Delphi Consensus on Diagnostic Criteria for LUMBAR Syndrome

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Objective To develop consensus on diagnostic criteria for LUMBAR syndrome, the association of segmental infantile hemangiomas that affect the Lower body with Urogenital anomalies, Ulceration, spinal cord Malformations, Bony defects, Anorectal malformations, Arterial anomalies and/or Renal anomalies.

Study design These diagnostic criteria were developed by an expert multidisciplinary and multi-institutional team based on analysis of peer-reviewed data, followed by electronic-Delphi consensus of a panel of 61 international pediatric specialists.

Results After 2 Delphi rounds, a 92% or higher level of agreement was reached for each Delphi statement. 98% of panelists agreed with the diagnostic criteria, and 100% agreed the criteria would be useful in clinical practice. The diagnosis of LUMBAR requires the presence of a segmental, or patterned, infantile hemangioma of the lumbosacral, sacrococcygeal, or pelvic cutaneous regions plus one additional criterion of the urogenital, spinal, bony, anorectal, arterial, or renal organ systems.

Conclusions These diagnostic criteria will enhance clinical care by improving screening, detection, and overall awareness of this poorly understood neurocutaneous disorder. The criteria can be utilized by a wide variety of pediatric subspecialists. In addition, formal criteria will improve phenotypic uniformity among LUMBAR syndrome cohorts and a patient registry, allowing investigators to assess clinical features, long-term outcomes, and results of genetic sequencing in a standardized manner. Finally, these criteria will serve as a starting point for prospective studies to establish formal screening and management guidelines. *(J Pediatr 2024;272:114101)*.

LUMBAR syndrome is the association of segmental infantile hemangiomas (IH) affecting the Lower body with Urogenital anomalies, IH Ulceration, spinal cord Malformations, Bony defects of the spine and lower extremity, Anorectal malformations, Arterial anomalies and/or Renal anomalies.[1] The syndrome is based on the presence of the characteristic cutaneous segmental IH, which is essential for the diagnosis. While partial features of LUMBAR have also been described by the acronyms PELVIS and SACRAL, LUMBAR is used in this consensus as the most comprehensive of the 3 acronyms.[2,3] LUMBAR

ACCORD	Accurate Consensus Reporting Document
e-Delphi	electronic Delphi
IH	Infantile hemangioma
IH-MAG	Infantile hemangioma with minimal or arrested growth
LUMBAR syndrome	Lower body infantile hemangioma, Urogenital anomalies, Ulceration, spinal cord Malformations, Bony defects, Anorectal malformations, Arterial anomalies, Renal anomalies
MRI	Magnetic resonance imaging
MURCS association	Mullerian duct aplasia-Renal anomalies-Cervicothoracic Somite dysplasia
OEIS complex	Omphalocele, Exstrophy, Imperforate Anus, Spinal Anomalies (also known as cloacal exstrophy)
PELVIS syndrome	Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus
PHACE syndrome	Posterior fossa brain malformations, facial segmental infantile Hemangioma, cerebrovascular Arterial anomalies, Cardiac abnormalities or Coarctation of the aorta, Eye or Endocrine anomalies
PST	Project steering team
RCEM	Recurrent constellations of embryonic malformations
SACRAL syndrome	Spinal dysraphism, Anogenital anomalies, Cutaneous anomalies, Renal and urologic anomalies, Angioma of Lumbosacral localization
VACTERL association	Vertebral, Anorectal, Cardiac, Tracheoesophageal fistula, Renal and Limb anomalies

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is considered the rarer, lower-body counterpart of the other, upper-body IH syndrome, known as PHACE (Posterior fossa brain malformations, segmental facial Hemangioma, cerebrovascular Arterial anomalies, Cardiovascular anomalies, and Eye anomalies), in which segmental IH are also associated with congenital, regional, vascular, and/or structural organ anomalies. In contrast to PHACE, little is known about the natural history and outcomes of individuals with LUMBAR, and no diagnostic criteria, formal screening, or management guidelines exist. PHACE has no known genetic or epigenetic cause, while neither have been studied in LUMBAR. Diagnostic criteria for LUMBAR are thus a necessary starting point for conducting clinical and genetics research and developing management guidelines. These criteria were derived from an international expert panel and Delphi consensus of pediatric specialists. This document also provides screening guidelines for at-risk infants.

