. Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med. 2011;365(7):611-9.
31. Brouillard P, Boon LM, Revencu N, Berg J, Dompmartin A, Dubois J, et al. Genotypes and

phenotypes of 162 families with a glomulin mutation. Molecular syndromology. 2013;4(4):157-64.
32. Lee BB: Congenital venous malformation: changing concept on the current diagnosis and management. Asian J. Surgery, 22(2):152-154, 1999.
33. Lee BB: Current concept of venous malformation (VM). Phlebolymphology 2003;43:197-203.
34. Lee BB. Critical issues on the management of congenital vascular malformation. Annals Vasc Surg 18(3):380-392, 2004.
35. Personal Communication with Blei F and Berlien P of ISSVA Scientific Committee & Executive Board.
36. North PE, Waner M, James CA, Mizeracki A, Frieden IJ, Mihm MC, Jr. Congenital nonprogressive hemangioma: a distinct clinicopathologic entity unlike infantile hemangioma. Arch Dermatol 2001;137(12):1607-20.
37. Berenguer B, Mulliken JB, Enjolras O, Boon LM, Wassef M, Josset P, Burrows PE, Perez-Atayde AR, Kozakewich HP. Rapidly involuting congenital hemangioma: clinical and histopathologic features Pediatr Dev Pathol. 2003 Nov-Dec;6(6):495-510.
38. Roncero M, Martinez de Salinas A, Izquierdo N, Unamuno P. Rapidly involuting congenital haemangioma. Clin Exp Dermatol 2009; 34:937.
39. Lee B, Andrade M, Bergan J, Boccardo F, Campisi C, Damstra R, Flour M, Gloviczki P, Laredo J, Piller N, Michelini S, Mortimer P, Villavicencio JL; International Union of Phlebology. Diagnosis and treatment of primary lymphedema. Consensus document of the International Union of Phlebology (IUP)-2009
40. Lee BB, Andrade M, Antignani PL, Boccardo F, Bunke N, Campisi C, Damstra R, Flour M, Forner-Cordero J, Gloviczki P, Laredo J, Partsch H, Piller N, Michelini S, Mortimer P, Rabe E, Rockson S, Scuderi A, Szolnoky G, Villavicencio JL. Diagnosis and Treatment of Primary Lymphedema. Consensus Document of the International Union of Phlebology (IUP)-2013. Int Angiol 2013;32(6):541-74
41. Lee BB: Advanced management of congenital vascular malformation (CVM). International Angiology 21(3):209-213, September 2002.
42. Mulliken JB. Classification of vascular birthmarks. In: Grainger RG, Allison DJ, eds. Vascular Birthmarks, haemangiomas, and Malformations. Philadelphia, Pa: WB Saunders; 1988:24-37.
43. Mulliken JB. Cutaneous vascular anomalies. Seminars in Vascular Surgery 1993;6:204-218.
44. Enjolras O, Riché MC, Merland JJ, Escandej P. Management of alarming hemangiomas in infancy: a review of 25 cases. Pediatrics. 1990;85:491-498.
45. Lee BB, Laredo J. Hemangioma and Venous/Vascular malformation are different as an apple and orange! Editorial, Acta Phlebol 2012, 13: 1-3.
46. Lee BB. Not all venous malformations needed therapy because they are not arteriovenous malformations. Comments on Dermatol Surg. 2010 Mar;36(3):340-6. Dermatol Surg. 2010 Mar;36(3):347.
47. Lee BB. Venous Malformation is NOT a Hemangioma. Editorial. Flebologia y Linfologia – Lecturas vasculares - 7 (17): 1021 - 1023, 2012.
48. Mulliken JB, Zetter BR, Folkman J. In vivo characteristics of endothelium from hemangiomas and vascular malformations. Surgery 1982;92-348-53.
49. Byard RW, Burrows PE, Izakawa T, Silver MM. Diffuse infantile hemangiomatosis: Clinicopathologic features and management problems in five fatal cases. Eur J Pediatr 1991;150:224-227.
50. Boon LM, Enjolras O, Mulliken JB. Congenital hemangioma: evidence of accelerated involution. J Pediatr. 1996;128:329-335.
51. North PE, Waner M, Mizeracki A, Mrak RE, Nicholas R, Kincannon J, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. Arch Dermatol. 2001;137(5):559-70.
52. Jones EW, Orkin M. Tufted angioma (angioblastoma). A benign progressive angioma, not to be confused with Kaposi's sarcoma or low-grade angiosarcoma. J Am Acad Dermatol 1989; 20:214.
53. Croteau SE, Liang MG, Kozakewich HP, et al. Kaposiform hemangioendothelioma: atypical features

and risks of Kasabach-Merritt phenomenon in 107 referrals. J Pediatr 2013; 162:142.
54. Zukerberg LR, Nickoloff BJ, Weiss SW. Kaposiform hemangioendothelioma of infancy and childhood. An aggressive neoplasm associated with Kasabach-Merritt syndrome and lymphangiomatosis. Am J Surg Pathol 1993; 17:321.
55. Lee, B.B., Laredo, J., Deaton, D.H., and Neville, R.F. Arteriovenous malformations: evaluation and treatment. In Handbook of Venous Disorders: Guidelines of the American Venous Forum, 3rd Edition; Gloviczki, P., Ed; A Hodder Arnold Ltd, 2009, London, UK.
56. Lee BB, Do YS, Yakes W, Kim DI, Mattassi R, Hyun WS, Byun HS: Management of arterial-venous shunting malformations (AVM) by surgery and embolosclerotherapy. A multidisciplinary approach. J. Vasc. Surg.39 (3):590-600, 2004.
57. Lee BB, Lardeo J, Neville R. Arterio-venous malformation: how much do we know? Phlebology 2009;24:193-200
58. Lee BB: Mastery of Vascular and Endovascular Surgery. Zelenock, Huber, Messina, Lumsden, Moneta (eds). Chapter 76. Arteriovenous malformation, pages 597- 607. Lippincott, Williams and Wilkins publishers, 2006, Philidelphia.
59. Lee BB: Fast Facts-Vascular Surgery Highlights 2006-07. Chapter: Management of Arteriovenous Malformation. pp 42-50. Health Press Limited, Elizabeth House, Queen Street, Abington, Oxford OX143LN, UK 2007
60. Lee BB, Villavicencio L: Chapter 68. General Considerations. Congenital Vascular Malformations. Section 9. Arteriovenous Anomalies. Pages 1046-1064. Rutherford's Vascular Surgery. 7th Edition. Cronenwett JL and Johnston KW, Eds. Saunders Elsevier, Philadelphia, PA, USA. 2010.
61. Horton, B.T. (1932) Hemihypertrophy of Extremities associated with Congenital Arteriovenous Fistula. Jr. A.M.A. 98: 373.
62. Ballock RT, Wiesner GL, Myers MT, Thompson GH. Current Concepts Review - Hemihypertrophy. Concepts and Controversies. J Bone Joint Surg Am, 1997 Nov 01(11):1731-8
63. Lee BB, Laredo J. Classification of congenital vascular malformations: the last challenge for congenital vascular malformations. Phlebology. 2012;27(6):267-9.
64. Lee BB. Venous embryology: the key to understanding anomalous venous conditions. Phlebolymphology. 2012;19(4):170-181.
65. Lee BB. Venous malformation and haemangioma: differential diagnosis, diagnosis, natural history and consequences. Phlebology. 2013;28 Suppl 1:176-87.
66. Lee BB, Villavicencio JL: Primary Lymphedema and Lymphatic Malformation: are they the two sides of the same coin? Eur J Vasc Endovasc Surg (2010) 39:646-653.
67. Lee BB, Laredo J, Seo JM, Neville R: Treatment of Lymphatic Malformations. In Hemangiomas and Vascular Malformations. Mattassi, Loose, Vaghi (eds) Chapter 29, Springer-Verlag Italia, 2009, Milan, Italy. Pages 231-250.
68. Lee BB, Kim YW, Seo JM, Hwang JH, Do YS, Kim DI, Byun HS, Lee SK, Huh SH, Hyun WS: Current concepts in lymphatic malformation (LM). Vasc Endovasc Surg 39(1) 67-81, 2005.
69. Jasim ZF, Handley JM. Treatment of pulsed dye laser-resistant port wine stain birthmarks. J Am Acad Dermatol. 2007; 57(4):677-82
70. Kono T, Groff WF, Sakurai H. Treatment of port wine stains with the pulse dye laser. Ann Plast Surg. 2006 Apr;56(4):460-3.
71. Berwald C, Salazard B, Bardot J, Casanova D, Magalon G. Port wine stains or capillary malformations: surgical treatment Ann Chir Plast Esthet. 2006 Aug-Oct;51(4-5):369-72.
72. Frigerio A1, Stevenson DA, Grimmer JF. The genetics of vascular anomalies. Curr Opin Otolaryngol Head Neck Surg. 2012 Dec;20(6):527-32. doi: 10.1097/MOO.0b013e3283587415.
73. Metry D, Heyer G, Hess C, Garzon M, Haggstrom A, Frommelt P, et al. Consensus Statement on Diagnostic Criteria for PHACE Syndrome. Pediatrics. 2009;124(5):1447-56.
74. Haggstrom AN, Garzon MC, Baselga E, Chamlin SL, Frieden IJ, Holland K, et al. Risk for PHACE syndrome in infants with large facial hemangiomas. Pediatrics. 2010;126(2):e418-26.

75. Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic hemangiomas of the airway in association with cutaneous hemangiomas in a "beard" distribution. The Journal of pediatrics. 1997;131(4):643-6.
76. Girard C, Bigorre M, Guillot B, Bessis D. PELVIS Syndrome. Arch Dermatol. 2006;142(7):884-8.
77. Frade F, Kadlub N, Soupre V, Cassier S, Audry G, Vazquez MP, et al. [PELVIS or LUMBAR syndrome: the same entity. Two case reports]. Archives de pediatrie : organe officiel de la Societe francaise de pediatrie. 2012;19(1):55-8.
78. Ghalamkarpour A, Debauche C, Haan E, Van Regemorter N, Sznajer Y, Thomas D, et al. Sporadic in utero generalized edema caused by mutations in the lymphangiogenic genes VEGFR3 and FOXC2. The Journal of pediatrics. 2009;155(1):90-3.
79. Mellor RH, Tate N, Stanton AW, Hubert C, Makinen T, Smith A, et al. Mutations in FOXC2 in Humans (Lymphoedema Distichiasis Syndrome) Cause Lymphatic Dysfunction on Dependency. J Vasc Res. 2011;48(5):397-407.
80. Irrthum A, Karkkainen MJ, Devriendt K, Alitalo K, Vikkula M. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. American journal of human genetics. 2000;67(2):295-301.
81. Lindhurst MJ, Parker VE, Payne F, Sapp JC, Rudge S, Harris J, et al. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA. Nat Genet. 2012;44(8):928-33.
82. Apak H, Celkan T, Ozkan A. et al. Blue rubber bleb nevus syndrome associated with consumption coagulopathy: treatment with interferon. Dermatology 2004;208 (4) 345- 348
83. Sapp JC, Turner JT, van de Kamp JM, van Dijk FS, Lowry RB, Biesecker LG. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. American journal of medical genetics Part A. 2007;143A(24):2944-58.
84. Lee BB, Mattassi R, Choe YH, Vaghi M, Ahn JM, Kim DI, Huh SH, Lee CH, Kim DY. Critical Role of Duplex Ultrasonography for the Advanced Management of a Venous Malformation (VM). Phlebology 2005; 20:28-37.
85. Lee BB, Choe YH, Ahn JM, Do YS, Kim DI, Huh SH, Byun HS. The new role of MRI (Magnetic Resonance Imaging) in the contemporary diagnosis of venous malformation: can it replace angiography? J Am Coll Surg, 198(4):549-558 2004.
86. Wallace MJ, Kuo MD, Glaiberman C, Binkert CA, Orth RC and Soulez G. Three-dimensional C-arm cone-beam CT: applications in the interventional suite. J Vasc Interv Radiol. 2009; 20: S523-37.
87. Redondo P. [Vascular malformations (II). Diagnosis, pathology and treatment]. Actas Dermosifiliogr. 2007 May;98(4):219-35
88. Legiehn GM, Heran MK. A Step-by-Step Practical Approach to Imaging Diagnosis and Interventional Radiologic Therapy in Vascular Malformations. Semin Intervent Radiol. 2010 Jun;27(2):209-31.
89. Lee BB, Laredo J, Lee SJ, Huh SH, Joe JH, Neville R. Congenital vascular malformations: general diagnostic principles. Phlebology. 2007;22(6):253.
90. Lee BB, Mattassi R, Kim BT, Kim DI, Ahn JM, Choi JY. Contemporary diagnosis and management of venous and AV shunting malformation by whole body blood pool scintigraphy (WBBPS). Int Angiol 2004;23:355-67.
91. Lee BB, Mattassi R, Kim BT, Park JM. Advanced management of arteriovenous shunting malformation with Transarterial Lung Perfusion Scintigraphy (TLPS) for follow up assessment. Int Angiol. 24(2) 173-184, 2005.
92. Lee BB & Laredo J: Contemporary role of lymphoscintigraphy: we can no longer afford to ignore! Editorial, Phlebology 2011;26:177–178
93. Trop I, Dubois J, Guibaud L, Grignon A, Patriquin H, McCuaig C, Garel LA. Soft-tissue venous malformations in pediatric and young adult patients: diagnosis with Doppler US. Radiology. 1999 Sep;212(3):841-5.

