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REVIEW

Loeys-Dietz syndrome: 2026 updated care management primer

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ABSTRACT

Loeys-Dietz syndrome (LDS) represents a clinically and genetically heterogeneous group of connective tissue disorders that share features similar to Marfan syndrome, first identified in 2005. Characterized by significant manifestations, such as aortic aneurysms, arterial tortuosity, craniofacial and skeletal anomalies, LDS results from pathogenic variants in key genes of the transforming growth factor-beta signaling pathway. Given its variable expressivity, a multidisciplinary approach to management is critical.

The article provides an updated overview of effective management practices since the first LDS primer in 2014. It aims to enhance clinical awareness, inform health care providers, and improve patient outcomes through individualized care strategies for those living with LDS.

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Introduction

Loeys-Dietz syndrome (LDS) comprises a group of etiologically and clinically related connective tissue disorders first described in 2005 after identification of patients with a condition that overlapped with Marfan syndrome (MFS; MIM 154700) but included highly atypical clinical features.[1,2] Although there is variable expression, LDS was initially characterized by aortic aneurysm, aneurysms throughout the arterial tree, arterial tortuosity, hypertelorism, and bifid uvula or cleft palate and a pathogenic variant in *TGFBR1* or *TGFBR2*. Five additional genes in the transforming growth factor-beta (*TGFβ*) pathway (*SMAD3*, *TGFB2*, *TGFB3*, SMAD2, and *IPO8*) have since been identified as causing an overlapping LDS phenotype requiring individualized multidisciplinary management.[1,3-10]

Materials and Methods

At the first International Research Meeting for LDS in Antwerp, Belgium (June 2023), clinician-researchers outlined updated management recommendations. A Johns Hopkins University librarian conducted a literature review of LDS related publications. Junior and senior clinicians drafted specialty-specific sections, combining evidence-based approaches with extensive clinical experience. Through monthly meetings, the group refined recommendations to reach consensus regarding diagnostic and management practices for people with LDS.

Genetics/inheritance

The LDS nomenclature currently includes 6 genes encoding proteins in the TGFβ signaling pathway (Table 1).[1,3-9] Although all conditions currently designated as LDS show dominant inheritance, we have included information about people with homozygous or compound heterozygous *IPO8* variants in this manuscript based upon mechanism and clinical presentation; this condition is not yet formally designated as LDS. Currently, diagnosis requires a pathogenic or likely pathogenic variant in the *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*, or *SMAD2* gene. All LDS types show incomplete penetrance and variable clinical expression.

We recommend partnerships with regional centers of excellence due to evolving knowledge and nuanced recommendations, particularly for imaging and cardiac surgery recommendations. Additionally, the Loeys-Dietz Syndrome Foundation (LDSF), a division of the Marfan Foundation (www.marfan.org) has professional staff to assist physicians and patients to access specialized organ system-specific expertise and local or regional care.

TGFBR1 and *TGFBR2* (LDS1 and 2) show the highest penetrance and the greatest clinical severity. *SMAD3* (LDS3) has intermediate penetrance and severity, whereas *TGFB2*, *TGFB3*, and *SMAD2* (LDS4,5,6) show notably lower penetrance and expressivity, particularly regarding vascular features. People with *IPO8* variants present with early onset and progressive aortic aneurysms, although no aortic dissections have yet been reported. All types of LDS have been associated with aortic root and arterial aneurysms requiring widespread imaging surveillance, although time frames may be partially dictated by age, gender, medical history, family history of events, and genotype-phenotype information (if reported).

The GenTAC registry documented sex-related penetrance in familial thoracic aortic aneurysm and dissection, with males presenting with a more severe aortic phenotype, a phenomenon that has also been described in MFS and vascular Ehlers-Danlos syndrome (VEDS; MIM 130050).[11-13] Similarly, LDS also exhibits sex-related penetrance. Males with pathogenic variants in all genes (except SMAD2 as vascular data are limited) show higher aortic event risk compared with females.[14-16] Current evidence is insufficient for reliable sex-specific risk estimations or imaging frequency recommendations. Importantly, a "normal" screening echocardiogram, irrespective of age or sex, cannot definitively rule out disease predisposition.

Table 1 Loeys-Dietz syndrome genes

Gene	Gene Name	LDS Subtype	Year Discovered	Phenotype MIM#	HGNC Gene ID	Inheritance
TGFBR1	transforming growth factor-beta receptor type 1	LDS1	2006	609192	11772	AD
TGFBR2	transforming growth factor-beta receptor type 2	LDS2	2006	610168	11773	AD
SMAD3	mothers against decapentaplegic, drosophila, homolog of, 3	LDS3	2011	613795	6769	AD
TGFB2	transforming growth factor-beta -2	LDS4	2012	614816	11768	AD
TGFB3	transforming growth factor-beta -3	LDS5	2015	615582	11769	AD
SMAD2	mothers against decapentaplegic, drosophila, homolog of, 2	LDS6	2015	619656	6768	AD
IPO8	Importin 8		2021	619472	9853	AR

AD, autosomal dominant; *AR*, autosomal recessive.

When to consider genetic testing

Given disease variability, molecular testing that includes screening for LDS should be considered in individuals with the following:

- a personal history of aortic root dilation (z-score ≥ 2.0) or type A/B aortic dissection in the absence of lens dislocation (currently, aortic root aneurysm or dissection with lens dislocation is diagnostic for MFS)
- a personal history of arterial aneurysm or extensive tortuosity at a young age or in the absence of identifiable environmental risk factors
- suggestive systemic features, especially when found in combination, in the skeletal (scoliosis, pectus deformity, contractures, clubfoot), cutaneous (skin translucency, abnormal scarring, milia), craniofacial (midface flatness, mandibular retrognathism, downslanting palpebral fissures, low-set ears, hypertelorism, tooth anomalies, cleft palate or bifid uvula), ocular (strabismus or retinal detachment) or immunologic (asthma, food or other allergies, eosinophilic gastrointestinal disease, inflammatory bowel disease) systems. A family history of aortic or arterial aneurysm would lower the threshold for molecular testing.
- documented family history of "pathogenic" or "likely pathogenic" variant in an LDS gene.

Genetic testing for LDS typically utilizes thoracic aortic aneurysm gene panels that are widely available through commercial laboratories. More comprehensive connective tissue disease panels can be utilized when clinically indicated. Panel testing should include Multiplex Ligation-dependent Probe Amplification to detect DNA copy-number variations, especially for LDS types 3-6 where haploinsufficiency is a mechanism of disease. Large deletions of *SMAD3*, *TGFB2*, *TGFB3*, and *SMAD2* may also be picked up on chromosome microarray. Genome sequencing will likely become mainstream as technology advances and costs decrease. If suspicion of LDS is high and panel testing is negative, consideration of testing through these other modalities could be considered. There will likely be additional aortopathy genes described over time that overlap with LDS phenotypes; therefore, consideration of additional aortopathy testing should be reassessed every few years if initial testing is normal. Of note, the *SMAD3* gene has been variably annotated in the human genome reference sequence due to inconsistent inclusion of a number of exons. Care should be taken to ensure that annotation tools correctly map variants and their predicted protein coding consequences through consistent utilization of the Matched Annotation from the National Center for Biotechnology Information and the European Molecular Biology Laboratory's European Bioinformatics Institute select (MANE-Select) transcript ENST00000327367.9/NM_005902.4 followed by validation with a "gaped-alignment" aware validation tool, such as VariantValidator to confirm the accuracy of the mapping from genome to transcript.

Differential diagnosis

The differential diagnosis for LDS includes MFS, VEDS, Shprintzen-Goldberg syndrome (SGS: MIM 182212), and familial thoracic aortic aneurysm and dissection. Other less common presentations of syndromic aortic or arterial aneurysm can generally be discriminated based on systemic clinical findings. Table 2 shows the overlap of features between LDS subtypes and other connective tissue disorders.

Recurrence and family testing

LDS1-6 show autosomal dominant inheritance with a 50% recurrence risk to the offspring of an affected individual. Risk to other first-degree family members depends on whether the LDS variant is de novo in the proband or inherited from an affected parent. If inherited, risk to siblings is 50%; if de novo, risk is ≤1%-2% (not zero because of possible germline or low-grade somatic mosaicism in an apparently unaffected parent). *IPO8*-associated disease shows autosomal recessive inheritance, with 25% risk to siblings of an affected individual if both parents are heterozygous for a pathogenic variant. Targeted variant testing should be offered to all at-risk first-degree relatives of the proband.

Cardiovascular

LDS carries a significant cardiovascular burden responsible for much of its morbidity and mortality. Thoracic aortic aneurysms, primarily of the aortic root, are the predominant aneurysm location at diagnosis. Management relies on imaging surveillance, medical therapy and timely preventative surgery (see Table 3).

Patients with LDS are predisposed to congenital heart defects including bicuspid aortic valve, (predominantly) atrial or ventricular septal defects, and patent ductus arteriosus, with rare reports of more severe anomalies (double outlet right ventricle, interrupted aortic arch, or hypoplastic left heart syndrome).[5,19-21]

Mild-to-severe mitral valve prolapse (MVP) and/or insufficiency can be seen in all types of LDS, albeit with lower frequency and severity than seen in MFS.[22] The prevalence of MVP and mitral annular disjunction (MAD) in adults with LDS is estimated at 20% and 43%, respectively.[22,23] Severe mitral valve disease is rarely reported in young children with LDS. MVP appears to be most strongly associated with *SMAD3* pathogenic variants.[24-26] Current mitral valve surgery guidelines mirror those for non-syndromic cases.[22,27-29]

MAD, now defined as a ≥2-mm separation between the left atrium-posterior mitral leaflet junction and the atrial margin of the left ventricular myocardium, is detectable by echocardiography or (with higher sensitivity) cardiac magnetic resonance imaging.[18,23,30,31] Although clinical

Table 2 Features of LDS compared with Marfan and Shprintzen-Goldberg syndromes

	TGFBR1 (LDS1)	*TGFBR2* (LDS2)	*SMAD3* (LDS3)	*TGFB2* (LDS4)	*TGFB3* (LDS5)	*SMAD2* (LDS6)	*IPO8*	*FBN1* (MFS)	*SKI* (SGS)
Aortic aneurysm	+++	++	++	++	+	+	++	+++	+
Arterial aneurysm	++	++	+	+	+	+	++	-	+
Early-onset aortic dissection	+++	+++	++	+	+	?	-	+	-
Mitral valve prolapse	+	+	++	+	+	+	+	++	+
Arterial tortuosity	++	++	+	+	+	+	+	+	+
Bicuspid aortic valve	++	++	+	+	+	+	-	-	+
Pectus deformity	++	++	+	+	+	+	++	++	++
Craniosynostosis	++	++	+	-	-	-	-	-	+++
C-spine instability	++	++	+	?	?	?	+	-	+
Scoliosis	++	++	++	++	++	++	++	++	++
Talipes equinovarus	++	++	+	++	+	-	+	-	+
Hyper-telorism	++	++	+	+	+	+	++	-	++
Abnormal uvula/cleft palate	++	++	+	+	+	+	+	-	+
Dental defects/ flaky enamel	++	+++	+	+	-	-	-	-	-
Eye muscle disease	+	+	-	+	+	+	?	+	+
Ectopia lentis	-	-	-	+	-	-	-	+++	-
Umbilical/ inguinal hernia	+	+	+	+	+	+	+	+	+
Allergic disease (asthma/ eczema)	++	++	+	?	?	?	+	-	?
GI (EOE, IBD)	++	++	?	?	?	?	+	-	?
Developmental delay	-	-	-	-	-	-	+ (motor)	-	+++

data on MAD remain limited and controversial, recent evidence suggests an association with left ventricular dysfunction, fibrosis, and arrhythmias.[32-34] Recent studies confirm high MAD prevalence in LDS and its association with disease severity and early aortic events (dissection risk or the need for earlier preventative surgery).[23,30] Indications for MVP intervention are informed by routine metrics including left atrium diameter and left ventricular dimension and ejection fraction. T-wave inversion and Holter monitoring are used to assess arrhythmia risk in association with MVP.[18]

Although aortic events cause most sudden deaths in LDS, sporadic reports exist of sudden death in individuals with LDS2 or 3 without defined structural causes, suggesting possible arrhythmias.[35] Abnormal electrocardiogram (ECG) repolarization has been observed in a small cohort of patients with *TGFBR2* variants, although a definitive mechanistic link to altered TGFβ signaling is lacking.[36,37] Providers should consider arrhythmia risk with compatible signs or symptoms, especially with concomitant MAD.