Methods

Study Design

An electronic-Delphi method was chosen for this institutional review board–approved consensus, but modified in that the initial criteria were drafted by a project steering team (PST) before being presented to an invited panel for Delphi participation (**Supplemental Table I**, online; available at www.jpeds.com). A Delphi has precedent in this context, having been used to establish diagnostic criteria for Down Syndrome regression disorder[4] and neuroleptic malignant syndrome,[5] and to update diagnostic criteria for neurofibromatosis type 2 and schwannomatosis.[6] This consensus adhered to the recently developed ACcurate COnsensus Reporting Document guidelines.[7]

Selection of Participants

Both the PST and invitees to the Delphi Panel included pediatric physician experts in IH syndromes and/or LUMBAR-specific congenital anomalies, representing varied geography, years of clinical experience, subspecialty expertise, and membership in vascular birthmark organizations.

Data Collection. This consensus was conducted over a 13-month period from November 2022 to November 2023. A thorough literature search was performed to identify published reports of individuals with an IH and at least one other lower-body, congenital anomaly. We selected peer-reviewed, English, Spanish, and French publications from PubMed and Google Scholar databases using multiple search terms with no limits by year. Search terms included but were not limited to LUMBAR, PELVIS, SACRAL, and hemangioma AND tethered cord, hemangioma AND bifid scrotum, and so forth to include all known potential anomalies with cross-referencing performed. Cases were excluded if the diagnosis of IH could not be verified via photograph or description. All articles were electronically stored in a centralized database for PST access. The PST reviewed controversial publications with inclusion or exclusion determined by majority vote.

Details of each subject were recorded and the incidence of each congenital anomaly within each organ category tabulated (**Table I**). This revealed numerous discrepancies in terminology, often outdated and/or ambiguous, as well as anomalies otherwise common to the general pediatric population and thus of uncertain significance.[1-3,8-60] All information was stored centrally for access by the PST, which was subdivided into 3 working groups and tasked with determining which anomalies should be eliminated or included, consolidating categories of anomalies where possible, and ensuring the most up-to-date nomenclature was utilized. In some instances, we included all terms and their definitions with the goal of "speaking the same language" across specialties. In other instances, we used majority consensus by our team of experts to determine the most appropriate nomenclature. Thus, the terminology used in the final diagnostic criteria (**Table II**) often differs from the original data in **Table I**. Discussion and reconciliation within the working groups and then the entire PST was performed via electronic communication and virtual conferencing to culminate in a preliminary draft.

Analysis

Invitees to the Delphi panel were provided with background information on LUMBAR, an explanation of the consensus process, **Table I**, and the criteria draft. The electronic-Delphi survey included demographic questions (round 1 only) followed by 5-point Likert-style responses, allowing opportunity for free-text comments, to statements regarding the proposed diagnostic criteria for each organ system, overall agreement with the criteria, and usefulness in clinical practice. Results and all comments from round 1 were reviewed by the PST via virtual conferencing and electronic communication, with the criteria draft revised accordingly. The Delphi panelists were then provided with the results from round 1, detailed responses to all free-text comments, a thorough explanation of all modifications to the criteria, and invited to participate in round 2, with the entire process repeated. The consensus threshold was 80% or higher level of agreement to each Delphi statement.

Results

Of 81, 61 invitees participated in the Delphi, equivalent to a 74% response rate (**Supplemental Table II**, online; available at www.jpeds.com). Demographic data were recorded for each panelist including pediatric specialty, representative country, and number of years in practice. Following round 1, the consensus threshold of ≥ 80% agreement on each Delphi statement was reached. This is a similar definition of agreement to that which has been used for diagnostic criteria consensus in other rare disorders. However, the PST reviewed and considered every free text comment and elected to revise the criteria further. Substantial revisions after round 1

Table I. Frequency of anomalies reported in LUMBAR syndrome (overall n = 144)[1-3,8-60]