94. Gold L, Nazarian LN, Johar AS, Rao VM. Characterization of maxillofacial soft tissue vascular anomalies by ultrasound and color Doppler imaging: an adjuvant to computed tomography and magnetic resonance imaging. J Oral Maxillofac Surg 2003;61 (1) 19- 31.
95. Yoshida H, Yusa H, Ueno E. Use of Doppler color flow imaging for differential diagnosis of vascular malformations: a preliminary report. J Oral Maxillofac Surg 1995;53 (4) 369- 374.
96. Laroche JP, Becker F, Khau-Van-Kien A, Baudoin P, Brisot D, Buffler A, CoupéM, Jurus C, Mestre S, Miserey G, Soulier-Sotto V, Tissot A, Viard A, Vignes S,Quéré I. [Quality standards for ultrasonographic assessment of peripheralvascular malformations and vascular tumors. Report of the French Society for vascular medicine]. J Mal Vasc. 2013 Feb;38(1):29-45
97. Dubois J, Patriquin HB, Garel L, Powell J, Filiatrault D, David M, Grignon A. Soft-tissue hemangiomas in infants and children: diagnosis using Doppler sonography. AJR Am J Roentgenol. 1998 Jul;171(1):247-52
98. Offergeld C, Schellong SM, Daniel WG, Huttenbrink KB. Value of color-coded duplex ultrasound in interstitial laser therapy of hemangiomas and vascular malformations Laryngorhinootologie. 1998 Jun;77(6):342-6.
99. McCafferty I.J., Jones R.G. Imaging and management of vascular malformations Clin Radiol 2011 ; 66 : 1208-1218
100. Dubois J., Alison M. Vascular anomalies: what a radiologist needs to know Pediatr Radiol 2010 ; 40:895-905
101. Dubois J., Garel L., Grignon A., David M., Laberge L., Filiatrault D., et al. Imaging of hemangiomas and vascular malformations in children Acad Radiol 1998; 5:390-400
102. Gloviczki P, Stanson AW, Stickler GB, Johnson CM, Toomey BJ, Meland NB, Rooke TW, Cherry KJ Jr. Klippel-Trenaunay syndrome: the risks and benefits of vascular interventions. Surgery. 1991 Sep;110(3):469-79.
103. Puig S, Casati B, Staudenherz A, Paya K. Vascular low-flow malformations in children: current concepts for classification,diagnosis and therapy. Eur J Radiol 2005 Jan;53(1):35-45
104. Park KB, Do YS, Lee BB, Kim DI, Wook Kim Y, Shin BS, et al. Predictive factors for response of peripheral arteriovenous malformations to embolization therapy:analysis of clinical data and imaging findings. J Vasc Interv Radiol. 2012Nov;23(11):1478-86.
105. Lee BB, Laredo J. Editorial. Venous malformation: treatment needs a bird's eye view. Phlebology 2013;28:62–63
106. Lee BB, Laredo J: Chapter 63. Venous Malformation and Tumors: Etiology, Diagnosis, and Managment. Part V. Congenital Venous Abnormalities. Page 541-548, The Vein Book. John J.Bergan and Nisha Bunke-Paquette (Eds), 2014, 2nd Edition, Oxford University Press, New York, NY, USA
107. Lee BB, Baumgartner I: Contemporary diagnosis of venous malformation. Journal of Vascular Diagnostics 2013:1 25–34
108. Gorenstein A, Shifrin E, Gordon RL, Katz S, Schiller M. Congenital aplasia of the deep veins of lower extremities in children: the role of ascending functional phlebography. Surgery. 1986 Apr;99(4):414-20.
109. Friedman EI, Taylor LM Jr, Porter JM. Congenital venous valvular aplasia of the lower extremities. Surgery. 1988 Jan;103(1):24-6.
110. Villavicencio JL, Gillespie DL, Eifert S. Venous Aneurysms: Presentation and Treatment. In: Current Therapy in Vascular Surgery, 4th Edition. Ernst CB, Stanley JC (Eds), Mosby Publ, Philadelphia, PA, 1999.
111. Zamboni P, Cossu A., Carpanese L.,Simonetti G., Massarelli G. Liboni A. The so-called venous aneurysms. Phlebology 1990;5:45-50.
112. Friedman SG, Krishnasastry KV, Doscher W, Deckoff SL; Primary venous aneurysms. Surgery 1990;108:92-5.
113. Maleti O, Lugli M, Collura M. Anévrysmes veineux poplités:expérience personnelle. Phlebologie 1997;50:53-9.

114. Katz ML, Comerota AJ. Diagnosis of a popliteal venous aneurysm by venous duplex imaging. J Ultrasound Med 1991;10:171-3
115. Lee BB. Invited Commentary on "Comments regarding 'Surgical Treatment of Patients with Congenital Vascular Malformation-associated Aneurysms'. Eur J Vasc Endovasc Surg (2011) 42, 523e524
116. Loose DA Die chirurgische Therapie venöser Aneurysmata. Gefässchirurgie 2005;6,143-150
117. Menegatti E, Zamboni P. Doppler haemodynamics of cerebral venous return. Curr Neurovasc Res. 2008 Nov;5(4):260-5.
118. Valdueza JM, von Munster T, Hoffman O, Schreiber S, Einhaupl KM. Postural dependency of the cerebral venous outflow. Lancet 2000 Jan 15;355(9199):200-1.
119. Schreiber SJ, et al Extrajugular pathways of human cerebral venous blood drainage assessed by duplex ultrasound. J Appl Physiol. 2003 May;94(5):1802-5.
120. Nedelmann M, Kaps M, Mueller-Forell W. Venous obstruction and jugular valve insufficiency in idiopathic intracranial hypertension. J Neurol. 2009 Mar 1.
121. Bush S, Khan R, Stringer M. Anterior jugular venous aneurysm. Eur J Pediatr Surg. 1999 Feb;9(1):47-8.
122. Ilijevski NS, Radak S, Novakovic B, Miholjcic A, Radak D. Images in vascular medicine. Jugular vein aneurysm--ultrasonographic evaluation. Vasc Med. 2006 Feb;11(1):51.
123. Loose DA. Die Chirurgie der Marginalvene. In: Loose DA, Weber J(eds.). Angeborene Gafaessmissbildungen; pp 230-244. Verlag Norlanddruck Lueneburg,1997
124. Vollmar JF, Voss E, Vena marginalis lateralis persistens- Die vergessene Vene der Angiologen. VASA 1979; 8.192-202
125. Weber J, Daffinger N, Congenital vascular malformations: the persistence of marginal and embryonal veinbs; VASA 2008; 35:67-77
126. Lee BB. Marginal Vein is Not A Simple Varicose Vein: It is A Silent Killer! Review. Damar Cer Derg 2013;22(1):4-14
127. Kim YW, Lee BB, Cho JH, Do YS, Kim DI, Kim ES. Haemodynamic and clinical assessment of lateral marginal vein excision in patients with a predominantly venous malformation of the lower extremity. Eur J Vasc Endovasc Surg. 2007 Jan;33(1):122-7
128. Christopoulos D, Nicolaides AN, Szendro G. Venous reflux: quantification and correlation with the clinical severity of chronic venous disease. Br J Surg. 1988;75:352–356
129. Weber J. Invasive Diagnostik angeborene Gefaessfehler (Invasive diagnostic of CVM). In: Loose DA, Weber J, eds. Angeborene Gefaessmissbildungen. Lueneburg: Verlag Nordlandddruck Gmbh, 1997;127–63
130. Kenneth J, Cherry Jr, Gloviczki P, Stanson W: (1996) Persistent sciatic vein: diagnosis and treatment of a rare condition. J Vasc Surg 23 (3): 490 – 497
131. Trigaux J: Vanbeers B, Delchambre F, de Fays F, Schoevaerdts J: (1989) Sciatic venous drainage demonstrated by varicography in patients with a patent deep venous system. Cardiovasc Intervent Radiol 12: 103 – 106
132. Hamilton, HEC, Drake SG.: (1999) Persistent sciatic vein – unusual case of reflux from the popliteal fossa and sural nerve damage.Eur J Vasc Endovasc Surg 17: 539 – 541
133. Lee BB: Lymphedema-Angiodysplasia Syndrome: a Prodigal form of Lymphatic Malformation (LM). Phlebolymphology, 47:324-332, 2005.
134. Lee BB: Current issue on the contemporary management of chronic lymphedema. Editorial, Lymphology, March, 2005.
135. Lee BB: Lymphedema-Diagnosis and Treatment. Tredbar, Morgan, Lee, Simonian, Blondeau (eds) Chapter 4. Lymphatic Malformation, Pages 31-42. Springer-Verlag London Limited 2008.
136. Lee BB, Antignani PL, Baroncelli TA, Boccardo FM, Brorson H, Campisi C, Damstra RJ, Flour M, Giannoukas A, Laredo J, Liu NF, Michelini S, Piller N, Rockson SG, Scuderi A, Szolnoky G, Yamamoto T. IUA-ISVI consensus for diagnosis guideline of chronic lymphedema of the limbs. In printing on Int. Angiol. 2014

