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ARTICLE

Diagnosis, natural history, and management in vascular Ehlers–Danlos syndrome

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Vascular Ehlers Danlos syndrome (vEDS) is an uncommon genetic disorders characterized by arterial aneurysm, dissection and rupture, bowel rupture, and rupture of the gravid uterus. The frequency is estimated as 1/50,000–1/200,000 and results from pathogenic variants in COL3A1, which encodes the chains of type III procollagen, a major protein in vessel walls and hollow organs. Initial diagnosis depends on the recognitions of clinical features, including family history. Management is complex and requires multiple specialists who can respond to and manage the major complications. A summary of recommendations for management include: Identify causative variants in COL3A1 prior to application of diagnosis, modulate life style to minimize injury, risk of vessel/organ rupture, identify and create care team, provide individual plans for emergency care ("vascular EDS passport") with diagnosis and management plan for use when traveling, centralize management at centers of excellence (experience) when feasible, maintain blood pressure in the normal range and treat hypertension aggressively, surveillance of vascular tree by doppler ultrasound, CTA (low radiation alternatives) or MRA if feasible on an annual basis. These recommendations represent a consensus of an international group of specialists with a broad aggregate experience in the care of individuals with vascular EDS that will need to be assessed on a regular basis as new information develops. © 2017 Wiley Periodicals, Inc.

KEY WORDS: Ehlers–Danlos syndrome; vascular EDS; aterial rupture

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INTRODUCTION

Vascular Ehlers–Danlos syndrome (vascular EDS, vEDS, or VEDS, previously known as Ehlers–Danlos type IV) is a dominantly inherited disorder that results from mutations in *COL3A1,* the gene that encodes the chains of type III collagen [Pope et al., 1975; Pepin et al., 2014; Frank et al., 2015a]. The initial diagnosis is usually suspected on the basis of family history, or a clinical history of arterial rupture, dissection or aneurysm, rupture of the large intestine, or pregnancy complications at young ages. Because of clinical overlap with some forms of Loeys–Dietz syndrome, Marfan syndrome, and familial arterial aneurysm and dissection syndromes, the diagnosis should be confirmed by identification of pathogenic variants in *COL3A1* to allow for appropriate surveillance, treatment, and family studies. Type III collagen is a major protein in the walls of blood vessels and hollow organs, which explains increased bruising, arterial and bowel fragility, and uterine, cervical and vaginal fragility during pregnancy and delivery. Mutations in *COL3A1* are currently the only explanation for the vascular EDS phenotypic spectrum. The clinical spectrum (see below) is explained, in part, by

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striking allelic heterogeneity. Clinical heterogeneity among individuals with the same pathogenic variant is probably explained by other genetic modifiers. About half of the probands identified have no family history of vascular EDS, which means the diagnosis is often made in the context of the major complications of the condition. Biallelic mutations have been found in less than 1% of all affected individuals [Plancke et al., 2009; Jorgensen et al., 2015].

Diagnostic Testing

Sequence analysis of *COL3A1* in a qualified clinical laboratory is very sensitive and is thought to identify the underlying pathogenic variant in more than 98% of individuals with vascular EDS. The sensitivity differs little among sequencing strategies so that analysis by Sanger sequencing, exome sequence analysis, or genome sequence analysis appear to be equally effective although genome sequence analysis could identify deep intronic mutations that result in splicing alterations. For individuals with clinical features consistent with vascular EDS in whom no *COL3A1* mutation has been identified, routine sequence analysis, genome sequence analysis, examination of mRNA from cultured fibroblasts, or genome sequence of the region can identify deep intronic variants that alter splicing. Whole exome sequencing is unlikely to uncover a *COL3A1* pathogenic variant in a patient who has previously been tested with a gene panel. In individuals with clinical features of vascular EDS in whom no *COL3A1* mutation has been identified, considerations should be given to analysis of other genes such as those that disrupt the TGFβ signaling pathways and may be referred for research studies to search for additional genetic alterations.