Organ category of anomaly (in descending order of frequency)	Overall incidence	Incidence of specific anomalies overall (N,%) in descending order of frequency
Spinal malformations	n = 113, 79%	• Tethered cord (77, 54) • Intraspinal lipoma (39, 27) Often involving the filum terminale with abnormal thickening • Lipomyelomeningocele, lipomeningocele or lipomyelocele (lipomyeloschisis) (26, 18) • Spina bifida (13, 9) • Syringomyelia/syrinx (14, 10) • Intraspinal hemangioma* (11, 8) • Other myelodysplasias (n = 1): arachnoid cyst, caudal duplication syndrome
Anorectal	n = 46, 32%	• Imperforate anus (17, 12) • Congenital fistulas† (13, 9) • Anteriorly displaced anus or anorectal malposition (11, 8) • Anorectal malformation (10, 7) • Cloacal anomalies (4, 3) • Anal atresia (3, 2)
Urogenital	n = 38, 26%	• Ambiguous/undifferentiated, atrophic, incomplete, absent external genitalia (18, 12) • Hypertrophied unilateral labia majora (8, 6) • Bifid scrotum (7, 5) • Hypospadias ± chordee (7, 5) • Rectovaginal/urethrovaginal fistula (5, 4) • Duplication of uterine cavity/vagina (4, 3) • Unilateral congenital ovarian cyst (3, 2) • Bladder exstrophy (2, 1) • Other urogenital anomalies (n = 1): bifid clitoris, malposition of the phallus, microphallus with phimosis, patent urachus, horizontally divided labia, clitoromegaly, scrotal asymmetry
Cutaneous	n = 37, 26%	• Skin tag, hamartoma‡, caudal appendage or pseudotail (23, 16) • Midline dimple, dermal sinus or tract (20, 14) • Aplasia cutis/meningocele manqué (3, 2) • Inferior umbilical raphe (2,1) • Other skin anomalies (n = 1): cutaneo-vascular web
Renal	n = 27, 19%	• Hydronephrosis/pelviectasis (13, 9) • Renal agenesis/hypoplasia (11, 8) • Renal and/or ureteral duplication (6, 4) • Pelvic kidney or abnormal renal position (4, 3) • Other renal anomalies (n = 1): fused renal ectopic, renal hypertrophy, bifid ureter, abnormal collecting system
Bony	n = 28, 19%	• Dysplasia, hypoplasia, agenesis or dissociation of the sacrum, vertebrae, or coccyx (17, 12) • Leg length discrepancy ± atrophy (6, 4) • Lower extremity deformity§ (6, 4) • Bilateral hip dysplasia (3, 2) • Other bony anomalies (n = 1): scoliosis, pelvic diastasis
Arterial	n = 12, 8%	• Aberrant origin or course, dysplasia or hypoplasia, stenosis/occlusion of major arteries of the lower body
Other anomalies with n > 1		• Segmental hemangioma of the upper body meeting criteria for definite of probable PHACE syndrome (5, 4) • Congenital pulmonary hypertension/stenosis (3, 2) • Abdominal/inguinal hernia (2)

*Often involved dura and admixed with adipose tissue and skeletal muscle.
†Fistula types: rectoscrotal, rectovaginal, rectovestibular, rectoperineal, perianal.
‡Hamartoma types: rhabdomyomatous mesenchymal (n = 2), "complex" (n = 1), "unclassified" (n = 1), rhabdomyoma of labia (n = 1), vaginal skin tags (n = 1), small keratotic plaque resembling epidermal nevus (n = 1).
§Deformity types: talipes equinovarus, calcaneo-valgus, cavus.

included (1) removal of midline lumbosacral skin lesions, (2) removal of all minor criteria, (3) removal of options for diagnosis with only an IH isolated to the lower extremity, and (4) moving most superscript information into the table to enable presentation as a "stand alone" document. Delphi participants were then provided with the results from round 1, the PST response to each free text comment in order of organ category with an explanation of all revisions to the criteria, the original version of the criteria with marked changes, a clean revised version, and invited to participate in round 2. Following the second round, ≥ 92% agreement was reached for each Delphi statement, 98% of panelists agreed with the diagnostic criteria, and 100% agreed the criteria would be useful in clinical practice. The final diagnostic criteria are shown in **Table II**.