Left ventricular dilation and systolic dysfunction can occur in connective tissue disorders. Although this is often attributable to aortic or mitral valve dysfunction, apparent primary cardiac muscle disease has been described in both MFS and LDS.[38-40]

Animal models suggest altered *TGFβ* signaling may disrupt cardiomyocyte homeostasis.[41,42] Severe cardiac dysfunction requiring mechanical support and heart transplantation has been documented in LDS.[43-45] Current evidence favors monitoring for and treating rhythm problems and ventricular dysfunction in LDS per standard protocols, although more research is needed.

Imaging of the aorta and arteries

Echocardiography remains the first-line tool in cardiovascular imaging, adequately assessing the most commonly involved segments of the thoracic aorta (aortic root, ascending aorta).

Per American Society of Echocardiography (ASE) guidelines, adult measurements should be taken perpendicular to the long axis of the aorta at specific anatomic landmarks, from leading edge to leading edge in diastole.[46,47] For pediatric patients, ASE guidelines recommend inner edge to inner edge measurements in systole.[48] *Z*-scores based on body surface area are essential for interpreting aortic diameters in children to account for somatic growth. A consistent measurement technique is crucial for accurate longitudinal comparisons.

Contrast-enhanced magnetic resonance angiography (MRA) is the standard for head to pelvis arterial tree imaging. If offers safety, reproducibility and accurate 3D data sets without exposure to ionizing radiation. Noncontrast ECG-gated MRA provides accurate thoracic aorta measurements without requiring IV access, which may be beneficial for young patients. Kaiser et al[49] published thoracic aorta z-score calculations for MRAs in children, which, despite limitations, remain the only available pediatric nomograms.

Computed tomography angiography (CTA) involves radiation exposure but excels in acute settings requiring rapid imaging and for surgical planning because of is excellent spatial resolution. Modern protocols use minimal radiation, making CTA increasingly acceptable for young patients and potentially replacing MRA in young children who would otherwise need anesthesia.

Table 3 Imaging recommendations for individuals with LDS

	Echocardiogram (Transthoracic)	CTA	MRA
Body segments	Heart valves, heart structure and function, aortic root and ascending aorta	Head to pelvis, including 3D images	Head to pelvis, including 3D images Chest: can consider noncontrast ECG gated studies (for aortic root)
Radiation	No	Yes	No
Study length	30-45 minutes	15 minutes	30 -120 minutes depending on regions included
Utility	Accessible, affordable, consistent	- Emergency situations - Surgical planning - Better definition of small arteries in head and branch vessels - Can give superior spatial resolution post-intervention compared with MRA - 3D imaging is especially important if PEARS procedure is planned.	- Useful modality when planning for longitudinal surveillance as no radiation and no major nephrotoxicity
Child considerations	- Aortic dimensions typically standardized to body surface area to give z-score (number of standard deviations away from the mean)	- Radiation exposure but usually can be performed without general anesthesia (GA) at any age	- GA or sedation may be necessary for young children (consider cervical stability before GA)
Contraindications (CI)		- Relative CI: severe renal impairment, thyroid dysfunction, severe allergy to contrast (pre-medication may be required)	- Absolute CI: MRI incompatible device - Relative CI: claustrophobia
	Timing yearly at a minimum; more frequently depending on findings including aortic size, aortic growth rate, valve regurgitation or other heart structure or functional issues - Consider echocardiogram after 6 months if initiating new medication to assess stability of the aorta - If moderate to severe z-score in children (>3.5-5), rapid growth or approaching surgical thresholds, echocardiogram may be suggested every 3-6 months - For LDS5 (*TGFB3*), which often is associated with non-penetrance, a more liberal screening time frame can be considered after documentation of prolonged stability	Children: Special considerations: - Need to balance anesthesia vs. vascular risk - For LDS1/2: Consider baseline studies at diagnosis; follow-up every two years - Might consider more frequent scans (yearly) during adolescence and/or if getting closer to surgical threshold - For LDS3-6 and IPO8: Could consider delay in young children until cooperation without anesthesia; in general follow-up about every 2-3 years - Triggers for shorter time frames: *TGFBR2* p.Arg528His/Cys variants, strong family history of early and aggressive arterial aneurysms or dissections, particularly severe systemic features. Adolescents & Adults: - At diagnosis for baseline - If normal, every 2-3 years - After aortic dissection: US guidelines: image at 1, 3, 6 and 12 months; if stable image every two years[17] European guidelines: image at 6, 9 and 12 months; if stable image every two years[18] ********** With cerebral or complex vascular disease consult with neurovascular and vascular colleagues for surveillance recommendations	

Arterial tortuosity is found in up to 90% of individuals with LDS (although percentages vary between studies); predominantly in cervical vessels.[24] This can complicate vascular access and should be assessed before angiography or other catheter-based procedures. The severity of vertebral or carotid artery tortuosity can correlate with the risk of early vascular events. Because this risk also correlates with the severity of other systemic manifestations in LDS, vascular tortuosity likely informs the severity of the underlying genetic predisposition rather than having a more direct influence on vascular integrity and risk.[16,50-54]

Other features, such as carotid bifurcation, chalice sign, and gothic aortic arch, have been identified in LDS but do not impose independent vascular risk nor inform disease severity.[53,55,56]

Medical therapy

Evidence for medical therapy to suppress abnormal aortic growth in vascular connective tissue disorders derives primarily from MFS/LDS animal models and MFS clinical studies.[57] In mouse models of MFS, both beta blockers (BBs) and angiotensin receptor blockers (ARBs) suppressed abnormal aortic root growth, with ARBs showing greater effect. In LDS mouse models, only ARBs were effective.[58] Both medications are commonly used in MFS or LDS clinical care. A recent meta-analysis showed ARB therapy halved aortic root growth rate in individuals with MFS patients compared with controls, with enhanced benefit in genetically confirmed cases.[57] There is suggestion that combined treatment with ARBs and BBs might afford synergistic benefit.[57]

ARBs' therapeutic effect stems from modification of arterial wall cellular signaling rather than hemodynamic (blood pressure) effects, addressing the increased TGFβ and extracellular signal-regulated kinase signaling seen in MFS/LDS mouse models.[59,60] Therefore, optimal dosing targets tolerance rather than hemodynamic response (2.0 mg/kg/day of losartan up to 100 mg or 8.0 mg/kg/day up to 300 mg of irbesartan).

For LDS, expert opinion recommends ARBs or BBs based on mouse data and mechanistic similarities to MFS. Dual therapy may be considered for progressive aortic growth on monotherapy. The dose of one medication should be fully optimized based on tolerance before up-titrating a second medication. Heart rate/rhythm issues may independently warrant BB therapy, whereas a history of refractory asthma or depression would strongly favor ARB use. If medication is discontinued, gradual tapering is suggested.[61,62] Consensus supports early medication initiation in LDS for maximum benefit.[63] For individuals with LDS with normal aortic diameters, medical treatment decisions should consider family history of aneurysm/dissection and genes or specific pathogenic variants previously associated with aggressive vascular disease. Note that ARBs are teratogenic and contraindicated during pregnancy.

Individuals with LDS should receive standard management for cardiovascular risk factors (hypertension, dyslipidemia) and avoid smoking and substance abuse. Medications potentially exacerbating blood pressure should be used judiciously, weighing risks and benefits based on vascular disease status (Table 4).[70,71]

Exercise

Expert consensus recommendations for LDS and genetic aortopathies previously advised avoiding contact or competitive sports, isometric exercises, exhaustive exertion, and activities with routine chest or head impacts.[72] The 2015 AHA/ACC guidelines for competitive athletes, extrapolated from MFS experience, permit competitive athletes with LDS to participate in low static/dynamic sports in the absence of high-risk features (aortic enlargement (z-score > 2) or dissection, branch vessel enlargement, moderate-to-severe mitral regurgitation, or hazardous extracardiac involvement (atlantoaxial/cervical instability, joint hypermobility, retinal detachment).[73] A family history of early and/or aggressive vascular disease should also be considered. Families and their multidisciplinary teams should use shared decision making for exercise recommendations.[73]

Exercise caution stems from established evidence that normal systolic blood pressure elevations during exercise increase hemodynamic wall stress on the aorta. Intensive isometric activities, such as weightlifting, can trigger systolic pressures as high as 250 mmHg.[74] The benefits of regular physical activity to control body weight, contribute to joint stabilization, reduce fatigue, and improve mental health and quality of life should be prioritized and discussed.[75]

Cardiac surgery

Prevention of aortic catastrophe (Stanford type A or type B dissection, rupture) through comprehensive cardiac surgical management remains the central objective of surveillance measures and prophylactic aortic surgery.[76,77] Aortic or mitral regurgitation can be observed and should be assessed in parallel with aortic aneurysm.[1] Isolated cases of coronary artery aneurysm and spontaneous coronary artery dissections have been reported in adults with LDS.[78-80]

Natural history data have refined our understanding of aortic disease severity across LDS subtypes and genetic variants. Current guidelines from ACC/AHA and EACTS/STS have evolved beyond focusing solely on aortic dimensions and growth rates, now incorporating individual factors, including genotype, extraaortic features, family history, and physician-patient preferences (Table 5).[64,83] These nuanced recommendations acknowledge risk uncertainty and emphasize genetic testing and multidisciplinary management. Although comprehensive genotype data remains limited, emerging evidence identifies specific variants associated with aggressive aortic phenotypes (eg, *TGFBR2* (*NC_000003.12:g.30691477G>A*; *NM_003242.6:c.1583G>A*; *NP_003233.4:p.Arg528His*), *TGFBR2* (*NC_000003.12:g.30691476C>T*; *NM_003242.6:c.1582C>T*; *NP_003233.4:p.Arg528Cys*),[14] and *TGFBR1* (*NC_000009.12:g.99137882C>T*; *NM_004612.4:c.599C>T*; *NP_004603.1:p.Thr200Ile*)).[20,84,85] Ongoing genotype-phenotype studies aim to improve risk stratification.