137. Lee BB, Laredo J, Neville R, Mattassi R: Primary lymphedema and Klippel-Trenaunay syndrome. Chapter 52. Section XI - Lymphedema and Congenital Vascular Malformation. Page 427-436, LYMPHEDEMA: A Concise Compendium of Theory and Practice. Lee, Byung-Boong; Bergan, John; Rockson, Stanley G. (Eds.), 1st Edition, Springer-Verlag, London, UK, 2011
138. Lee BB, Laredo J, Neville R:. Primary lymphedema as a truncular lymphatic malformation. Chapter 51, Section XI - Lymphedema and Congenital Vascular Malformation Page 419-426, LYMPHEDEMA: A Concise Compendium of Theory and Practice. Lee, Byung-Boong; Bergan, John; Rockson, Stanley G. (Eds.), 1st Edition, Springer-Verlag, London, UK, 2011
139. Kim W, Chung SG, Kim TW, Seo KS. Measurement of soft tissue compliance with pressure using ultrasonography. Lymphology. 2008;41(4):167-177.
140. Matter D, Grosshans E, Muller J, et al. Apport de l'échographie à l'imagerie des vaisseaux lymphatiques par rapport aux autres méthodes. J Radiol. 2002;83:599-60
141. Gniadecka M. Localization of dermal edema in lipodermatosclerosis, lymphedema and cardiac insufficiency: high-frequency ultrasound examination of intradermal echogenicity. J Am Acad Dermatol 1996;35:37-41
142. Ayres AW, Pugh SK. Ex utero intrapartum treatment for fetal oropharyngeal cyst. Obstet Gynecol Int. 2010;2010:273410. doi: 10.1155/2010/273410. Epub 2010 Jan 20.
143. Stefini S, Bazzana T, Smussi C, Piccioni M, Frusca T, Taddei F, Tomasoni G, Recupero D, Cavazza A, Villani P, Nicolai P, Eivazi B, Wiegand S, Werner JA, Schmidt S, Maier RF, Torossian A. EXIT (Ex utero Intrapartum Treatment) in lymphatic malformations of the head and neck: discussion of three cases and proposal of an EXIT-TTP (Team Time Procedure) list. Int J Pediatr Otorhinolaryngol. 2012 Jan;76(1):20-7.
144. Brorson H. Liposuction in arm lymphedema treatment. Scand J Surg. 2003;92(4):287-95.
145. Brorson H. Liposuction gives complete reduction of chronic large arm lymphedema after breast cancer. Acta Oncol. 2000;39(3):407-20.
146. Szuba A, Rockson SG.Lymphedema: classification, diagnosis and therapy. Vasc Med. 1998;3(2):145-56.
147. Antignani PL, Benedetti Valentini F, Aluigi L, baroncelli T et al. Guidelines of Italian Society for vascular Investigation. Int Angiol. 2012; 5:1-78
148. Paltiel H J, Burrows P E, Kozakewich H P, Zurakowski D, Mulliken J B. Soft-tissue vascular anomalies: utility of US for diagnosis. Radiology. 2000;214:747–754.
149. Trop I, Dubois J, Guibaud L, et al. Soft-tissue venous malformations in pediatric and young adult patients: diagnosis with Doppler US. Radiology. 1999;212:841–845.
150. Yamamoto H, Yamamoto F, Ishibashi K, Yamaura G, Shiroto K, Motokawa M, Tanaka F. Intermediate and long-term outcomes after treating symptomatic persistent sciatic artery using different techniques. Ann Vasc Surg. 2011Aug;25(6):837.e9-15
151. Wang B, Liu Z, Shen L. Bilateral persistent sciatic arteries complicated with chronic lower limb ischemia. Int J Surg Case Rep. 2011;2(8):309-12.
152. Patel MV, Patel NH, Schneider JR, Kim S, Verta MJ. Persistent sciatic artery presenting with limb ischemia. J Vasc Surg. 2013 Jan;57(1):225-9.
153. Vaghi M, Mattassi R, Tacconi A, Persistence of sciatic artery:case report, In: Belov St, Loose DA, Weber ,J,(eds.) Vascular Malformations,1989,pp132-135, Einhorn Presse Verlag Reinbek/Hamburg
154. Altstaedt HO, Teisinger P, Persistent sciatic artery: a case report and overview of literature, In:Belov St, Loose DA, Weber J.(eds.) Vascular Malformations,1989, pp125-131,Einhorn Presse Verlag,Reinbek/Hamburg
155. JL Villavicencio The desperate plea of women with the nutcracker syndrome Phlebologie 2010;39:1-8
156. Takebayashi S, Ueki T, Ikeda N Diagnosis of the nutcracker syndrome with color Doppler sonography : correlation with flow patterns on retrograde left renal venography.Am J Roentgenology 1999; 172: 29-43

157. Rudloff U, Holmes RJ, Jeffrey T Prem, Glenn RF, Moldwin R , Siegel D Mesoaortic compression of the left renal vein : case reports and review of the literature Ann Vasc Surg 2006;20:120-129
158. Cho KJ, Stanley JC. Non neoplastic congenital and acquired renal arterio-venous malformations and fistulas. Radiology 1978;129:333-343
159. Naganuma H, Ishida H, Konno K, Sato M, Ishida J, Komatsuda T, Sato A, Watanabe S. Renal arteriovenous malformation: sonographic findings Abdom Imaging. 2001 NovDec; 26(6):661-3
160. Cura M, Elmerhi F, Suri R, Bugnone A, Dalsaso T. Vascular malformations and arteriovenous fistulas of the kidney. Acta Radiol. 2010 Mar;51(2):144-9
161. Patiño-Seijas B, Lorenzo-Franco F, Rey-Sanjurjo JL, González-Cuesta M, López-Cedrún Cembranos JL. Vascular Lesions: GLUT-1 expression as a diagnostic tool to discriminate tumors from malformations.J Oral Maxillofac Surg. 2012 Oct;70(10):2333-42.
162. North PE, Waner M, Mizeracki A, et al. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol 2000;31: 11–22
163. Benoit M.M., North P.E., McKenna M.J., et al Facial nerve hemangiomas: Vascular tumors or malformations? Otolaryngol Head Neck Surg, 142 (2010), p. 108.
164. Rössler J, Haubold M, Gilsbach R, Jüttner E, Schmitt D, Niemeyer C and Hein L. β1-Adrenoceptor mRNA level reveals distinctions between infantile hemangioma and vascular malformations.Pediatric Research V73. N4. April 2013. Nature Publishing Group.
165. Lee BB, Villavicencio L, Kim YW, et al. Primary Budd-Chiari syndrome: outcome of endovascular management for suprahepatic venous obstruction. J Vasc Surg 2006;43:101-10
166. Valla DC. Primary Budd-Chiari syndrome. J Hepatol. 2009 Jan;50(1):195-203.
167. Zamboni P, Pisano L, Mari C, Galeotti R, Feo C, Liboni A. Membranous obstruction of the inferior vena cava and Budd-Chiari syndrome. Report of a case. J Cardiovasc Surg (Torino). 1996 Dec;37(6):583-7.
168. Guttmacher, A.E., Marchuk, D.A., White, R.I., 1995. Hereditary hemorrhagic telagiectasia. N. Engl. J. Med. 333, 918_924.
169. Johnson, D.W., Berg, J.N., Baldwin, M.A. et al., 1996. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nat. Genet. 13, 189_195.
170. Abdalla S.A., Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. *J. Med. Genet.* 2006*;*43*:*97-110.
171. Dubois J, Garel L. Imaging and therapeutic approach of hemangiomas and vascular malformations in the pediatric age group. Pediatr Radiol. 1999;29:879–893.
172. Konez O, Hopkins KL, Burrows PE. Pediatric techniques and vascular anomalies. In CT and MR Angiography. Rubin GD, Rofosky NM. 1118-1187. Lippincott, 2009.
173. Legiehn GM, Heran MK. Classification, diagnosis, and interventional radiologic management of vascular malformations. Orthop Clin North Am. 2006;37(3):435-74
174. Navarro OM, Laffan EE, Ngan BY. Pediatric soft tissue tumors and pseudotumors: MR imaging features with pathologic correlation. I. Imaging approach, pseudotumors, vascular lesions, and adipo-cystic tumors. Radiographics. 2009; 29(3): 887-906
175. Stepansky F, Hecht EM, Rivera R, et al. Dynamic MR angiography of upper extremity vascular disease: pictorial review. Radiographics 2008;28
176. Wenzel R, Wegener OH, Computertomographie und Kernspintomographie bei Gefäßmalformationen. In: Loose DA, Weber J (eds.) Angeborene Gefaessmissbildungen; 1997;Nordlanddruck,Lueneburg
177. Moukaddam H, Pollak J, Haims AH. MRI characteristics and classification of peripheral vascular malformations and tumors. Skeletal Radiol 2009;38(6):535–547.
178. Rak KM, Yakes WF, Ray RL, Dreisbach JN, Parker SH, Luethke JM, Stavros AT, Slater DD, Burke BJ. MR imaging of symptomatic peripheral vascular malformations. AJR Am J Roentgenol. 1992;159(1):107-12.
179. Meyer JS, Hoffer FA, Barnes PD, Mulliken J. Biological classification of soft-tissue vascular anomalies: MR correlation. AJR Am J Roentgenol. 1991;157(3):559-64.