NATURAL HISTORY

The key element to the creation of an effective assessment and management plan for people with vascular EDS is a comprehensive knowledge of the natural history of the disorder. The most common presentation in childhood is easy bruising that may be accompanied by striking skin lucency and vascular visibility. There may be excessive bleeding with circumcision. In some instances, childhood bruising has been sufficient to raise the question of abuse [Roberts et al., 1984]. Other signs such as talipes, congenital hip dislocation, and the facial features are often recognized only in retrospect. There appears to be an increased risk of sudden death under the age of 20, as a consequence of vascular rupture in males [Pepin et al., 2014]. The reason for the selective effect in males is not clear but does not appear to be related exclusively to sporting injuries. In most instances, the diagnosis in these individuals had not been identified prior to death, so that, in part, because they had no family history of the disorder, the diagnosis was made post-mortem. Usually, in the absence of family history, the diagnosis of vascular EDS is rarely considered in childhood, even in the face of unexplained bruising.

The key element to the creation of an effective assessment and management plan for people with vascular EDS is a comprehensive knowledge of the natural history of the disorder.

In the absence of a family history, the diagnosis of vascular EDS is often not considered until after a vessel or hollow organ rupture. Additional features which can raise concern about the diagnosis include with less severe consequences which should raise the suspicion of vascular EDS include unusual bruising without identified cause, acrogeria, recurrent pneumothorax talipes, early onset varicose veins, and characteristic facial features with prominent eyes.

Life Span and Predictors

At present, the life span for affected individuals is a median age of about 51 years (49 for males and 53 for females) but with a very large range (roughly from 10 to 80 years) [Pepin et al., 2014; Frank et al., 2015a]. The major cause of death is arterial dissection or rupture with organ failure. The nature of the underlying mutation in *COL3A1* influences life expectancy. Splice site mutations that lead to exon skipping have the lowest median survival although numbers with this mutation type are small. Substitutions of bulky residues (arginine, aspartic acid, glutamic acid, and valine) for triplet glycine residues in the triple helical domain (Gly-Xaa-Yaa) are usually less severe than splice site mutations, but more consequential than substitutions by smaller residues (alanine, serine, cysteine). Pathogenic variants that alter sequences in the carboxyl-terminal propeptide of the chains can have the full range of effects. Heterozygosity for *COL3A1* null alleles (which accounts for less than 5% of recognized mutations) delays onset of complications on average by almost 2 decades. In some instances, individuals in those families may have few clinical manifestations, even into the 9th decade even though the family was ascertained through an individual with a typical presentation, which emphasizes that life span estimates are population estimates and not strictly applicable to the individual. Knowledge of the familial mutation facilitates care choices, assists with reproductive options, and may be important in the choice of treatment modalities.

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Bowel rupture is uncommon in early childhood, begins to be recognized in the late childhood, and continues as a risk into adulthood. Bowel rupture ultimately affects about 25–30% of individuals but rarely leads to death.

Spontaneous pneumothorax can also occur during the late childhood with a high risk of recurrence. Active interventions that range from simple needle aspiration to chest drain are often needed and surgical pleurectomy, bleb removal, or chemical pleurodesis may be necessary to control recurrent pneumothoraces.

Pregnancy

The Kaplan–Meier survivals of women who have been pregnant and those who have not are similar [Murray et al., 2014]. However, disease-related complications during pregnancy remain the most common cause of death in women of childbearing age. Pregnancy is associated with death in about 5% of women and first pregnancies seem to account for 50% of those maternal pregnancy-related deaths [Pepin et al., 2014], but only a small number have complications that lead to death that are pregnancy specific (e.g., uterine rupture). The remainder die from arterial complications that are similar to those seen in non-pregnant women. Complications occur in about half the pregnancies and include premature rupture of membranes with preterm delivery, rare uterine rupture during labor, severe perineal tears, and antepartum and post-partum hemorrhage. Some of these complications may be avoided by delivery by cesarean.

OVERALL MANAGEMENT

Life Style—Sense and Sensibility

The goals of medical management are to minimize the likelihood of adverse events and to assure that quality of life is minimally impaired. The general approach to medical management includes the creation of an informed care team, the avoidance of activity choices that are likely to cause adverse effects, and the management of ordinary medical conditions where there is additional risk in individuals with vascular EDS such that this risk is minimized