Aortic root replacement surgery is generally advised for people with LDS1-3 at 4.0 to 4.5 cm diameter, with lower thresholds for those with additional risk factors (Table 5). There is comparatively less experience with LDS4-6; however, they typically present with less aggressive aortic phenotypes and intervention at aortic root dimensions ≥ 4.5 cm may be reasonable. Other potential indications for

Table 4 Medications that require careful consideration of risks and benefits and frequent monitoring in people with selected vascular connective tissue disorders including LDS

Medication Type and Use	Examples (US-Based)	Alternatives	Reasoning
Calcium channel blockers for blood pressure	amlodipine, verapamil	Angiotensin receptor blockers, beta-blockers	Mouse models of MFS as well as case control studies in MFS and other inherited aortopathy patients in the GenTAC registry showed deleterious effects of long-term calcium channel blocker use. It may be best to avoid these agents in patients with MFS (and by extension LDS) unless necessary to achieve BP control[64]
Attention deficient, hyperactivity disorder (ADHD) stimulants	amphetamine dextroamphetamine (ex. Adderall); methylphenidate (Concerta, Ritalin)	Non-stimulants: atomoxetine (Straterra), viloxazine (Qelbree), guanfacine (Intuniv), clonidine	Long-term exposure to ADHD medications is associated with an increased risk of hypertension and arterial disease. Could first explore non-stimulant medications. However, quality of life must be weighed; BP and heart rate should be monitored throughout the course of treatment[65]
Vasoconstrictors/triptans for migraines	sumatriptan (Imitrex)	Discuss with headache specialist; Prophylaxis: supplementation like magnesium, beta-blockers or candesartan (even in patients with normal aortic dimensions and low risk variants); Abortive strategy: soluble Aspirin +Tylenol +/- caffeine Calcitonin gene-related peptide receptor blockers (CGRP; Rimegepant, Ubrogepant) or 5HT agonists (Nurtec)	A case/non-case analysis for the Food and Drug Administration Adverse Event Reporting system in 2014 revealed three main groups of unexpected associations between triptans and serious vascular events: ischemic cerebrovascular events, aneurysms and arterial dissections, and pregnancy-related vascular events[66]
Decongestants (with Ephedrine) for allergies and congestion	pseudoephedrine phenylephrine, phenylpropanolamine and oxymetazoline	Antihistamines including Allegra, Benedryl, Travist, Zyrtec. Formulations of Allegra and Zyrtec that contain pseudoephedrine exist and should be used with caution)	Ephedrine increases blood pressure by stimulating heart rate and cardiac output and variably increasing peripheral vascular resistance (FDA Approved Drug Products: Akovaz Ephedrine Sulfatre Intravenous Injection)
Epinephrine Auto-injector	EpiPen, Auvi-Q	Treat with antihistamine if mild symptoms involve a single system after exposure to allergen (ex: localized hives, vomiting only). If reaction involves the respiratory system (wheezing, difficulty breathing), hypotension, fainting or turning blue, or more than one body system(such as hives and vomiting), an epi-pen should be administered	Epinephrine causes spikes in blood pressure, increased heart rate and contractions of the heart which may be dangerous for individuals with connective tissue disorders[67]

(continued)

Table 4 Continued

Medication Type and Use	Examples (US-Based)	Alternatives	Reasoning
Antibiotics	Fluoro-quinolones like cipropoflaxacin levofloxacin, gemifloxacin, moxifloxacin	Other classes of antibiotics to which the specific pathogen is sensitive.	FDA reviewed data that fluoroquinolones were associated with increased incidence of aortic aneurysm formation in US adults, and not just in high risk aortopathy patients. This association was consistent across adults aged 35 years or older, sex, and comorbidities[68]
Non-selective beta-blockers (specifically for patients with active and chronic asthma) using inhaler	propranolol, labetolol, carvedilol	selective beta-blockers include atenolol (Tenormin), metoprolol succinate (Toprol XL)	Non-selective β-blockers should not be prescribed for the management of comorbidities in patients with asthma, whereas cardio-selective β-blockers, preferably in low doses, may be used when strongly indicated and other therapeutic options are not available[69]

Medications that require careful consideration of risks and benefits and frequent monitoring in people with selected vascular connective tissue disorders including LDS. This does not mean these medications should not be used, but conversation and shared decision making should be considered for their use.

surgical intervention for aortic root enlargement include emergence of significant aortic valve regurgitation or a rapid rate of aortic growth, in excess of 0.5 cm/year. Valve-sparing aortic root replacement with reimplantation technique (VSARR with David procedure) is preferred unless prohibited by irreparable valve morphology. Acute aortic dissection cases require root replacement during the index operation, either with composite valve-graft replacement (bioprosthetic versus mechanical dependent on age) or valve-sparing aortic root replacement with reimplantation technique. Although bicuspid aortic valve (found in ~10% of people with LDS) may affect long-term durability it is not an absolute contraindication to valve-sparing surgery.[86] These operations should be performed at centers with extensive experience with hereditary aortopathies. Early case reports of coronary artery pseudoaneurysm following root operations may be related to felt buttress use in coronary anastomoses, rather than LDS tissue itself. Care is taken to remove as much aortic tissue around the coronary arteries as feasible as reimplanting large patches of aortic tissue with coronary buttons may predispose to development of coronary button aneurysms over the long term. Pulmonary autografts (Ross operation) should not be used in LDS patients owing to concerns about tissue integrity and neoaortic aneurysm formation.

Personalized external aortic root support (PEARS), available in select European centers, has been used in 57 people with LDS and 375 people with MFS among 1024 total procedures (ages 3-80 years) as of May 2024. With only 3 deaths in 862 aneurysm cases (perioperatively, 43 days and 7 months postoperatively), patient uptake over the past 8 years has increased. Although a large registry and further follow-up studies would be beneficial, PEARS may be considered for preventative aortic root surgery at smaller dimensions (low-4-cm range) in adults with LDS.[87] Benefits may include avoidance of extracorporeal circulation and reduced risk for pseudoaneurysm development. It can be performed in conjunction with surgery for mitral valve dysfunction, patent ductus arteriosus, and septal defects.[88] Concerns remain about coronary artery complications and the potential for acceleration of risk for aneurysm or dissection of more distal aortic segments.

For isolated ascending (supracoronary) and aortic arch dilation, similar 4-to-4.5-cm thresholds apply, although more research is indicated to refine recommendations.

Replacement of the proximal thoracic aorta with rigid Dacron material affects hemodynamic and biomechanical forces distal to the graft, but relevance to downstream aortic pathology remains uncertain.[89,90] Clinical experience has demonstrated that people with LDS exhibit more frequent aneurysm and/or dissection of the residual distal ascending aorta, arch, and proximal descending thoracic aorta relative to those with MFS after root operations.[77,91,92] Some centers advocate for complete replacement of the ascending aorta at the time of initial surgical intervention for aortic root aneurysm in LDS.[17]

Selected high-volume centers advocate for partial and total arch replacement strategies with initial aortic root surgery.[91,93] The challenge is to balance the perceived risk of future events against potential complications related to more complex surgery, longer cross-clamp time, and need for circulatory arrest during arch reconstruction. When performing arch replacement, circumferential resection to at least the takeoff of the left subclavian (zone 2) is preferred by some

Table 5 Surgical thresholds for prophylactic aortic root replacement in Loeys-Dietz syndrome based on genetic variant/type of Loeys-Dietz syndrome

Genetic Variant	Range of Aortic Diameters for Surgical Threshold*
TGFBR1 (LDS1)	4.0-4.5 cm
TGFBR2 (LDS2)	4.0-4.5 cm
SMAD3 (LDS3)	4.0-4.5 cm
TGFB2(LDS4)	4.5 or > cm
TGFB3 (LDS5)	5.0 cm
SMAD2 (LDS6)	5.0 cm (not well studied; may need refinement based on larger patient cohorts)
IPO8	Insufficient data

*Lower range of surgical threshold indicated when medical team perceives higher risk of aortic dissection including the following:

- Family history of early dissection or dissection at relatively small diameters
- Literature describing aggressive vascular disease with genetic variant
- Severe extra-aortic features (ie, craniosynostosis, cleft palate, hypertelorism, marked arterial tortuosity, widened scars)[3,81]
- Rapid aortic growth (Adults: >0.3 cm/yr in 2 consecutive years or 0.5 cm in 1 yr)
- Progressive or severe aortic valve regurgitation
- Aortic valve size: >2.0 cm preferred in children
- Desire for pregnancy

PEARS considerations

- Preference for smaller diameters in low 4 cm range
- Absence of aortic valvular disease, maximum AI one-third or mild aortic regurgitation on tricuspid aortic valve; bicuspid valve with well-appearing cusps
- Consider concomitant aortic root replacement if needing surgery for MVP and aorta is in the low 4-cm range (expert opinion)[82]

centers over hemi-arch replacement of only the lesser curve of the arch in order to remove all tissue that may provoke a difficult future redo operation via sternotomy. These operations should only be performed in experienced centers due to technical complexity and increased neurovascular risk. Determination of the optimal arch management strategy for individual patients remains an area of investigation and will require long-term multicenter long-term follow-up.

In children with LDS, valve-sparing operations have been successful in infants under 1 year of age. Optimally, initial surgery can be delayed until the annulus diameter exceeds 2.0 cm, allowing placement of a graft of sufficient size to accommodate somatic growth. Postoperative, sometimes delayed, anastomotic pseudoaneurysms have been reported and should be managed operatively.[94] Pulmonary artery aneurysm may occur, with fatal pulmonary artery dilation and rupture reported in 2 unrelated cases of infants with *TGFBR1* T200I variants and complex congenital defects.[20,95]

Vascular

In LDS, comprehensive aortic and arterial imaging is crucial as people show arterial pathology throughout the arterial tree, with LDS2 (*TGFBR2*) showing the most aggressive aortic disease.[24]

After establishing a baseline, surveillance imaging should be considered every 2 years in the absence of any new or worrisome findings. Intervals can be tailored based on genotype and clinical stability. Consultation with a cardiothoracic, vascular, and/or neurological surgeon can inform surveillance methods and frequency and the establishment of thresholds for intervention.