180. Van Rijswijk CS, van der Linden E, van der Woude HJ, van Baalen JM, Bloem JL.Value of dynamic contrast-enhanced MR imaging in diagnosing and classifying peripheral vascular malformations. AJR Am J Roentgenol. 2002 ;178(5):1181-7.
181. Konez O, Burrows PE. Magnetic resonance of vascular anomalies. Magn Reson Imaging Clin N Am. 2002;10(2):363-88
182. Goyal M, Causer PA, Armstrong D. Venous vascular malformations in pediatric patients: comparison of results of alcohol sclerotherapy with proposed MR imaging classification. Radiology. 2002;223(3):639-44.
183. Gloviczki P, Driscoll DJ. Klippel–Trenaunay syndrome: current management. Phlebology. 2007; 22: 291–298.
184. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc. 1998;73(1):28-36.
185. Consensus document of the International Society of Lymphology Executive Committee. The diagnosis and treatment of peripheral lymphedema. Lymphology 1995; 28(3):113–17.
186. Werner GT, Rodiek SO. Value of nuclear magnetic resonance tomography in leg edema of unknown origin. Preliminary report. Z Lymphol 1993;17(1):2–5.
187. Case TC, Witte CL, Witte MH, et al. Magnetic resonance imaging in human lymphedema: comparison with lymphangioscintigraphy. Magn Reson Imaging 1992;10:549-558.
188. Fayad L.M, Hazirolan T, Bluemke D, Mitchell S. Vascular malformations in the extremities: emphasis on MR imaging features that guide treatment options Skeletal Radiol, 35 (2006), pp. 127–137.
189. Konez O, Burrows P.E. An appropriate diagnostic workup for suspected vascular birthmarks Cleve Clin J Med, 71 (Jun 2004), pp. 505–510.
190. Abernethy LJ. Classification and imaging of vascular malformations in children. Eur Radiol 2003;13(11):2483–2497.
191. Dubois J, Soulez G, Oliva VL, Berthiaume MJ,Lapierre C, Therasse E. Soft-tissue venous malformationsin adult patients: imaging and therapeuticissues. RadioGraphics 2001;21(6):1519–1531
192. Barnes PD, Burrows PE, Hoffer FA, et al. Hemangiomas and vascular malformations of the head and neck: MR characterization. AJNR Am J Neuroradiol 1994;15(1):193-5.
193. Enjolras O, Wassef M, Mazoyer E, et al. Infants with Kasabach-Merritt syndrome do not have "true" hemangiomas. J Pediatr. 1997;130(4):631-640.
194. el-Dessouky M, Azmy A, Raine P, Young D (1988). "Kasabach–Merritt syndrome". J Pediatr Surg 23 (2): 109–11.
195. Khaled M. Elsayes KM, Menias CO, Dillman JR, Platt JF, Willatt JM and Heiken JP Vascular Malformation and Hemangiomatosis Syndromes: Spectrum of Imaging Manifestations. AJR 2008; 190:1291-1299.
196. Elsayes KM, Menias CO, Dillman JR, Platt JF, Willatt JM, Heiken JP. Vascular malformation and hemangiomatosis syndromes: spectrum of imaging manifestations. Am J Roentgenol. 2008 May;190(5):1291-9.
197. Hyodoh H, Hori M, Akiba H, Tamakawa M, Hyodoh K and Hareyama M. Peripheral Vascular Malformations: Imaging, Treatment Approaches, and Therapeutic Issues. RadioGraphics 2005;25:S159-S171.
198. Rauch RF, Silverman PM, Korobkin M et al. Computed tomography of benign angiomatous lesions of the extremities. J Comput Assist Tomogr 1984; 8:1143-46.
199. Lidsky M, Spritzer C, and Shortell C. The role of dynamic contrast-enhanced magnetic resonance imaging in the diagnosis and management of patients with vascular malformations. J Vasc Surg. I 2011;53(1):131-137.
200. Burrows PE, Mulliken JB, Fellows KE, Strand RD. Childhood hemangiomas and vascular malformations: angiographic differentiation. AJR Am J Roentgenol. 1983;141(3):483-8.
201. Belov St, Hemodynamic pathogenesis of vascular bone-syndromes in congenital vascular defects. Inter Angio 1990; 9:175-182

202. Mattassi R, Vaghi M: Vascular bone syndrome-angi-osteodystrophy : Current Concept. Phlebology. 2007; 22: 287-290.
203. Belov S.Correction of lower limbs length discrepancy in congenital vascular-bone diseases by vascular surgery performed during childhood. Semin Vasc Surg. 1993 Dec;6(4):245-51.
204. Weber J, Phlebographie. Bein-, Becken- und Abdominalvenen in Anatomie und Funktion.Rabe Verlag,Bonn 2010;327-348
205. Rutherford RB. Congenital vascular malformations: diagnostic evaluation. Seminars in Vascular Surgery 1993;6:225-232.
206. Puig S, ArefH, Chigot V, Bonin B, Brunelle F. Classification of venous malformations in children and implications for sclerotherapy. Pediatr Radiol 2003;33:99–103.
207. Alomari A. Diversion Venography A modified Technique In Klippel Trenaunay syndrome. Initial experience. J Vasc Interv Radiology 2010;21:685-689
208. Campisi C, Bellini C, Eretta C, Zilli A, da Rin E, Davini D, Bonioli E, Boccardo F. Diagnosis and management of primary chylous ascites. J Vasc Surg. 2006;43(6):1244-8.
209. Boccardo F, Bellini C, Eretta C, Pertile D, Da Rin E, Benatti E, Campisi M, Talamo G, Macciò A, Campisi C, Bonioli E, Campisi C. The lymphatics in the pathophysiology of thoracic and abdominal surgical pathology: immunological consequences and the unexpected role of microsurgery. Microsurgery. 2007;27(4):339-45.
210. Nadolski GJ, Itkin M. Feasibility of ultrasound-guided intranodal lymphangiogram for thoracic duct embolization. J Vasc Interv Radiol. 2012 May;23(5):613-6.
211. Rajebi MR, Chaudry G, Padua HM, Dillon B, Yilmaz S, Arnold RW, Landrigan-Ossar MF, Alomari AI. Intranodal lymphangiography: feasibility and preliminary experience in children. J Vasc Interv Radiol. 2011 Sep;22(9):1300-5
212. Dentici R, Mattasi R, Vaghi M. La diagnostica per immagini in medicina nucleare. Capitolo 19. In: Mattassi , Belov S, Loose DA, VaghiM (eds). pp 32-39. Malformaziono vascolari ed emangiomi. Testo-atlantie di diagnostica e terapia, Springer-Verlag, Milano, Italy
213. Lee BB, Kim BT, Choi JY, Cazaubon M: Prise en charge des malformations vasculaires congénitales (MVC) en 2003: rôle de la scintigraphy corps entier dans las surveillance évolutive. Angeiologie 55(3): 17-26, 2003.
214. Hollerman JJ, Bernstein MA, Froelich JW, Schkudor G. Detection of hemangiomas using whole-body imaging with technetium-99m labeled RBCs. Clin Nucl Med. 1986 Oct;11(10):716-7.
215. Fukuda Y, Murata Y, Umehara I, Yamashita T, Ono C, Iwai T, Shibuya H. Perfusion and blood pool scintigraphy for diagnosing soft-tissue arteriovenous malformations. Clin Nucl Med. 1999 Apr;24(4):232-4.
216. Inoue Y, Wakita S, Ohtake T, Ohkubo T, Hayashi N, Nishikawa J, Sasaki Y. Use of whole-body imaging using Tc-99m RBC in patients with soft-tissue vascular lesions. Clin Nucl Med. 1996 Dec;21(12):958-9.
217. Front D, Israel O, Groshar D, Weininger J. Technetium-99m-labeled red blood cell imaging. Semin Nucl Med. 1984 Jul;14(3):226-50.
218. Vaisnyte B, Vajauskas D,Nevidomskyte D, Misonis N, Palionis D, Kurminas M,Mataciunas M, Arteriovenous malformations treatment strategies based on transarterial lung perfusion scintigraphy(TLPS) Communication at the 19th Int.Workshop on Vascular Anomalies, June 16.-19.2012,Malmö Sweden
219. Pecking AP, Alberini JL, Wartski M, Edeline V, Cluzan RV. Relationship between lymphoscintigraphy and clinical findings in lower limb lymphedema: towards a comprehensive staging Lymphology. 2008;41:1-10.
220. Fukuda Y, Murata Y, Umehara I, Yamashita T, Ono C, Iwai T Perfusion and blood pool scintigraphy for diagnosing soft-tissue arteriovenous malformations. Clin Nucl Med 1999;24:232-4.
221. Bourgeois P, Munck D, Becker C, Leduc O, Leduc A. Reevaluation of a three-phase lymphoscintigraphic investigation protocol for the lower limb-edemas. Eur J Lymphology Relat Probl.1996;6:10-21.