In general, most of the usual aspects of daily living and recreational activities are within the expected possibilities. Collision sports and isometric activities are generally discouraged. There are examples of individuals who have played football, rugby, soccer, and water polo with only bruising occurring during the activity. However, there are rare deaths that can be attributed directly to the involvement in these activities. The increase risk for early death in young males does not seem to be explained by athletic activities in most individuals. The two concerns in high level sports activities are that the trauma of collisions can lead to vascular rupture and that rapid and recurrent increase in blood pressure and rate can compromise normal vascular structure and lead to dissection or rupture. Specific limits on the extent of activity are difficult to establish. The concept that to retain the capacity to converse with a partner during activity, good breath control while lifting, and light weights to retain tone and strength rather than building mass seem like appropriate guidelines. Weight limits depend not only on previous strength and fitness, but also on history of joint hypermobility, pain, and dislocations. Shoulder, hip, and knee injuries can be minimized by use of light resistance and/or weights. Aerobic fitness through mild to moderate conditioning exercises are encouraged, but with use of pools, stationary bicycle, elliptical trainers, or well cushioned treadmills. Running on hard surfaces and for long distances may exacerbate foot, ankle, knee, and hip pain. Activities with rapid acceleration/deceleration should be discouraged as these may increase the risk of vessel dissection.

Creation of a Care Team

A frequent concern is that the physician does not know anything about this type of EDS. Given the rarity of vascular EDS, outside of medical geneticists, vascular surgeons, and cardiologists few clinicians would be expected to have had significant (any) experience with people with the disorder. With this in mind, at the time of diagnosis, an affected individual should be referred to a center in which there is both experience and expertise. The referral pattern will vary depending on the geographic region. In some settings, centers of excellence have been established and referral patterns institutionalized. This is the case in France and the United Kingdom and in European countries in which reference networks have been set up. In others, the search for an expert may be ad hoc and success not guaranteed. Consultation with the national or international peer groups or University Medical Centers or large free-standing clinical centers with large referral populations may help to identify clinicians with experience and knowledge.

Each individual with vascular EDS should have a primary physician, who acts as the care coordinator, and who is linked to a geneticist or other specialist with detailed knowledge of the disorder. The care team should include the primary care practitioner, a vascular surgeon, and a general surgeon. A genetic consultation will help in identifying possible affected relatives who should be offered cascade testing. The psycho–social impact of the disease is too often neglected and often requires psychological care. It is helpful to have backups, and the team members should be introduced to the patient and family. This team exists to care for the affected individual in the case of major complications, such as bowel rupture, arterial dissection or rupture. A clear protocol

should be created, the local emergency room or rooms should have data about the individual and both the affected individual and relevant family members should know the protocol for contact. A protocol for the emergency room evaluation needs to be established and the on-call caretakers must recognize the needs of the patient. Each affected individual should have letter or "passport"/Emergency Care Card to be carried and provided to the ER physicians at the time of consultation. Copies of such documents are available from several resources once the diagnosis has been established by genetic testing. For younger women planning pregnancy, a high risk team should be assembled that includes experienced obstetricians and vascular surgeons.

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Surveillance

The objective of surveillance is to identify the potential for complications before they occur and substitute a planned elective procedure in an experienced setting for an ad hoc approach that may occur in the closest available resource. Currently there are no guidelines for surveillance that have been created on an evidence-based formula and, as a consequence programs and institutions vary in their approach. These approaches range from no interim evaluations other than routine and directed physical examination following an interim medical history with perhaps some imaging of the aorta, to detailed assessment of the arterial tree by MRA or CTA on a periodic basis, usually yearly. Even in the latter settings, the criteria for intervention have not been well established and the use of endovascular stenting compared to open surgical replacement of arterial segments remains uncertain. It is hoped that data emerging from established centers with broad experience will provide well-vetted protocols for surveillance and intervention.

TREATMENT

Medical Intervention

The major target of medical intervention has been the maintenance of blood pressure in the normal or low normal range and prevention of surges in blood pressure with the intent to minimize the likelihood of arterial dissection or rupture. Over time, a variety of medications have been suggested that include diuretics, β-adrenergic blockers, angiotensin processing blockers or receptor blockers, and other antihypertensive agents that may depend on knowledge and experience of the clinician. Reports of only one systematic investigation of efficacy of any of these drugs is available, a trial of the mixed β1 antagonist and β2 agonist, celiprolol [Ong et al., 2010]. The study suggests that treatment of individuals with vascular EDS with the drug extends the time to vascular complications compared to those not treated. Selection of subjects was made on clinical grounds and the allocation to treatment or control was based on demographic and clinical criteria for the whole group. Part way through the study it was determined that for about a third of participants no COL3A1 mutation could be identified. Although individuals with COL3A1 mutations who were treated appeared to benefit in the secondary prevention of vascular events, the failure to determine if the comparison groups were equivalent compromises the ability to come to clear conclusions whether treatment with the drug can delay or prevention of vascular events in people with vascular EDS. The drug has been used in this population in Europe and Great Britain (it is not yet available in the US) and it is hoped that analysis of those individuals can clarify whether and under what circumstances there is benefit.