Although surveillance tracks aortic and arterial dilation to mitigate rupture and dissection risk, type B aortic dissections have been reported with minimal or no prior enlargement of the involved aortic segment in several LDS subtypes, with the potential for subsequent rapid aneurysmal expansion.[76,96] This propensity for rapid change after dissection should guide postevent imaging follow-up (typically at discharge, 3, 6, and 12 months, then yearly if stable; the European guidelines in (Table 3) are somewhat less stringent). Guidelines suggest repair of the descending and abdominal aorta in LDS at smaller diameters than the general population (≥4.5 cm in patients with LDS1-3) with threshold adjustment for high-risk features, including age, aortic growth rate, concomitant surgical risk factors and significant family history of more aggressive disease.[64] For other LDS subtypes, some advocate for genotype-specific approaches similar to thoracic aortic guidelines, with larger dimensions for LDS5/6, and slightly lower diameters in LDS4.[64] All people with LDS should be considered for referral to centers with multidisciplinary teams given improved outcomes for patients with genetic aortopathies in this setting.[97]

Extraaortic vascular pathology occurs in nearly all vascular beds including the iliac, femoral, popliteal, splenic, mesenteric, and renal arteries; all have been addressed via both open and endovascular means.[24,98,99] Surgical intervention should be considered with rapid expansion or when arterial size exceeds 2 to 3 times the expected diameter.

Although these recommendations are similar to those for the general population, additional risk-benefit considerations may differ from nongenetic disease patients.[100] Although high-level data on stenting versus open repair are lacking, case reports suggest successful application of endovascular stenting within visceral arteries. Stent oversizing should not exceed 10% of the arterial diameter and aggressive balloon dilation should be avoided to prevent dissection. Branch vessel stenting for aneurysms may require more frequent intervention than in the general population and should be used sparingly when open surgery is a viable option.

For aortic intervention, open, endovascular and hybrid strategies are options, although only open repair has been validated by long-term data. Open repair remains optimal for elective thoracic or abdominal aortic procedures for those who can tolerate the cardiopulmonary stress of an open operation. Because many people with LDS require multiple arterial interventions, strategies facilitating staged repair should be considered in the course of operative planning.[101-103] Examples include frozen elephant trunk techniques anticipating future endovascular extension of a proximal repair or clamping for future replacements.[104] Emerging evidence suggests that people with LDS may have higher risk for late pseudoaneurysm at suture lines warranting felt reinforcement and targeted postoperative surveillance.[94,96]

A general rule is to avoid the implantation of endovascular stent grafts in the native aorta because of the theoretical risk for complications due to uncertain LDS aortic response to the associated radial force. Although historically avoided, contemporary approaches are exploring endovascular stenting as both a primary and hybrid strategy for LDS aortic pathology.[103,105]

No data exist on aortic stent graft safety specific to LDS because patients with genetic aortopathies are excluded from relevant trials. Endovascular stent grafts are considered safe with a stable proximal landing zone (ie, a surgically repaired arch), which obviates the concern for retrograde type A dissection, although secondary procedures for seal problems are common.[103,104,106] No retrograde type A dissections in LDS have been reported, but proximal landing zone complications may be higher in LDS patients when compared with other genetic aortopathies when TEVAR is deployed in a native proximal landing zone.[106] In emergencies, stent-graft oversizing should be limited to 10% to mitigate risk of retrograde dissection. There have been isolated reports of modifying commercially available stent grafts to reduce radial forces to improve safety.[107] Early evidence suggests that percutaneous closure devices appear safe without increased risk of access site complications or need for femoral cutdown.[108]

Regardless of approach, a comprehensive understanding of arterial anatomy is essential to ensure safe and effective operative planning. In addition to the propensity to develop spontaneous aneurysms and dissections, LDS arterial tortuosity can influence the clamping strategy for an open surgery and the delivery strategy for an endovascular procedure. Dural ectasia does not preclude lumbar catheter placement for cerebrospinal fluid drainage, although patients face a higher risk of complications such as postdural puncture headache requiring a blood patch. One series of people with MFS and LDS found a 3-fold increased risk of cerebral spinal fluid (CSF) leak compared with the general population.[109] Experienced anesthesia teams should help manage lumbar drains, use ultrasound guidance for arterial and central venous line placement, and maintain strict hemodynamic control during surgery to prevent iatrogenic dissection and spinal cord injury. Postoperative care should include frequent neurovascular checks and hemodynamic monitoring to quickly address complications.

Neurovascular

Neurovascular manifestations of LDS include increased incidence of intracranial aneurysms, cervical and intracranial vessel tortuosity, and cervical arterial dissection or rupture.

Intracranial aneurysms

Intracranial aneurysms have a reported prevalence of 10% to 32% in LDS (*TGFBR1* 19%, *TGFBR2* 20.8%, *SMAD3* 46.2%, *TGFB2* 13.3%, *TGFB3* 14.3%), versus 1% to 4% in the general population.[110-113] Individuals with *SMAD3* variants show the highest frequency (23%-46%.)[5,110,114,115] Only 1 patient with *IPO8* has been reported with carotid or cerebral aneurysm, although this remains underexamined.[116]

In the general population, unruptured intracranial aneurysms are most commonly located in the middle cerebral artery (35%), anterior communicating artery (15%), or posterior communicating artery (10%-15%).[117,118] In LDS cohorts, aneurysms predominantly affect the internal carotid artery in the paraclinoid/supraclinoid (11%-46%), cavernous (17%-21%), and ophthalmic (14%-17%) segments, or along the anterior cerebral (4%-14%) or middle cerebral (8%-11%) arteries.[110,111,119] Aneurysms are primarily saccular in morphology (71%-88%).[110,119]

Rick factors for intracranial aneurysms in LDS include active smoking (OR 4.3-7.6), Chiari malformations, and nonaortic arterial dissections.[110,119-121] Cervical vessel tortuosity does not demonstrate consistent predictive value for intracranial aneurysms.[53] Aortic pathology does not show consistent association with intracranial aneurysms. People can have normal aortas and cerebrovascular aneurysms.[110,121] Similarly, common phenotypic features in LDS (craniosynostosis, hypertelorism, abnormal uvula, teeth crowding, doughy skin texture, thin/translucent skin, and the composite craniofacial index score) fail to predict intracranial aneurysms.[120]

Given the relatively high rate of intracranial aneurysm in LDS, screening CT- or MR- angiography of the head and neck is recommended. Age and frequency of head/neck imaging should be tailored based on genotype and family history of intracranial aneurysms. As we tend to obtain head to pelvis imaging, this would follow other screening

recommendations for the entire vasculature (Table 3). Although CT angiography offers slightly higher sensitivity for detection of small aneurysms, MR angiography is preferred for routine screening, especially in younger people, to minimize radiation exposure.[122] When an intracranial aneurysm is identified, neurosurgical referral is recommended to determine the need for catheter angiography, ongoing surveillance, or treatment.[72,123] Unlike VEDS, LDS does not appear to carry increased risks with invasive catheter angiography compared with the general population, and the authors believe that this diagnostic and/or treatment modality can be used safely and effectively.[124,125]

Intracranial aneurysms in LDS are typically small (3.0-4.8 mm average diameter.)[110-112] Individuals with LDS show a do novo aneurysm rate of 3.11%/patient year (compared with 1.14%/person year in the general population) with growth rate averaging 0.43 ± 0.53 mm/year, similar to that of the general population.[52,126] These finding suggest that aggressive early intervention is likely not needed.

For ruptured, symptomatic, large, or growing intracranial aneurysms, treatment options may include open surgical or endovascular interventions. Although isolated reports note increased vessel reactivity and vessel friability during surgery of intracranial aneurysms, other cases demonstrate uncomplicated outcomes.[119,127-129] Endovascular treatments (coiling, stent-assisted coiling, flow-diverting stents) have been successfully employed, although one case in a 3-patient series experienced vertebral artery occlusion causing transient hemiparesis.[52,119,130-133]

Despite the high prevalence of intracranial aneurysms, intracranial hemorrhage remains uncommon (0%-7%), with bleeding events attributed to ruptured aneurysms, cervical vessel dissections, or due to unclear etiology.[3,111,119]

Cervical and cerebral arterial tortuosity and dissection

Both cervical and intracranial vessel tortuosity are hallmarks of LDS.[111] Cervical tortuosity correlated with worse neurovascular outcomes, including higher rates of cervical vessel dissection, ischemic stroke, and intracranial hemorrhage.[53] Cervical vessel dissection is common (7%-38%).[111,114] Although often incidental or asymptomatic, these dissections can lead to thromboembolic events and large or multiple vessel dissections resulting in stoke have been reported.[5,53,111,134]

For acute dissections, we recommend following national guidelines using either antiplatelet agents or anticoagulation.[135] Carotid and vertebral arterial stenting, not advocated for acute cervical dissections in the general population, are likely even less beneficial in LDS. Cervical pseudoaneurysms, resulting from arterial wall disruptions during dissection, rarely rupture because of the thick layer of adventitia seen in the cervical carotid vasculature. Therefore, antiplatelet therapy with serial imaging is generally preferred, reserving surgical or endovascular intervention for extreme or progressive cases.

Given the pervasiveness of neurovascular involvement in LDS, management is best conducted at specialized LDS referral centers with cerebrovascular specialists.

Craniofacial and orodental

There is significant variability in the craniofacial phenotypes with LDS, with higher prevalence of craniofacial anomalies in LDS1/2.[24,136] The most common craniofacial and oral features include: midface flatness, mandibular retrognathia, downslanting palpebral fissures and blepharoptosis, eye asymmetry, low-set ears, hypertelorism, TMJ symptoms, enamel defects, high-arched/narrow palate, and bifid uvula/cleft palate.[136,137] A comprehensive craniofacial anomalies index has been developed for clinical research purposes.[136]

Craniosynostosis of 1 or more cranial sutures has been described in most subtypes of LDS.[138-140] The majority are mild, nonsurgical cases that result in asymptomatic skull asymmetry but may impact self-esteem over time. Surgical cases follow standard protocols, typically followed by helmet therapy. Early intervention improves neurological and developmental outcomes.

Functional craniofacial anomalies include retrognathic mandibles, causing dental overbite.[7,136,139,141] Temporomandibular joint disorders (TMDs) and obstructive sleep apnea (OSA) have also been described at an early age.[136,137] TMD correlates with reduced oral health-related quality of life, necessitating early monitoring and possible radiographic evaluation of the TMJ, even at an early age.[142] OSA symptoms require careful assessment because of the correlation between OSA and pulmonary hypertension.

Hard and soft cleft palates are reported and require multidisciplinary treatment.[24,136] Although a bifid uvula needs no intervention, it necessitates examination for submucous cleft palate, which may require surgical correction if there is impact on speech. Clefts should be managed according to typical protocols by a craniofacial anomalies team.

Early orthodontic/facial orthopedic treatment may be needed to correct mandibular retrognathia or maxillary growth alterations from cleft palate. Correcting dentoskeletal discrepancy improves oral function and may reduce OSA and TMD risks.

Distinct dental manifestations have also been described, most prominently in LDS2 and 1, with enamel defects ranging from mild discoloration (grade 1), severe pitting and grooving (grades 2 and 3), to enamel flaking off with dentin exposure (grade 4).[24,137,143] This severe enamel defect (grade 4) is highly suspicious for LDS2, although not all patients present with it.[137] Other findings include delayed permanent tooth eruption, retained deciduous teeth, dental crowding, increased risk of caries, and Angle's class II malocclusion or overbite (upper teeth protruding over lower teeth).[4,137] These anomalies can contribute to a lower oral health-related quality of life.[142] Tooth sensitivity due to exposed dentin from enamel defects and difficulty chewing and speech impairments can also arise from malocclusion

and palatal abnormalities. Good dental management is important to prevent further complications, such as pain, infection, and tooth loss.[143] This includes regular dental care, fluoride treatments to strengthen the teeth, orthodontic treatment, and, when necessary, restorative procedures, such as fillings or crowns, to repair damaged teeth.