222. Pui MH, Yueh TC. Lymphoscintigraphy in chyluria, chyloperitoneum and chylothorax. J Nucl Med. 1998;39:1292-1296.
223. Bellini C, Boccardo F, Campisi C, Villa G, Taddei G, Traggiai C, Bonioli E. Lymphatic dysplasias in newborns and children: the role of lymphoscintigraphy. J Pediatr. 2008;152(4):587-9.
224. Celebioglu F, Perbeck L, Frisell J, Gröndal E, Svensson L, Danielsson R :Lymph Drainage Studied by Lymphoscintigraphy in the Arms after Sentinel Node Biopsy Compared with Axillary LymphNode Dissection Following Conservative Breast Cancer Surgery. Acta Radiologica: Vol. 48(5), 488-495, 2007
225. Cambria RA, Gloviczki P, Naessens JM, Wahner HW. Noninvasive evaluation of the lymphatic system with lymphoscintigraphy: a prospective, semiquantitative analysis in 386 extremities. J Vasc Surg. 1993;18:773-82.
226. Choi JY, Hwang JH, Park JM, Kim DI, Lee BB, Kim BT: Risk assessment of dermatolymphangioadenitis by lymphoscintigraphy in patients with lower extremity lymphedema. Korean J Nucl Med, 33(2):143-151, 1999.
227. Szuba A, Strauss W, Sirsikar SP, Rockson SG. Quantitative radionuclide lymphoscintigraphy predicts outcome of manual lymphatic therapy in breast cancer-related lymphedema of the upper extremity. Nucl Med Commun. 2002;23:1171-5.
228. Solari N, Gipponi M, Stella M, Queirolo P, di Somma, et al: Predictive role of preoperative lymphoscintigraphy on the status of the sentinel lymph node in clinically node-negative patients with cutaneous melanoma. Melanoma Research: Vol 19 (4): pp 243-251, 2009
229. Gloviczki P, Calcagno D, Schirger A, et al. Noninvasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphy examinations. J Vasc Surg. 1989;9:683-9; discussion 690.
230. Lee BB, Bergan, JJ: New Clinical and Laboratory Staging Systems to Improve Management of Chronic Lymphedema. Lymphology 38 (3):122-129, 2005.
231. Lee BB, Laredo J. Classification: Venous-Lymphatic Vascular Malformation. Chapter 21, Part 3, Page 91-94. News in Phlebology, C.Allegra, P.L. Antignani, E. Kalodiki (Eds). Edizioni Minerva Medica 2013, Turin, Italy
232. Kasabach HH, Merritt KK. Capillary hemangioma with extensive purpura: report of a case. Am J Dis Child 1940;59:1063–1070
233. Mazoyer E, Enjolras O, Laurian C et al. Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach–Merritt syndrome. Clin Lab Haematol. 2002; 24:243–51.
234. Sarkar M, Mulliken JB, Kozakewich HPW, et al. Thrombocytopaenic coagulopathy (Kasabach-Merritt Phenomenon) is associated with Kaposiform hemangioendothelioma and not with common infantile hemangioma. Plast. Reconstr. Surg. 1997; 100: 1377–86.
235. Dompmartin A, Acher A, Thibon P, et al. Association of localized intravascular coagulopathy with venous malformations. Arch. Dermatol. 2008; 144: 873–7.
236. Dompmartin A, Ballieux F, Thibon P, et al. Elevated D-dimer level in the differential diagnosis of venous malformations. Arch Dermatol 2009;145:1239-44.
237. Dompmartin A, Vikkula M, Boon M. Venous malformation: update on aetiopathogenesis, diagnosis and management. Phlebology. 2010;25:224–235.
238. Wouters V, Limaye N, Uebelhoer M, Irrthum A, Boon LM, Mulliken JB, et al. Hereditary cutaneomucosal venous malformations are caused by TIE2 mutations with widely variable hyper-phosphorylating effects. European journal of human genetics : EJHG. 2010;18(4):414-20.
239. Blumenthal GM, Dennis PA. PTEN hamartoma tumor syndromes. European journal of human genetics: EJHG. 2008;16(11):1289-300.
240. Eerola I, Boon LM, Mulliken JB, Burrows PE, Dompmartin A, Watanabe S, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. American journal of human genetics. 2003;73(6):1240-9.

241. Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013;368(21):1971-9.
242. Lindhurst MJ, Wang JA, Bloomhardt HM, Witkowski AM, Singh LN, Bick DP, et al. AKT1 Gene Mutation Levels Are Correlated with the Type of Dermatologic Lesions in Patients with Proteus Syndrome. J Invest Dermatol. 2013.

Appendix A. Ratings of the quality of evidence and grading recommendation system used in the Consensus:

Grading Recommendations According to Evidence[1] (Chest, 2006;129:174-181.)

Grade of Recommendation/Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patient in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or	Strong recommendation, can apply to most patient in most circumstances without reservation

		imprecise) or exceptionally strong evidence from observational studies	
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Appendix B. Abbreviations

AVM	Arteriovenous Malformation
CM	Capillary Malformation
CT	Computed Tomography
CVM	Congenital Vascular Malformation
CW-Doppler	Continuous Wave Doppler
DUS	Duplex Ultrasound
GLUT-1	Glucose Transporter-1
GVM	Glomovenous Malformation
HHT	Hereditary Hemorrhagic Telangiectasias
HOI	Hemagioma of Infancy
KHE	Kaposiform Hemangioendothelioma
KTS	Klippel-Trenaunay Syndrome
LM	Lymphatic Malformation
MRI	Magnetic Resonance Imaging
NICH	Non-involuting Congenital Hemangioma
RICH	Rapidly Involuting Congenital Hemangioma
VM	Venous Malformation