Surgical Intervention

Arterial events

Many symptomatic arterial events are dissections that are self-limiting and may not require radiologic intervention or surgery. In the case of arterial rupture, urgent repair by any possible means is required.

Not all dissections are symptomatic. Indeed, it is not uncommon to discover silent arterial defects during routine arterial monitoring [Frank et al., 2015a]. Symptoms of arterial dissection may be pain secondary to the tear in the arterial wall, to capsular stretch, or related to ischemia in organs or limbs located distal to the dissection. Locations that are commonly symptomatic are iliac and femoral arteries, mesenteric and celiac vessels, renal arteries, aorta (any location), and peripheral arteries of the limbs. Acute management of symptomatic dissection requires pain control, blood pressure control, and monitoring for signs of deterioration in case of ischemia. Anticoagulant or antiplatelet therapy may be required when there is a high risk of ischemia due to narrowing of the vessel or peripheral embolization. Given the risk of complication due to these therapies, their use is generally limited to a short period of time.

In the event of arterial rupture, interventional therapy may be indicated. Anatomically contained (partial) ruptures may be treated medically but require close monitoring to detect recurrent bleeding. Non-contained ruptures or clinically unstable aneurysms (pre-rupture) or false aneurysms most often require intervention. According to the location, interventional radiology or open surgery may be indicated, although invasive procedures may be more likely to provoke further morbidity. The nature of

treatment depends on the location of the arterial rupture. Often occlusion by embolization of the bleeding artery is necessary.

The best setting for vascular surgery is the planned repair of aneurysms and dissecting aneurysms, especially those affecting the aorta or iliac vessels. Open intervention however requires specific repair techniques because of the inherent vessel friability and should be avoided as much as possible.

Repeated arterial events

Patients with symptomatic arterial events may present during the acute phase of their dissection/rupture with repeated arterial accidents in distant arterial territories in the hours/days following the initial event. The risk of secondary accidents may increase with the severity of the initial event, the length of the hospital stay, the invasive character of treatment, and the extent of fluid overload. No specific causal factors have been formally identified to explain these events.

We suggest a protocol of "permissive hypotension" in which hypotension is permitted as long as it does not compromise intellectual or other organ function, the avoidance of inotropic agents, and the judicious use of IV fluids to increase pressure. Additional precautions are required with indwelling catheters because of the risk to the integrity of vascular or organ walls.

Evaluation

Evaluation at the time of emergency referral depends on the signs and symptoms. In general, non-invasive evaluation of the abdomen, chest, and head are preferred using MRI, CT, and venous angiographic approaches to understand blood loss. Use of arteriography with high pressure injection is generally avoided because of the risk of further vascular injury. Some vascular events can be dealt with effectively with embolization [Brooke et al., 2010; Okada et al., 2014]. Although covered stents are being placed in life-threatening situations to forestall active bleeding, it is not known if and how arteries will withstand the pressure of the stents over the long course. Aneurysmal dilation may occur in some while others may require open surgical intervention.

Bowel rupture almost always requires surgical intervention and usually leads to isolation of the distal bowel, removal of the ruptured segment, and creation of a colostomy. Repair of colostomy has become more commonplace and is frequently successful. Recurrent surgery may be associated with ilio-colic fistula formation and subtotal colectomy may prevent further colonic ruptures [Frank et al., 2015a]. This possibility could be discussed at the time of the first colonic rupture if the diagnosis of vascular Ehlers–Danlos syndrome has been established.

ORGAN SYSTEM INVOLVEMENT

Cardiac

There is no increased risk of cardiac valvular abnormalities or structural cardiac defects. Mitral valve prolapse probably occurs at the same frequency as in the general population. There is an increased risk of coronary artery dissection and, as a consequence, myocardial infarction [Pepin et al., 2014]. In the event of myocardial infarct, there is an increased risk of ventricular rupture and pericardial tamponade with sudden death. Non-MI related mitral valve papillary muscle rupture has been described in vascular EDS patients.