Audiologic and otolaryngologic/ENT

Recent studies show 30% to 42% of people with LDS experience hearing loss ($n = 72$ and 36, respectively).[144,145] Jeon et al[145] found conductive hearing loss primarily in LDS1/2 and sensorineural hearing loss in LDS3/4. Submucosal and hard cleft palate occur more frequently in LDS1/2, and 73% of people with cleft-related Eustachian tube dysfunction requiring ventilation tubes (myringotomy or tympanostomy) for recurrent otitis media. Posttube tympanic membrane perforation rate (50%) significantly exceeds that in typical cleft palate cases (16%-18%). LDS5/6 remain understudied.

Audiological evaluations with Otology are essential to assess hearing aid needs to optimize language acquisition and communication. LDS hearing loss progression rates remain unknown. Adults should undergo baseline testing. Children need regular assessment beyond newborn screening because even mild hearing loss affects educational outcomes and speech development. Beyond newborn screening, testing should be considered at age 2 years of age, kindergarten entry and every 3 to 4 years thereafter (or sooner with hearing concerns or frequent ear infections).

Palate anomalies cause Eustachian tube dysfunction leading to chronic/recurrent otitis media and hearing loss. Although ventilation tubes treat persistent otitis media, their placement requires careful consideration due to higher nonhealing tympanic membrane perforations after extrusion. Both outer and middle ear cholesteatomas result from chronic Eustachian tube dysfunction and/or epithelial migration defect and are more frequent in LDS. This necessitates thorough microscopic ear examination, especially in those with clefts. Diagnosed cholesteatomas require prompt referral to an otologist or pediatric otolaryngologist.

Ocular

Individuals with LDS exhibit various ocular manifestations. External features include down slanting palpebral fissures, telecanthus, hypertelorism, blepharoptosis, proptosis, strabismus, and blue/dusky sclera.[24,72,136,146]

LDS-associated myopia is typically mild to moderate and primarily axial in nature. It is often less severe than in MFS, which involve both axial and lenticular components.[147] Rare reports of rapid myopic shifts have been reported.[148]

Strabismus is relatively common in LDS.[146,149] Notably, extraocular muscle hypoplasia/atrophy, affecting rectus muscles has been reported which requires consideration during surgical planning.[148,150]

Rare corneal manifestations including keratoconus, cornea plana, reduced central corneal thickness, corneal endothelial cell loss, and glutatta.[151,152] Central corneal thickness reduction may affect intraocular pressure readings, but does not increase corneal rupture risk.[138] These corneal findings also occur in MFS.

Unlike MFS, LDS typically lacks ectopia lentis, although exceedingly rare case reports of mild presentations exist.[2,146] It remains unclear whether this incidence exceeds findings in the general population. Adult cataracts have been reported.[24]

Retinal complications occur in all LDS types except for LDS3 (thus far).[72,146,153-155] These include retinal detachment, moderate-to-severe retinal arterial tortuosity (clinical significance undetermined), peripheral retinal nonperfusion, and retinal arterial macroaneurysm.[156] True prevalence rates remain unknown.

Systemic arterial dissection in LDS can cause ocular manifestations, as in 1 case of Horner syndrome from subclavian aneurysm leak.[157]

No evidence-based guidelines exist for eye examination frequency in LDS. Baseline full ocular evaluation with dilated fundus examination is recommended with follow-up as indicated, with low threshold for evaluation with change in vision. Specific vigilance is warranted in early childhood to prevent amblyopia.

People should be educated about retinal detachment symptoms (new and persistent photopsia, floaters, and vision loss) and instructed to seek immediate care. To date, no evidence suggests LDS requires modified surgical approaches for retinal detachment.

As with all connective tissue disorders, no data support or refute topical atropine eyedrops for myopia control, nor is there substantial evidence regarding refractive surgeries including laser-assisted in-situ keratomileusis, photorefractive keratectomy, or small incision lenticule extraction. Although algorithms exist for refractive surgery in connective tissue disorders, they mainly guide future trial questions rather than establishing current clinical standards.[158]

Allergy and immunology

LDS1 and LDS2 have been associated with an increased prevalence of allergic diseases including asthma, immunoglobulin E (IgE)-mediated food allergy, eczema, and allergic rhinitis.[159-161]

Elevated total and allergen-specific IgE levels and peripheral eosinophilia are common.[159] Rates of allergic disease may also be increased in LDS3.[162] HyperIgE, eosinophilia, and allergic phenotypes are reported in *IPO8*-related disease as well.[163] Clinical presentation, work-up, and treatment responses in people with LDS mirror the general population. Common food allergens include milk, peanut, egg, tree nuts, soy, and wheat. Antihistamines should be used to treat cutaneous or milder food allergic reactions, and epinephrine should be reserved only for life-threatening reactions because of the need to avoid blood vessel constriction and tachycardia in people with underlying vascular disease. Avoid Palforzia, (FDA-approved peanut oral immunotherapy) because of the high rate of allergic reactions and need to use epinephrine.[164]

Omalizumab, an FDA-approved monoclonal antibody that sequesters free IgE and prevents its binding to the IgE receptor could be considered as a suitable therapy to prevent allergic reactions following accidental food allergy exposures.[165] There are no specific contraindications for Dupilumab, an anti-IL-4/13 receptor antagonist used to treat eczema, asthma, and eosinophilic esophagitis, for those with LDS.

LDS may predispose to a greater predisposition for autoimmune disease. LDS3 and 5 have been reported to have autoimmune features, including thyroid disease, HLA-B27 positive spondylarthritis, rheumatoid arthritis, and Sjogren's syndrome.[8,160,161] Vaccine responses and antibody levels are generally normal, with total immunoglobulin G levels often at the upper limit of normal.[8,163] Immune deficiency is not common. Sinus disease and ear infections may result from mucus buildup secondary to allergen exposure, as well as altered craniofacial anatomy. Aggressive treatment of sinus infections often improves asthma control.

Gastroenterology

Constipation is frequent in LDS.[166,167] Initial treatment includes proper hydration and daily oral polyethylene glycol 3350 (PEG-3350).[168] For longstanding constipation, bowel clean-out (either oral or via nasogastric tube) may be necessary before beginning daily PEG-3350. Stimulants of bowel motility, such as bisacodyl or senna, may supplement this regimen, if needed. Pelvic floor dysfunction, common in adult females with LDS, may contribute to constipation difficulties.[169]

Failure to thrive is common in infants and children with LDS1/2, but prevalence is unknown in other types.[159] Monitor height, weight, and body mass index (weight for length for those less than 2 years old) at each visit. Provide caloric supplementation when indicated, especially presurgery. Management generally follows traditional protocols. Consider extensively hydrolyzed or isolated amino acid formulas with signs or symptoms of cow's milk or soy formula intolerance.[159] Nasogastric feedings and gastrostomy tubes (placed surgically or percutaneously), have been successfully used in LDS with severe or refractory failure to thrive.[170]

Failure to thrive is less common in adults; half of adults with LDS in 1 small study were obese by percentage body fat criteria.[171] Potentials causes of failure to thrive include repeated surgeries/hospitalizations, mastication muscle weakness, difficulty accruing subcutaneous fat (similar to MFS), cleft palate, dysphagia, or food avoidance due to allergies and increased caloric expenditures from incompletely treated conditions (asthma, eczema, and/or intestinal inflammation). There is also an increased risk of gastroesophageal reflux in LDS.[166,167]

Given the skeletal fragility and low bone mass seen in LDS, monitor calcium intake and supplement if below age/sex-specific recommended levels.[172,173] Periodically check vitamin D levels and supplement per guidelines.[174]

LDS is associated with a high prevalence of IgE-mediated food allergies, chronic gastrointestinal (GI) symptoms, and eosinophilic gastrointestinal disease (EGID), including eosinophilic esophagitis.[159] A recent case series showed 66% of patients reported GI complaints (poor growth, repetitive vomiting, chronic abdominal pain, and dysphagia) with 60% of those who had undergone endoscopy showing evidence of eosinophilic esophagitis, eosinophilic gastritis, and/or eosinophilic colitis. The majority of patients with EGID improved on allergen-avoidance diets. People with *IPO8* may also present with allergic symptoms and eosinophilia.[116,163]

Inflammatory bowel disease (IBD, ulcerative colitis and Crohn's disease) occurs in approximately 4% of people with LDS1/2, sometimes with very early onset (<6yo) and treatment challenges.[163,175-177] Use standard protocols for investigating and managing EGID and IBD.

For endoscopy, determine cervical spine stability beforehand (although instability is not an absolute contraindication). Consider anesthesiologist assistance and maintain good blood pressure control. Exercise care when positioning patients due to fracture and joint instability risks. Although connective tissue abnormalities theoretically increase perforation risk during scoping procedures, we have not seen this as a common occurrence (A. Guerrerio, personal communication), although 1 case occurred during colonoscopy in a patient with severe pancolitis.[177] Screening colonoscopies have no contraindications.

Malrotation and congenital diaphragmatic hernia have been reported in children with LDS.[113,166,177,178] Other reported conditions include hiatal hernias (widely reported) and a single gastric perforation after minor trauma in LDS6 and gastric volvulus (2 cases, A. Guerrerio, personal communication).[8,166,179] Celiac disease is reported in LDS5, but not LDS1/2.[8,159] GI manifestations are better documented in children than adults.

Orthopedics

Spine-scoliosis

Scoliosis occurs in all 6 subtypes of LDS, developing early with incidence up to 62% in some studies.[180,181] Physicians should monitor for spinal deformity and refer to orthopedics if there is concern of new-onset or progression. Bracing (considered at 15-30 degrees) is less effective than in adolescent idiopathic scoliosis and often only delays surgical intervention.[180]

Surgery is often indicated for rapidly progressing curves ($\geq$ 50 degrees postpuberty; $\geq$ 70 degrees prepuberty to allow growth).[180] Growing rods and fusion correct deformity but carry higher complication rates that in adolescent idiopathic scoliosis.[180,182,183] Surgical challenges include difficult anchor placement due to thin pedicles/laminae, and osteopenia; frequent CSF leaks (related to dural ectasia in up to 70% of patients); increased intraoperative blood loss; and requirements for pelvic fixation and/or extended fusion.[180,182] Anchor failure or junctional deformity commonly occur postoperatively (P. Sponseller, personal communication)

Spine-spondylolysis and spondylolisthesis

Spondylolysis and spondylolisthesis occur more frequently and severely in LDS because of joint laxity and osteopenia, with incidence around 17% (types 1-4), exceeding general population rates.[184] These conditions commonly present together as isthmic spondylolisthesis. In patients with an intact posterior ring, vertebral slippage can increase neural compression, causing cauda equina syndrome. About 40% of people with LDS with spondylolisthesis will develop ≥50% vertebral slippage, necessitating spine stabilization.[184]

Spine-cervical spine instability

Midline defects and cervical spine anomalies (C1 arch midline fusion defect, bifid anterior or posterior atlas) frequently occur in LDS1/2.[185] Cervical kyphosis, particularly at the C2-C3 level, often results from C3 hypoplasia causing C2 anterior subluxation over C3. Cervical instability can present in early childhood with neurological deficits, warranting flexion/extension neck radiographs during initial LDS evaluations. Ongoing assessment is recommended at key developmental stages; infancy (1-2 years)/time of diagnosis, childhood (6 years), adolescence (14 years), early adulthood (21 years old) and after spinal fusion. Intervention is typically undertaken when the cervical cord appears at risk (considering any stenosis and degree of abnormal anterior-posterior translation).[185]

Given limited data on cervical instability in other LDS types, a low threshold should be in place to obtain baseline radiographs in all patients.