Appendix C. Genetic Mutations in Vascular Anomalies

Syndrome Clinical Manifestations	Genetic Mutation (Reference)
Cutaneous and/or Cutaneomucosal Venous	Tie-2 activating mutation
Malformations	Germline mutation
	Wouters et al, 2010 (1)
Hereditary Hemorrhagic Telangiectasia (HHT)	HHT1 - Endoglin
Multifocal arteriovenous malformations	HHT2 - ALK-1 (ACVRL-1)
Punctate small AVMS in skin, mucous membranes;	HHT + juvenile polyposis MADH4
larger AVMS in lungs, liver, and brain	Germline mutation
Epistaxis, gastrointestinal and intra-oral bleeding	
	McDonald et al (2)
PTEN Hamartoma Syndrome	PTEN mutation
Arteriovenous malformation/thyroid	Germline mutation
disorders/tricholemmas/cancer predisposition	
	Tan, et al 2007;Blumenthal et al, 2008
	(3, 4)

Arteriovenous malformation/capillary malformation	RASA-1 mutation Germline mutation
Arteriovenous malformation with multiple cutaneous capillary malformations	Germline mutation (5)
Glomuvenous malformation	Glomulin Gene mutation
Multifocal nodular, or plaque-like and segmental, variable color (pink, purple, dark blue)	(6)
CLOVE Syndrome **C**ongenital **L**ipomatous **O**vergrowth (fatty truncal mass), **V**ascular **M**alformations, **E**pidermal nevi +/- renal, orthopedic anomalies	PIK3CA somatic mutation Kurek et al (7)
Capillary malformation	GNAQ somatic mutation Shirley et al (8)
Proteus Syndrome	AKT1 somatic mutation Lindhurst el al 2001&2013 (9, 10)
Capillary Malformation Microcephaly	STAMBP (**S**ignal-**T**ransducing **A**daptor **M**olecule **B**inding **P**rotein) 2p13.1 McDonell et al 2013 (11)
Lymphedema	Many genes – see below Connell et al 2013 (12)

Appendix D. Genetic Mutations in Lymphedema Syndromes

Syndrome	Clinical Features	Genetic Information (Reference)
Turner Syndrome	Short stature, broad chest, widely spaced nipples, skeletal and endocrine abnormalities, congenital lymphedema, infertility	XO
Noonan's Syndrome	Lymphedema, characteristic facies webbed neck, cardiac skeletal, ophthalmologic, hematologic, neurologic abnormalities	Sporadic or autosomal dominant genetic heterogeneity mutations of genes involved in RAS-mitogen-activated protein kinases (MAPK) signal transduction pathway PTPN11 (Protein-Tyrosine Phosphatase, Nonreceptor-Type, 11) 12q24.1 SOS1, RAF1, KRAS, MEK1 (MAP2K1), NRAS, BRAF, SHOC2, CBL Tartaglia, et al (13, 14)
Klinefelter Syndrome	Tall stature, sparse facial and body hair, taurodontism,	XXY

	lymphedema, gynecomastia, microorchidism, sterility, autoimmune disorders, emotional and learning disorders.	
Primary congenital lymphedema		Autosomal Recessive Chr 5q35.3 Flt4 (VEGFR3 mutation) Ghalamkarpour, et al (15, 16)
Hereditary Lymphedema Type IA Nonne-Milroy Lymphedema Milroy Disease Primary Congenital Lymphedema; PCL	Early onset lymphedema	Autosomal Dominant, or sporadic (de novo) Chr 5q35.3 Heterozygous mutations in kinase domain of VEGFR3 Ghalamkarpour, et al Karkkainen, et al Irrthum, et al (16-18)
Lymphedema type IB (LMPH1B; 611944) locus on chromosome	Onset occurred in early childhood, maximum manifestations at puberty, lower limb lymphedema	Autosomal Dominant Chr 6q16.2-q22.1 Malik, et al (19)
Hereditary lymphedema, Type IC	early onset, between 0 and 20 years of age, lower limb lymphedema, then upper lim	Chr 1q41-q42 GJC2 gene mutation(Gap Junction Protein, Gamma-2 Connexin 47) Ferrel, et al (20)
Primary non-syndromic lymphedema (Meige disease; Lymphedema Praecox) Hereditary lymphedema type I	peripubertal onset lymphedema Female predominance	Familial however gene mutation not yet identified
Recessive primary congenital lymphedema	pubertal or later onset lymphedema	VEGFR3 mutation Ghalamkarpour, et al (16)
Lymphedema-Distichiasis Syndrome	lower-limb lymphedema, often asymmetric, peripubertal onset, distichiasis (anomalous eyelashes - double set or a single hair), cardiac defects, cleft palate, extradural cysts,	Autosomal Dominant Chr 16q24.3 FOXC2

	and photophobia, early onset varicose veins	Brice, et al, Fabretto et al, Fauret et al, Mellor, et al (21-24)
Hypotrichosis-lymphedema-telangiectasia (HLTS)	Leg lymphedema, telangiectasias	Autosomal recessive or dominant Chr 20q13.33 SOX18 Irrthum, et al, Downs et al (25, 26)
Microcephaly Lymphedema Chorioretinopathy Syndrome	Microcephaly, microphthalmos, +/- non-inflammatory chorioretinopathy, +/- menta retardation, lymphedema	Autosomal Recessive Chr 10q23.33 KIF11 (Kinesin Family Member 11) Ostergaard, et al, Hazan, et al (27, 28)
Emberger Syndrome	Myelodysplasia (+/- monosomy 7-)□ acute myeloid leukaemia (AML), primary lymphedema, +/- warts, deafness, mild hypotelorism, webbed neck, thin fingers	Familial reports Chr 3q21.3 GATA2 Mansour, et al (29)
Epidermodysplasia verruciformi (WILD Syndrome)	**W**arts, cell-mediated **I**mmunodeficiency, **L**ymphedema, anogenital **D**ysplasia	Human Papilloma Virus-associated Kreuter, et al (30)
Lymphedema-lymphangiectasia mental retardation (Hennekam) syndrome	Lymphedema, lymphangiectasia, developmental delay, flat face, flat, broad nasal bridge, hypertelorism, glaucoma, dental anomalies, hearing loss, renal anomalies	Chr 18q21.32 CCBE1 gene (Collagen And Calcium-Binding EGF Domain-Containing Protein 1) Hennekam et al, VanBalkom, et al, Alders, et al (31-33)
Yellow nail syndrome	Chronic sinusitis, bronchiectasis/pleural effusion, yellow nails (distinctive appearance from	N/A

	lymphedema-associated yellow nails)	
Lymphedema-cholestasis syndrome (Aagenaes syndrome)	Severe neonatal cholestasis, chronic extremity lymphedema	Chr 15q Bull et al, Fruhwirth et al (34, 35)
Osteopetrosis, lymphedema, hypohidrotic ectodermal dysplasia, and immunodeficienc (OL-HED-ID)	osteopetrosis, lymphedema, hypohidrotic ectodermal dysplasia, immunodeficiency	Chr Xq28 Nemo (NF-Kappa-B Essential Modulator) Gene Mutation Roberts et al (36)
Stewart-Treves syndrome	Lymphangiosarcoma in chronic lymphedema	Durr, et al, Komorowski, et al (37, 38)

References for Appendix C and D:

1. Wouters V, Limaye N, Uebelhoer M, Irrthum A, Boon LM, Mulliken JB, et al. Hereditary cutaneomucosal venous malformations are caused by TIE2 mutations with widely variable hyper-phosphorylating effects. European journal of human genetics : EJHG. 2010;18(4):414-20.
2. McDonald J, Bayrak-Toydemir P, Pyeritz RE. Hereditary hemorrhagic telangiectasia: an overview of diagnosis, management, and pathogenesis. Genetics in medicine : official journal of the American College of Medical Genetics. 2011;13(7):607-16.
3. Tan WH, Baris HN, Burrows PE, Robson CD, Alomari AI, Mulliken JB, et al. The spectrum of vascular anomalies in patients with PTEN mutations: implications for diagnosis and management. Journal of medical genetics. 2007;44(9):594-602.
4. Blumenthal GM, Dennis PA. PTEN hamartoma tumor syndromes. European journal of human genetics : EJHG. 2008;16(11):1289-300.
5. Eerola I, Boon LM, Mulliken JB, Burrows PE, Dompmartin A, Watanabe S, et al. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. American journal of human genetics. 2003;73(6):1240-9.
6. Brouillard P, Boon LM, Revencu N, Berg J, Dompmartin A, Dubois J, et al. Genotypes and phenotypes of 162 families with a glomulin mutation. Molecular syndromology. 2013;4(4):157-64.
7. Kurek KC, Luks VL, Ayturk UM, Alomari AI, Fishman SJ, Spencer SA, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. American journal of human genetics. 2012;90(6):1108-15.
8. Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013;368(21):1971-9.
9. Lindhurst MJ, Sapp JC, Teer JK, Johnston JJ, Finn EM, Peters K, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. N Engl J Med. 2011;365(7):611-9.
10. Lindhurst MJ, Wang JA, Bloomhardt HM, Witkowski AM, Singh LN, Bick DP, et al. AKT1 Gene Mutation Levels Are Correlated with the Type of Dermatologic Lesions in Patients with Proteus Syndrome. J Invest Dermatol. 2013.
11. McDonell LM, Mirzaa GM, Alcantara D, Schwartzentruber J, Carter MT, Lee LJ, et al. Mutations in STAMBP, encoding a deubiquitinating enzyme, cause microcephaly-capillary malformation syndrome. Nat Genet. 2013;45(5):556-62.

12. Connell FC, Gordon K, Brice G, Keeley V, Jeffery S, Mortimer PS, et al. The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. Clinical genetics. 2013;84(4):303-14.
13. Tartaglia M, Zampino G, Gelb BD. Noonan syndrome: clinical aspects and molecular pathogenesis. Molecular syndromology. 2010;1(1):2-26.
14. Tartaglia M, Gelb BD, Zenker M. Noonan syndrome and clinically related disorders. Best practice & research Clinical endocrinology & metabolism. 2011;25(1):161-79.
15. Ghalamkarpour A, Debauche C, Haan E, Van Regemorter N, Sznajer Y, Thomas D, et al. Sporadic in utero generalized edema caused by mutations in the lymphangiogenic genes VEGFR3 and FOXC2. The Journal of pediatrics. 2009;155(1):90-3.
16. Ghalamkarpour A, Holnthoner W, Saharinen P, Boon LM, Mulliken JB, Alitalo K, et al. Recessive primary congenital lymphoedema caused by a VEGFR3 mutation. Journal of medical genetics. 2009;46(6):399-404.
17. Karkkainen MJ, Ferrell RE, Lawrence EC, Kimak MA, Levinson KL, McTigue MA, et al. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. Nat Genet. 2000;25(2):153-9.
18. Irrthum A, Karkkainen MJ, Devriendt K, Alitalo K, Vikkula M. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase. American journal of human genetics. 2000;67(2):295-301.
19. Malik S, Grzeschik KH. Congenital, low penetrance lymphedema of lower limbs maps to chromosome 6q16.2-q22.1 in an inbred Pakistani family. Human genetics. 2008;123(2):197-205.
20. Ferrell RE, Baty CJ, Kimak MA, Karlsson JM, Lawrence EC, Franke-Snyder M, et al. GJC2 missense mutations cause human lymphedema. American journal of human genetics. 2010;86(6):943-8.
21. Brice G, Mansour S, Bell R, Collin JR, Child AH, Brady AF, et al. Analysis of the phenotypic abnormalities in lymphoedema-distichiasis syndrome in 74 patients with FOXC2 mutations or linkage to 16q24. Journal of medical genetics. 2002;39(7):478-83.
22. Fabretto A, Shardlow A, Faletra F, Lepore L, Hladnik U, Gasparini P. A case of lymphedema-distichiasis syndrome carrying a new de novo frameshift FOXC2 mutation. Ophthalmic genetics. 2010;31(2):98-100.
23. Fauret AL, Tuleja E, Jeunemaitre X, Vignes S. A novel missense mutation and two microrearrangements in the FOXC2 gene of three families with lymphedema-distichiasis syndrome. Lymphology. 2010;43(1):14-8.
24. Mellor RH, Tate N, Stanton AW, Hubert C, Makinen T, Smith A, et al. Mutations in FOXC2 in humans (lymphoedema distichiasis syndrome) cause lymphatic dysfunction on dependency. Journal of vascular research. 2011;48(5):397-407.
25. Irrthum A, Devriendt K, Chitayat D, Matthijs G, Glade C, Steijlen PM, et al. Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. American journal of human genetics. 2003;72(6):1470-8.
26. Downes M, Francois M, Ferguson C, Parton RG, Koopman P. Vascular defects in a mouse model of hypotrichosis-lymphedema-telangiectasia syndrome indicate a role for SOX18 in blood vessel maturation. Hum Mol Genet. 2009;18(15):2839-50.
27. Ostergaard P, Simpson MA, Mendola A, Vasudevan P, Connell FC, van Impel A, et al. Mutations in KIF11 cause autosomal-dominant microcephaly variably associated with congenital lymphedema and chorioretinopathy. American journal of human genetics. 2012;90(2):356-62.
28. Hazan F, Ostergaard P, Ozturk T, Kantekin E, Atlihan F, Jeffery S, et al. A novel KIF11 mutation in a Turkish patient with microcephaly, lymphedema, and chorioretinal dysplasia from a consanguineous family. American journal of medical genetics Part A. 2012;158A(7):1686-9.
29. Mansour S, Connell F, Steward C, Ostergaard P, Brice G, Smithson S, et al. Emberger syndrome-primary lymphedema with myelodysplasia: report of seven new cases. American journal of medical genetics Part A. 2010;152A(9):2287-96.

30. Kreuter A, Hochdorfer B, Brockmeyer NH, Altmeyer P, Pfister H, Wieland U, et al. A human papillomavirus-associated disease with disseminated warts, depressed cell-mediated immunity, primary lymphedema, and anogenital dysplasia: WILD syndrome. Arch Dermatol. 2008;144(3):366-72.
31. Hennekam RC, Geerdink RA, Hamel BC, Hennekam FA, Kraus P, Rammeloo JA, et al. Autosomal recessive intestinal lymphangiectasia and lymphedema, with facial anomalies and mental retardation. American journal of medical genetics. 1989;34(4):593-600.
32. Van Balkom ID, Alders M, Allanson J, Bellini C, Frank U, De Jong G, et al. Lymphedema-lymphangiectasia-mental retardation (Hennekam) syndrome: a review. American journal of medical genetics. 2002;112(4):412-21.
33. Alders M, Hogan BM, Gjini E, Salehi F, Al-Gazali L, Hennekam EA, et al. Mutations in CCBE1 cause generalized lymph vessel dysplasia in humans. Nat Genet. 2009;41(12):1272-4.
34. Bull LN, Roche E, Song EJ, Pedersen J, Knisely AS, van Der Hagen CB, et al. Mapping of the locus for cholestasis-lymphedema syndrome (Aagenaes syndrome) to a 6.6-cM interval on chromosome 15q. American journal of human genetics. 2000;67(4):994-9.
35. Fruhwirth M, Janecke AR, Muller T, Carlton VE, Kronenberg F, Offner F, et al. Evidence for genetic heterogeneity in lymphedema-cholestasis syndrome. The Journal of pediatrics. 2003;142(4):441-7.
36. Roberts CM, Angus JE, Leach IH, McDermott EM, Walker DA, Ravenscroft JC. A novel NEMO gene mutation causing osteopetrosis, lymphoedema, hypohidrotic ectodermal dysplasia and immunodeficiency (OL-HED-ID). European journal of pediatrics. 2010;169(11):1403-7.
37. Durr HR, Pellengahr C, Nerlich A, Baur A, Maier M, Jansson V. Stewart-Treves syndrome as a rare complication of a hereditary lymphedema. VASA Zeitschrift fur Gefasskrankheiten. 2004;33(1):42-5.