Gastrointestinal

The most common complication is spontaneous rupture of the colon, usually the sigmoid [Pepin et al., 2014; Frank et al., 2015a]. The clinical presentation is one of rapid crescendo of unremitting pain, generally in the lower left quadrant. Treatment is similar to that in individuals without vascular EDS and generally leads to colostomy which can be successfully reversed a few months after the initial event without further complications. Recurrence is more frequent than in the non-EDS population and may lead to partial colectomy. Awareness of the genetic diagnosis may help to shape care.

Small bowel rupture appears to be less common and may in some result from intramural hemorrhage and in others as a consequence of adhesions from previous surgery. Fistula formation is not uncommon following abdominal surgery and may lead to rapid transit time and problems with nutrition. Surgical intervention with partial bowel resection can be successful.

Esophageal and gastric rupture have also been reported [Reis et al., 1998].

Pulmonary

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Spontaneous pulmonary hemorrhage resulting in hemoptysis is a rare complication and can result from rupture of small pulmonary vascular nodules or arteriovenous fistulae [Ishiguro et al., 2009; Kawabata et al., 2010].

Treatment of this complication follows the same pathways as for those without vascular EDS.

Vascular

Superficial venous insufficiency (SVI) is more prevalent in patients with vascular EDS than in the general population (37% vs. 17–23%; Frank et al., 2015b). SVI is characterized by its precocity (44% of patients with SVI declare their venous disease before the age of 20 years; Frank et al., 2015a) and is characterized by the early presence of significant (>3 mm) varicose veins (stage C2 CEAP). Vein stripping may result in extensive vascular damage (femoral vein/artery rupture) and/or in uncontrolled bleeding and should therefore be avoided. Commonly however, the early onset of SVI competes with the first vascular EDS-related events and thus the genetic diagnosis of the patient's condition. Because of this, it is not rare that the diagnosis of vEDS is suspected after an unusually complicated surgical stripping. Therapy primarily consists in medical compression. Endovenous laser or radiofrequency endovenous thermal ablation have been successfully reported in patients with vEDS [Okada et al., 2014; Frank et al., 2016]. In countries where it is available, foam sclerotherapy may also be a complementary or alternate treatment.

Skin

Although thin skin with readily visible venous patterning is one of the typical features described in individuals with vascular EDS, it is often a subtle finding and bruising that is not explained by trauma is more common. Acrogeria is uncommon and usually accompanies mutations that appear near the carboxyl-terminal end of the triple helical domain. Bruising may increase with aspirin or non-steroidal anti-inflammatory medications and certain in the presence of anti-coagulant treatment. Alopecia occurs inconstantly but can be striking in some women.

Musculoskeletal

Height varies through the normal range although small for family may be more common. Congenital hip dislocation is increased as is congenital talipes and limb reduction defects (perhaps secondary to amputations by amniotic bands) [Young et al., 1985] when compared to the average population but these alone are generally insufficient to warrant diagnostic testing.

Distal joint contractures occur in a small proportion of individuals, these are progressive and can be disabling.

There also appears to be an increase in the relative frequency of muscle and tendon rupture, but these data have not been aggregated.

Ocular

Carotid cavernous fistula: Globe protrusion as a consequence of retrograde arterial flow through the venous system around the globe occurs as a result of "carotid-cavernous sinus fistula" formation and is a medical emergency. This may be recognized by the affected individual because of sudden onset of a swishing sound in the temporal region of the head followed by injection of the veins of the eye, pain around the eye, and protrusion with slow loss of visual acuity. The only treatment is closure of the fistula, usually by an arterial catheter and coiling or occlusion of the carotid proximal to the fistula [Halbach et al., 1990; Linfante et al., 2015].

Subtle globe protrusion is also a common feature of the "characteristic facial appearance" and may result in failure to completely close the lids during sleep with recurring conjunctivitis.