Limb deformities and disorders—hip, knee, and feet

Hip subluxation, acetabular protrusion, and femoral neck shaft angle alterations are common in LDS.[186] Genu valgum is also common, and can be treated with hemiepiphysiodesis, requiring timely implant removal to prevent overcorrection.

Foot deformities affect up to 81% of people with LDS, typically bilaterally, including pes planovalgus (flatfoot), talipes equinovarus (clubfoot), hindfoot valgus, and metatarsus adductus.[187] Pes planovalgus prevalence stems from ligamentous laxity and musculoskeletal imbalance. Paradoxically, contractures such as camptodactyly or clubfoot often occur despite ligamentous laxity—a pathogenesis not yet explained. Serial Ponseti casting improves LDS clubfoot without overcorrection risk.[188] Posteromedial release is indicated when casting fails to enable comfortable shoe-wearing or standing, although it risks overcorrection into hindfoot valgus.[187]

Adult LDS phenotypes affecting the musculoskeletal system

Although less studied, adult LDS musculoskeletal features can be significant. Scoliosis frequently causes pain from secondary inflammation and osteoarthritis, particularly at points of maximal strain at the top and bottom of fixation rods. Foot abnormalities can involve tendinopathy and tendon and ligament tears. Secondary osteoarthritis may occur from knee valgus and varus deformities. Both joint malalignment and intrinsic disease biology (TGFβ pathway) are likely to contribute to these risks. Joint dislocation and subluxation (in both large and small joints) may persist into adulthood, though patients often self-manage these events.

Bone fragility and endocrinology

Skeletal fragility commonly occurs in LDS with cross-sectional series demonstrating low bone density on dual-energy X-ray absorptiometry, and frequent long bone fractures.[172,189] Notably, vertebral compression fractures appear in 24% of children undergoing spinal imaging in one series, indicating severe bone fragility.[172] Evidence suggests that individuals with LDS1/2 may have lower bone density and higher fracture rates than LDS3,4,5.[172]

Risk factors for poor bone health include lower body mass index, skeletal features of LDS (pectus deformity, pes planus, arachnodactyly, camptodactyly, and spinal abnormalities), and comorbid asthma and/or eosinophilic gastrointestinal disease, potentially indicating more severe LDS manifestations.[172]

Bisphosphonates are the primary treatment for osteopenia/osteoporosis, based on observed high bone turnover on histomorphometric analyses and serum markers.[172,190,191] In 5 patients, intravenous bisphosphonates improved bone density without significant adverse effects.[172]

Clinicians should counsel about skeletal fragility and emphasize adequate intake of calcium and vitamin D, as well as optimal nutrition. Managing underlying comorbidities (asthma and gastrointestinal disease) is crucial for bone health. Dual-energy X-ray absorptiometry with vertebral fracture analysis should be considered, particularly for individuals with fractures or back pain.

Osteopenia or osteoporosis in aging individuals remains unstudied.

Pulmonary

Reactive airways disease affects a subset of people with LDS with allergic feature, most documented in LDS1/2 (45%).[159] Aubart et al[162] (2014) reported allergic asthma in 18% of a small LDS3 cohort ($n = 22$). Diagnosis relies on history of episodic cough and wheezing with defined triggers and pharmacologic reversibility of spirometry changes.[192,193] Additional diagnostics may include fractional exhaled nitric oxide assessment, allergy panels, and IgE and eosinophil levels. Although standard population practices generally guide treatment, considerations specific to LDS include potentially compromised efficacy of beta-2 agonists in patients on nonselective beta blockers and increased cardiovascular risk from chronic tachycardia induced by beta-2 agonists.[194,195]

Emphysema and pneumothorax occur in up to 5% of people with LDS across all subtypes.[7,196,197] Emphysema and pulmonary blebs are likely developmental in origin, similar to MFS.[198,199] Although blebs may remain asymptomatic, they increase pneumothorax risk. Standard pneumothorax treatment includes oxygen administration and chest tube placement. For large or resistant pneumothoraces, mechanical pleurodesis is preferred over chemical pleurodesis to limit pleural scarring. Prophylactic bleb treatment is not recommended without respiratory compromise (hypoxemia, dyspnea); however, bleb resection may be indicated when blebs enlarge, cause respiratory limitations, or accompany a history of prior spontaneous pneumothoraces.[198]

Tracheobronchomalacia involves extreme wall thinning and dilatation of the trachea/bronchi causing airway collapse during breathing. Symptoms include breathing difficulty, wheezing, coughing, and shortness of breath. Tracheobronchomalacia can be congenital or acquired (sometimes from aneurysm compression on the trachea).[95,200] Management may include saline nebulizer treatments, positive expiratory pressure devices, oscillating vest physiotherapy, and/or targeted antibiotics for lung infections.[201,202]

Hemoptysis presents a challenging late postoperative complication after thoracic aortic surgery. In LDS, some hemoptysis cases have stemmed from pseudoaneurysm or bronchovascular fistula development, requiring multidisciplinary management with bronchoscopy, high-resolution CTA imaging, and vascular surgery.[94,203]

Pectus excavatum and scoliosis commonly occur in LDS. Their associated lung function impairments remain understudied in skeletal reviews, although both conditions can cause restrictive lung disease when severe.[204] Studies on pre- and postoperative lung function in LDS are needed to establish pulmonary benefits of pectus repair and define complications. Data demonstrate relationship between thoracic scoliosis severity, restrictive lung physiology and necessity for interventions to improve or stabilize pulmonary function.[205,206]

OB-GYN

Individuals with LDS can have successful pregnancies but are at risk for cardiovascular complications and should be managed by a high-risk, multidisciplinary team. Current pregnancy management recommendations for LDS are primarily extrapolated from studies in women with MFS, as data on LDS pregnancies are limited by the absence of large studies with systematic peri-partum imaging and lack of stratification based on pre-pregnancy diagnosis awareness.

LDS1/2 pregnancies

In a series of 316 pregnancies in 122 individuals with LDS1/2, prepregnancy diagnosis was unknown in 84%.[81] Five aortic dissections occurred during pregnancy (1.6%), including 1 type A dissection in a woman with a 3.5 cm aortic diameter, 1 dissection at the distal margin of the graft anastomosis of a previous root repair, and 2 type B dissections. No uterine ruptures were reported. A recent systematic review of 222 people with LDS (522 pregnancies) showed a 4% pregnancy-associated aortic dissection rate (10 type A, 8 type B, 5 unspecified) and 1% pregnancy-associated mortality.[24]

LDS3 pregnancies

Among 46 pregnant individuals with LDS3, 1 type A reported in the second trimester of a third pregnancy in a patient unaware of her diagnosis.[207] Three first-degree relatives of individuals with *SMAD3* pathogenic variants (genotype not established) experienced pregnancy-associated vascular events, including a type A dissection at 39 weeks, a type B dissection 6 days postpartum, and an unspecified aortic dissection during childbirth. In another series of 34 pregnancies in 17 individuals with LDS3, no pregnancy-associated aortic dissections were observed.[208] In this cohort, 88% were diagnosed with LDS after pregnancy, and no uterine rupture occurred.

LDS4 pregnancies

In individuals with LDS4 (*TGFB3*), no pregnancy-associated aortic dissections complications occurred in 6 women with 18 pregnancies.[209]

Preconception recommendations

Preconception counseling is critical for individuals with LDS and should begin in adolescence, covering sexual health, contraception, and pregnancy risks. Preimplantation genetic diagnosis and prenatal testing options should be discussed.

Before pregnancy, patients need genetic counseling, medication review, aortic and arterial imaging, and consultation with maternal-fetal medicine and cardiology specialists. Shared decision making is essential.[64] To mitigate pregnancy-associated type A dissection, elective preconception aortic root replacement surgery is recommended when aortic dimensions are $\geq$4.5 cm in LDS4/5 and $\geq$4.0 cm in LDS1/2/3.[64] Pregnancy guidelines need refinement based on vascular aneurysms, previous vascular events, aortic growth rate, and family history. Alternative options for becoming a parent should be discussed, including surrogacy/gestational carrier, and adoption.

Antepartum recommendations

Manage pregnancy with a multidisciplinary team (maternal-fetal medicine, cardiology, and obstetric anesthesia) and plan delivery at a hospital capable of emergency aortic

repair. Down titrate and discontinue ARB therapy before conception and consider beta blocker therapy during pregnancy and in the early postpartum period.[64]

Monitor with transthoracic echocardiography each trimester.[210] Obtain full body CTA or MRA before conception. Noncontrast MRA provides effective imaging in pregnant persons when needed.[211] Educate patients about type A and B aortic dissection symptoms, which may resemble events during a normal pregnancy. Highest risk of dissection is during the third-trimester and postpartum.[212]

Monitor for fetal LDS manifestations including aortic root aneurysm, congenital heart disease, and musculoskeletal features.[20,213,214] Recommended fetal monitoring includes level II anatomy ultrasound, fetal echocardiogram and monthly third-trimester growth ultrasounds (particularly important with beta blocker therapy, which can cause fetal growth restriction).[215]

Delivery recommendations

All deliveries cause hemodynamic changes that may increase aortic stress through uterine contractions, placental autotransfusion, and pain-induced blood pressure fluctuations. An anesthesia team trained in cardio-obstetrics with knowledge of LDS risks is essential. Slow-dosed epidural anesthesia is preferred to minimize tachycardia and hypotension.[64] Whelan et al[216] (2024) reported no complications with regional anesthesia in LDS. Preconception spinal MRI is recommended to address potential dural ectasia and anesthesia planning.[217] General anesthesia is indicated when neuraxial methods are contraindicated or for emergent delivery. Delivery teams should consider risks for cervical spine instability and cervical artery dissection during intubation.[217]

No randomized trials exist for optimal delivery modalities in LDS. Although early reports noted uterine rupture in LDS1/2, larger cohorts indicate extremely low risk across all subtypes.[3,208,210,216] Patients at lower aortic dissection risk (aortic root diameter $\leq$ 4 cm; no family history of dissection) may consider trial of labor after risk counseling.[64] Assisted-vaginal delivery with forceps or vacuum can reduce second-stage Valsalva effort.[64,218] Cesarean delivery is recommended for those with chronic aortic dissection, aortic root of >4.5 cm, or rapid aortic growth in pregnancy, although its protective effect against aortic dissection requires further study.[64]

Postpartum recommendations

Aortic dissection risk persists during the postpartum period (6-12 weeks after delivery).[219] Beta-blockade and imaging surveillance of the aorta and arterial tree should continue postpartum.[64] Mouse models of MFS and VEDS suggest lactation and oxytocin may contribute to aortic aneurysm and dissection.[220,221] Some experts discuss breastfeeding risks based on mouse data showing lactation avoidance prevents postpartum aortic dissection. However, no human studies have been performed to date. Postpartum contraception should be addressed during routine obstetric care.

Contraception and family planning

For patients with medical problems, the risks associated with pregnancy are often greater than the risks associated with contraceptive use, including those with LDS (Table 6).[222] In general, estrogen-containing contraceptives increase the risk of venous and arterial thromboembolic events, whereas progestin-only contraceptives do not.[223] There is a theoretical concern that estrogen-containing contraceptives may increase risks for aortic aneurysm growth, hypertension and aortic dissection however there is no direct correlation between estrogen use and aortic dissection. Nearly all patients are eligible for at least 1 of the reversible long-acting contraceptive methods (implant or intrauterine device [IUD]).[211,224-226] Patients on anticoagulants should generally avoid the copper IUD because it can potentially increase menstrual blood loss, whereas the levonorgestrel IUD will decrease menstrual blood loss. Additionally, for patients with complicated cardiac valve and graft issues, there is concern regarding estrogen use increasing the risk of thromboembolic disease; therefore, progestin-only methods are preferred even when on anticoagulation. Permanent contraception with female sterilization procedures is also an option if the patient is stable for surgery; additionally, vasectomy for the partner would avoid any risk to the patient.

Gynecological health in individuals with LDS

Gynecologic issues remain understudied in LDS. Research shows that persons with LDS experience pelvis floor dysfunction at a higher rate (affecting 2/3 of respondents) than the general population.[169] Furthermore, the impact of hormone exposures from contraception, IVF, replacement therapy, or gender-affirming interventions on aortic health in LDS individuals is poorly understood.

Anesthesia

People with LDS may require anesthesia for various surgical procedures in emergent or elective settings. Anticipate difficult airways due to structural abnormalities of the skull, mandible, palate, and cervical spine, as well as esophageal dysfunction. Airway difficulties occur in 20% of patients and gastroesophageal reflux in up to one-third.[167]

Preoperative assessment should include ECG and echocardiogram for all patients, with additional imaging based on planned surgery and vascular access needs. Evaluate and manage restrictive or obstructive lung disease before elective procedures.[185] Because of increased allergic susceptibility in LDS patients, thoroughly review previous anesthetic exposures and responses, consulting prior

Table 6 Contraception Advice in LDS

	Cu-IUD	LNG-IUD	Implant	DMPA	POP	CHC
Uncomplicated LDS	No restrictions	No restrictions	No restrictions	No restrictions	No restrictions	No restrictions
Aortic root dilation (>4 cm)	No restrictions	No restrictions	No restrictions	No restrictions	No restrictions	Risks of use outweigh benefits (*Concern about estrogen-containing methods causing hypertension)*
Mechanical prosthetic valve and anticoagulation	Risks of use outweigh benefits (*Concern about anticoagulation causing heavy menstrual bleeding; depends on thrombotic risk)*	No restrictions	No restrictions	No restrictions	No restrictions	Risks of use outweigh benefits/ Contraindicated

CHC, combined hormonal contraception; *Cu-IUD*, copper intrauterine device; *DMPA*, depot medroxyprogesterone acetate; *LNG-IUD*, levonorgestrel intrauterine device; *POP*, progestin only pill.

anesthetic records when available. There is no evidence that food allergy confers cross-reactivity to any drugs used in the perioperative setting.[227]

Most patients take ARBs and/or beta blockers chronically.[167] Continue beta blockers perioperatively but discontinue renin-angiotensin system modifying medications 1 day before surgery to prevent hypotension under general anesthesia. Resume these medications as soon as possible to avoid hypertension, tachycardia, and accelerated aneurysm growth.[228]

Given limited literature on LDS anesthesia management, use familiar techniques. Before induction, ensure difficult airway equipment accessibility and establish arterial pressure monitoring. Have ultrasound available for vessel cannulation because tortuosity may complicate access. Both general and neuraxial anesthesia are safe options, alone or combined, with hemodynamic stability being crucial. Neuraxial approaches may be challenging because of scoliosis, vascular anomalies, and dural ectasia but remain viable when clinically indicated.[229] For elective cases, MRI can guide neuraxial needle placement by revealing dural ectasia extent,[217] provide appropriate postoperative support for patients with OSA,[141] maintain effective analgesia throughout to minimize sympathetic stimulation, and preserve arterial homeostasis.

Other manifestations

Both pectus excavatum (PE) and carinatum (PC) are common in LDS.[24] Successful PE repairs via NUSS or modified Ravitch procedure have been reported.[230] Debate exists whether intervention is primarily cosmetic versus providing cardiopulmonary benefits.[231] Consider surgical intervention in relation to thoracic aortic pathology, potentially delaying if thoracic surgery is anticipated. Perform when adolescent bone growth is nearly complete. Obtain MRA imaging before chest bar placement for routine vascular screening because metal artifacts will obscure future imaging. Postsurgical complications may include chest pain and reactive pectus carinatum.[232] Pectus repair during aortic surgery increases operative times, infection risks, bleeding, and postoperative hospitalization.[231] For PC, dynamic compression bracing is an option with patient motivation crucial for compliance.[233]

Umbilical, ventral and inguinal hernias are common in LDS, often occurring postsurgically or recurrently.[76] Consider mesh for repair stability, although aneurysmal disease may later require reoperation and mesh division.[234] Hiatal and diaphragmatic hernias are rare but can develop throughout life.[178] Extremely rare manifestations include spontaneous rupture of the spleen, bowel, and peripartum uterus.[24,147]

Cutaneous features include soft, velvety, and/or translucent skin with easy bruising and atrophic scarring. Striae distensae, varicose veins, and milia (often on the face and extending into adulthood) have been reported.[3,235] Consider plastic surgery for wound closure because dehiscence or delayed healing may require wound-care specialist intervention.

Regarding body art, piercings, and breast implantation in LDS: infective endocarditis is a rare but serious complication requiring consideration of antibiotic prophylaxis, similar to dental or surgical procedures. Breast implants may impair echocardiogram acoustic windows and affect ECG readings.[236,237]

Lessons about dural ectasia, anterior meningocele, and Tarlov cysts from the MFS literature likely apply to LDS. Dural ectasia is often asymptomatic on imaging, but meningoceles can progressively enlarge throughout adulthood, causing bony erosion, pain, and neurologic dysfunction.[238] Treatment options include conservative, medical and invasive approaches.[239] Alternative causes of back pain warrant investigation.

Spontaneous CSF leaks typically present with orthostatic headaches from spontaneous intracranial hypotension and are usually treated with prolonged bed rest or epidural blood patches.[240] Chronic CSF leak can occur after spinal surgery in LDS.[181]

Developmental delay in LDS likely stem from hydrocephalus, craniosynostosis, or intracerebral bleeding, whereas early gross/fine motor, feeding, or speech delays typically relate to hypotonia and hypermobility.[1,144]

Neurological concerns require further exploration in aging LDS patients. Aubart et al[162] (2014) found that 68% (15/22) of people with LDS3 across 6 families exhibited neurological symptoms (muscle cramps, paresthesia, hypoesthesia, or gait disturbance) reminiscent of a type 2 Charcot Marie Tooth presentation. Later onset neuropathies related to spinal disease also warrant investigation.

Hydrocephalus and Chiari malformation have also been reported.[111,120] Huguenard et al[120] found a 7.4% prevalence rate of Chiari type 1 (CM-1) in their retrospective cohort (highest in LDS1/2). Although requiring further validation, their study indicated those people with LDS with intracranial aneurysms had higher CM-1 prevalence (22.2%) than those without (3.2%).

Migraines and headaches

Limited data exist on headache prevalence in LDS. Recurrent headaches or migraines affect 50% (15/30) of patients with LDS3 without association of cerebrovascular abnormalities-significantly higher than general population rates of migraines (14%) and frequent headaches (4.6%).[5,241]

In addition to migraines, there are a number of other types of headaches, such as tension headaches, cervicogenic headaches, medication overuse headaches, and headaches from CM-1 (J Richer, personal communication). Although headaches typically do not indicate brain aneurysms, thunderclap headaches warrant emergency imaging.

Initial treatment should include lifestyle modifications (exercise, sleep hygiene, healthy diet and hydration, weight management, and smoking cessation) and trigger avoidance.[242] Evaluate for treatable secondary causes, such as sleep dysfunction and vision impairment. Use triptans with extreme caution due to vasoconstrictive effects (see Table 4).[243] Over-the-counter medications suffice for most tension headaches.

For prevention, ARBs and BBs show efficacy in migraine prevention—making them preferred options for migraine management in LDS[244] Anti-calcitonin gene-related peptide receptor blockers monoclonal antibodies, although effective for prevention and abortion of migraines, raise theoretical cardiovascular safety concerns.[245] Magnesium supplements and stress-reduction therapies can serve as useful adjuncts.

Fatigue and hypermobility

In some studies, severe fatigue affects 40% to 64% of people with LDS, whereas 85% report chronic musculoskeletal pain with the majority experiencing moderate-to-severe pain.[5,246-249] Fatigue correlates with sleep problems, anxiety, pain, cardiovascular burden, vocational dissatisfaction, and reduced physical activity.[246-248]

Joint hypermobility occurs in 50% to 80% of people with LDS.[120,196,209] Pain initially manifests as nociceptive pain in lax joints (especially weight-bearing and multidirectional joints), stemming from microtraumas or injuries such as dislocations. Impaired proprioception and reduced muscle strength exacerbate these issues. Over time, neuropathic pain may develop from nerve entrapment, compression neuropathies, and small fiber neuropathy.[250] Joint hypermobility also correlates with[142] decreased quality of life, gastrointestinal and autonomic problems, hyperalgesia, and anxiety.[251]

Interestingly, TMJ demonstrates some restriction and deviation in range of motion (not hypermobility) and/or joint sounds, and/or pain in nearly 40% in people with LDS, which is higher than the average US population, and correlated with decreased oral health-related quality of life.[136]

Pain and sleep disturbances reinforce each other; pain disrupts sleep, and poor sleep diminishes pain inhibition.[252] OSA was identified in nearly 23% of individuals with LDS.[136] Pain also associates with disability, depression, anxiety, and reduced quality of life, limiting participation in daily activities.[147,249,253]

Because pain and fatigue inversely correlate with physical activity, our experience suggests benefits from improved cardiovascular fitness, core strength, and proprioception training for LDS patients with joint hypermobility.