Keratoconus, thinning of the cornea, is a very rare feature of vascular EDS but the frequency has not been determined. The diagnosis requires measure of the corneal thickness and architecture. It can lead to sufficient visual distortion that cannot be well treated with contact lenses so that the only effective remedy is corneal transplant, which has been successful. Retinal disorders do not appear with increased frequency. Keratoconus, globe rupture, and blue sclerae are features of a different type of EDS that results from mutations in two separate genes (*ZNF469* and *CHST14*) [Rohrbach et al., 2013; Kosho, 2016]. Globe rupture is not a feature of vascular EDS. Isolated keratoconus is a rare disorder that does not appear to result from mutations in *COL3A1* or the other Ehlers–Danlos-related genes. Isolated keratoconus may be more frequent than vascular EDS.

Oral

The most common oral problem is gum fragility with bleeding after brushing or flossing [Ferré et al., 2012]. In some individuals, there is marked loss of gingival tissue with recession that can lead to tooth loss. This may lead to confusion about the diagnosis and raise the concern of the periodontal form of EDS [Kapferer-Seebacher et al., 2016]. Therapy is limited to fastidious oral hygiene but even that may not be sufficient to safe guard gingival integrity.

Hyperlaxity of the temporomandibular articulation can also result in repetitive subluxations and pains.

Renal

Intrinsic renal disease is not increased. The major renal concern results from renal artery dissection that may lead to diminished renal blood flow, loss of renal parenchyma, and renal hypertension. In some instances, stenting of the stenotic vascular regions can restore flow and result in normalization of blood pressure (unlikely approach in these patients in clinical practice). In others, appropriate and aggressive treatment of blood pressure to maintain the normal range is indicated, in first instance with a blocker of the renin angiotensin system (ACEI, ARB).

Genitourinary

There do not appear to be specific genitourinary complications. Iatrogenic bladder perforation has been reported during C-section.

ANIMAL MODELS

Currently there are two available mouse models for vascular EDS, both are homozygous or heterozygous nulls which represent only about 5% or less of all known instances of human vascular EDS [Liu et al., 1997; Cooper et al.,

2010; Smith et al., 2011]. In these models, a very small proportion of the homozygotes survive until birth and then they uniformly develop arterial ruptures and died by about 6 months of age. Hypertension converts an asymptomatic heterozygote to one that develops large arterial rupture. In one model, use of doxycycline to inhibit matrix metalloproteinases appeared to change the arterial topography but the effect on aortic rupture was unclear. Animal models with missense and splicing mutations are currently under investigation.

FUTURE NEEDS

Vascular EDS is an uncommon genetically homogeneous, but with substantial allelic heterogeneity, disorder (perhaps as frequent as 1/50,000) that results from pathogenic variants in *COL3A1*. There is no consensus on the best practice for medical surveillance, for medical intervention, or for surgical intervention. In part, these limitations result from the rarity of the disorder, the difficulty in assembling clinical data, and the relative paucity of natural history data. The following pathways may lead to better diagnosis, management, and treatment:

- make educational materials about the disorder available to the medical community: Undergraduate medical education, medical and surgical teaching programs, and ER facilities,
- collect all sequence data from testing laboratories and facilitate contact with all individuals with pathological variants and those with VUS for follow-up,
- create centers of excellence to provide expert periodic evaluation to develop standardized care, surveillance, and intervention,
- assist in the provision of local "care teams" for each individual identified,
- create an international web-based registry of individuals with vascular EDS with permission to contact and re-contact for both clinical information and involvement in clinical trials,
- promote international cooperation and collaboration through yearly scientific/clinical meetings in revolving venues,
- use registry and other clinical data to provide clear natural history descriptions,
- create animal models with common types of mutations—heterozygous substitutions for glycine in the triple helical domain and splice site mutations,
- identify or develop "biomarkers" for surveillance (enrollment closed),
- develop clinical trials for small molecular intervention (enrollment about to begin), and
- develop models for genetic intervention.

Summary of Management Recommendations

- identify causative variants in COL3A1 prior to application of diagnosis,
- modulate life style to minimize injury, risk of vessel/organ rupture,
- identify and create care team,
- provide individual plans for emergency care ("vascular EDS passport") with diagnosis and management plan for use when traveling,
- centralize management at centers of excellence (experience) when feasible,
- maintain blood pressure in the normal range and treat hypertension aggressively, and
- surveillance of vascular tree by doppler ultrasound, CTA (low radiation alternatives) or MRA if feasible on an annual basis.

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