Rehabilitation and pain management

A thorough medical, psychiatric history, and physical exam reveals pain sources and chronicity factors. Chronic pain treatment requires a multidisciplinary team addressing all contributing factors. Individualized treatment plans should target specific pain subtypes using appropriate pharmacotherapy (neuromodulators such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitor antidepressants, anticonvulsants, calcium-channel blockers, and alpha-2 receptor modulators [T. Speed, personal communication]). Interventional approaches (nerve blocks, trigger point injections, Botox) may be indicated. Non-pharmacological interventions (physical therapy, cognitive behavioral therapy, biofeedback, and relaxation) complement medical management. Opioid therapy should be prescribed sparingly, weighing risks against benefits.

Comprehensive multidisciplinary rehabilitation should begin early for people with LDS, with timing based on severity of neuromusculoskeletal involvement. The goal is to address physical limitations while establishing safe exercise routines that improve function and reduce pain.

For infants and children, monitor developmental milestones and promptly refer to rehabilitation if concerns arise. The core team should include a physiatrist, physical therapist, and occupational therapist, with speech language pathologist added for oral motor issues. Early intervention addresses hypotonia, joint issues, developmental delays, and feeding problems[1,144]

As patients grow, rehabilitation should progress to include spinal musculature stabilization with gentle

Table 7 Community Resources: A noncomprehensive but useful collection of resources for patients with LDS

	Website	Country-Based	Languages Served
Support Organizations (select LDS organizations; There are additional support groups around the world dedicated to genetic aortic disease that provide resources.)			
Loeys-Dietz Syndrome Foundation (LDSF)	www.loeysdietz.org	US (with international focus)	English, French, Spanish, Chinese
Loeys-Dietz Syndrome Foundation -Canada (LDSF-C)	https://loeysdietzcanada.org/		English, French
Other medical support			
Pain Foundation	https://uspainfoundation.org/	US	English, Spanish
Standing Up To POTS	https://www.standinguptopots.org/	US	English
Job Accommodation Network	https://askjan.org/	US	English, Spanish
National Headache Foundation	https://headaches.org/	US	English
VASCERN	https://vascern.eu/	European countries	24 languages
Book resources			
Life with Aortic Disease: Caring For Your Mental Health	https://johnritterfoundation.org/mental-health/	US	English
Aortic Dissection: The Patient Guide	https://www.aortichope.org/resources; https://aorticdissectionawareness.org/	US; UK and Ireland	English

LDS, Loeys-Dietz syndrome.

strengthening in an anatomically neutral position (avoiding hyperextension and kyphosis), gentle strengthening of the shoulder and hip girdle musculature, joint protection education, energy conservation, and proper breathing techniques.

People with LDS frequently experience foot, ankle, and subtalar joint pain requiring alignment intervention. Supportive shoes and orthotics improve lower extremity alignment for those with pes planus, calcaneovalgus, genu valgus, genu recurvatum, or lumbar hyperextension.[181,186] Severe cases may require ankle foot orthotics or supramalleolar orthotics. Functional splinting/orthotics helps manage patellar, knee, or ankle subluxations/dislocations, whereas serial casting addresses contractures.[3]

Occupational therapy provides adaptive equipment for posture, ergonomics, and daily activities. Hand therapy should focus on finger extensors and abductors with joint protection (avoid grip-strengthening exercises that risk deformities). Various splints may be needed for joint laxity.

Kinesiotape reportedly helps with proprioception, posture training, edema control, and stabilizing subluxation-prone joints (M. Perry, personal communication). Aquatic therapy and noncompetitive swimming offer effective low-impact conditioning. All rehabilitation must strictly adhere to LDS cardiovascular exercise restrictions and precautions.

Orthostatic intolerance

LDS can be associated with orthostatic intolerance—postural symptoms relieved by recumbency. A comparative study found autonomic dysfunction (syncope, presyncope, and orthostatic intolerance) more prevalent in LDS than VEDS (30.8% vs 8.96%), affecting quality of life and daily functioning.[166]

Most orthostatic intolerance cases in LDS are mild, manageable with physical conditioning, and increased fluid and salt intake. Although the mechanism remains unclear, the connective tissue abnormality in LDS may cause blood vessel dysfunction and cardiovascular dysregulation that predisposes patients to this condition.

Mental health

People with chronic conditions, including vascular connective tissue disorders, face higher risks of anxiety, depression, and medical posttraumatic stress disorder.[254,255] Strong emotions often emerge during uncertainty (new diagnoses, surgeries, imaging, and emergencies) or when health events occur to others in the LDS community. Chronic stress negatively affects overall health and requires treatment that optimize patients' health and living conditions. Regular mental health assessment with psychiatry and counseling referrals is essential.

Growing older

Aging with connective tissue disorders brings additional health complications from both the disease and its treatments. Beyond cardiovascular complications, earlier mentioned comorbidities significantly affect mortality and treatment options, including pain management. Key concerns in adults include (1) continued need for adaptive physical activity guidance as abilities change, (2) correlation between low life satisfaction and higher levels of fatigue and anxiety, and (3) health care burden's impacts on mental health, medical follow-up, lifestyle, and work decisions, including early retirement or disability.[247,248,256] Disease burden, sleep problems, anxiety, chronic pain, and fatigue create a mutually reinforcing cycle affecting quality of life as patients age.[249]

Table 8 Key takeaways for multidisciplinary care of people with LDS

Cardiovascular	• Surveillance imaging and timely preventative surgery are the cornerstones of care (Tables 3,4) • Angiotensin receptor blockers (ARB) or beta-blockers (BB) treatment should begin early; consider dual therapy for progressive aortic growth. Discontinue ARBs before pregnancy; Optimal ARB dosage is Irbesartan 8mg/kg/day and Losartan 2mg/kg/day • Monitor and treat congenital heart defects, MVP, left ventricular dysfunction and arrhythmias per standard protocols • Use shared decision-making for exercise recommendations while encouraging regular physical activity
Cardiothoracic, vascular and neurovascular surgery	• Cardiothoracic surgery: Valve-sparing root replacement is primary strategy unless valve morphology prohibits. See Table 5 for thresholds • Vascular surgery: Intervene with rapid expansion or when arterial size exceeds 2-3× expected diameter. Open repair has most long-term data. Use endovascular stents cautiously. Plan for potential staged repairs • Neurovascular surgery: Consult for intervention needs and imaging follow-up. Follow national guidelines for cervical dissections, aneurysms and pseudoaneurysms
Craniofacial, Orodental, Oropalatal, ENT/ Audiological and Ophthalmologic	• Craniofacial: Early orthodontic/facial orthopedic treatment for mandibular retrognathia, TMD or maxillary growth issues. Monitor for obstructive sleep apnea • Oropalatal and orodental: Treat clefts and dental anomalies with multidisciplinary approach. Regular dental care and orthodontics as needed • ENT/Audiology: Perform baseline audiological evaluations in adults. In pediatric population assess hearing at age 2 and at Kindergarten entry. Refer cholesteatoma to otolaryngologist • Ophthalmology: Full baseline ocular evaluation with dilated fundus exam; individualized follow-up. Monitor for retinal detachment risk. Consider extraocular muscle hypoplasia before strabismus surgery
Allery, Immunology, Gastroenterology and Nutrition	• Allergy and Immunology: Use antihistamines for cutaneous/mild food reactions; reserve epinephrine for life-threatening reactions. Avoid Palforzia; consider omalizumab for food allergies. Treat sinus infections to improve asthma control • Nutrition: Monitor growth curves; have a low threshold for caloric supplementation. Optimize BMI before surgery. Consider food allergies when selecting formula • GI: Use PEG-3350 for constipation. Evaluate for EGID/IBD with endoscopy if clinically indicated, with appropriate precautions for cervical instability. Monitor calcium/vitamin D levels. Standard colonoscopy screening protocols apply
Orthopedics and Endocrine	• Spine: Monitor for scoliosis; refer to orthopedics for progression. Surgical intervention for large/progressive curves. Evaluate cervical instability with flexion/extension radiographs • Extremities: Treat genu valgum with hemiepiphysiodesis; clubfoot with Ponseti casting • Adult Musculoskeletal: Manage pain for secondary inflammatory changes and osteoarthritis • Bone health: Optimize calcium/vitamin D intake. Consider DEXA with vertebral fracture analysis, particularly after fractures or with back pain
Pulmonary	• PFTs for significant thoracic/spinal deformities • Allergy testing, IgE and eosinophil counts for asthma diagnosis • Pulmonary consultation for pneumothorax, radiographic emphysema, or tracheo/ bronchomalacia • Multidisciplinary management of hemoptysis with pulmonary, radiology and vascular surgery
Pregnancy and Reproductive Health	• Comprehensive preconception counseling including vascular imaging review • Manage with high-risk multidisciplinary team • Consider pre-pregnancy elective aortic surgery at 4.0-4.5 cm diameter • Echocardiography each trimester and postpartum • Base delivery mode on aortic size and obstetric indications • Shared decision-making for lactation • Recommend contraception when not pursuing pregnancy
Anesthesia	• Focus preoperative assessment on cardiovascular, respiratory, skeletal systems, allergies and medications • Anticipate difficult airway management • Discontinue renin-angiotensin system medications day before surgery • Maintain hemodynamic stability throughout perioperative period
Other	• Pectus deformities: Consider cosmetic intervention in context of thoracic aortic pathology • Hernias: Consider mesh for repair stability • Migraines: Start with lifestyle modifications; use triptans cautiously; ARBs/beta-blockers for prevention • Hypermobility/Fatigue: Improve fitness, tone, and proprioception; consider aquatic therapy within cardiovascular restrictions • Pain: Use multidisciplinary, individualized approach; judge opioid use clinically; start rehabilitation early • Orthostatic intolerance: Manage mild cases with rehabilitation, conditioning, increased fluid/salt • Mental health: Refer for therapy/pharmacotherapy as needed

ARB, angiotensin receptor blocker; *EGID*, eosinophilic gastrointestinal disease; *MVP*, mitral valve prolapse; *TMD*, temporomandibular joint disorder.

Community resources

For medical providers caring for individuals with LDS, comprehensive care should include documentation outlining emergency instructions (aortic/arterial dissection, pneumothorax, and retinal detachment risks), as well as school, physical education or work accommodations. Proactive discussions about palliative care, mental health, and other support services should be initiated. Community resources, research opportunities and support information should be distributed (Table 7). It is important to discuss the benefits and challenges of connecting with other families and online communities to ensure patients feel supported throughout their care journey.

Conclusion

This 2026 LDS primer update offers comprehensive management recommendations, emphasizing multidisciplinary care and shared decision making (Table 8). It highlights vigilant cardiovascular monitoring alongside multisystem screening and management. The update promotes personalized care plans, expert consultation and proactive complication management to enhance patient outcomes and quality of life.

Data Availability

This article is a review/primer and does not contain original data. All references and information discussed are derived from previously published literature and expert opinion. For inquiries regarding specific studies or data discussed in this review, please refer to the respective original sources cited throughout the article.

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Ethics Declaration

This manuscript does not involve original research or the use of individual patient-level data.

Conflict of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the author(s) used Type.AI to edit grammar for conciseness. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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