Discussion

The IH in LUMBAR is characteristically segmental in morphology. Segmental IH are typically plaque-like and cover a territory of skin, rather than occurring within a confined area seemingly arising from a single focal point. Some segmental IH cross midline, while others strictly respect the midline. Segmental IH associated with LUMBAR

Table II. Diagnostic Criteria for LUMBAR syndrome

Diagnostic criteria for LUMBAR syndrome Requires a segmental infantile hemangioma of the lumbosacral, sacrococcygeal and/or pelvic cutaneous regions* plus 1 additional criterion

Organ system	Criteria
Urogenital	• Differences in sexual development† or urogenital sinus anomalies
	• Other anomalies of the external genitalia
	▪ Including malpositioned, bifid, atrophic, incomplete, absent, asymmetric, hypertrophied or duplicate genitalia
	• Uterine duplication (uterine didelphys) or vaginal duplication‡
	• Bladder exstrophy/epispadias complex
Spinal Cord Malformations	• Lumbosacral spinal dysraphism/tethered cord§
	▪ Abnormal filum terminale in association with tethered cord¶
	▪ Intraspinal lipomas, intraspinal hemangiomas, myelocystocele, congenital dermal sinus tract
	• Syringomyelia/syrinx**
Bony	• Dysplasia, hypoplasia, dysgenesis, agenesis, or dissociation of the sacral or coccygeal spine
Anorectal	• Anorectal malformations
	▪ Including perineal, rectourethral, recto-bladder neck, rectovaginal, or vestibular congenital fistulas
	• Anal or rectal stenosis
	• Rectal atresia
	• Cloaca or cloacal exstrophy
Arterial	• Aberrant origin or course, dysplasia or hypoplasia, aneurysm, stenosis, or occlusion of the aortic, renal, mesenteric, iliac, femoral, popliteal, tibial, or peroneal arteries
Renal	• Renal agenesis/solitary kidney
	• Renal ectopia and fusion anomalies
	▪ Including pelvic kidney, horseshoe kidney, crossed-fused ectopia, or other renal malpositions

*A segmental infantile hemangioma is required for the diagnosis of LUMBAR syndrome. "Segmental" hemangiomas are typically plaque-like and irregular in shape, covering a "territory" of skin, vs "localized" hemangiomas that occur within a confined area, seemingly from a single focal point, and are typically round or oval. The lumbosacral region is defined as the midline lower back superior to the gluteal cleft, the sacrococcygeal region as the top of the gluteal cleft to the tip of the coccyx and includes the intergluteal fold and immediate surrounding gluteal skin, and the pelvic region as the pubic/genital, perineal (area between the genitals and anus), and perianal regions (**Figure 2**).

†Preferred term for ambiguous/undifferentiated genitalia.

‡Also known as Mullerian defects, which can occur along with renal agenesis and skeletal defects in Meyer-Rokitansky- Kuster-Hauser syndrome.

§In addition to segmental infantile hemangioma, spinal dysraphism may be associated with other increased-risk, midline lumbosacral skin lesions.

¶Abnormal filum defined as fatty infiltration with a low-lying conus medullaris (inferior third of L2 vertebral body or lower) or >2 mm in thickness.

**True syrinx defined as >3 mm in size, present in isolation (without another identifiable cause such as Chiari malformation or spinal cord neoplasm), and not a terminal ventricle (a slight, <3 mm, widening of the central spinal canal located immediately above the conus medullaris).

may involve the lumbosacral, sacrococcygeal, and/or pelvic regions, and the leg (**Figure 1**, A and B). We used the terms "lumbosacral" to define the region of the midline lower back superior to the gluteal cleft (**Figure 2**, A and B), "sacrococcygeal" for the intergluteal region from the top of the gluteal cleft to the palpable tip of the coccyx, including the buttocks and perianal skin (**Figure 2**, C and D), and "pelvic" for the pubis/genitalia and perineal skin between the genitals and anus (**Figure 2**, E and F).

In general, segmental IH can also vary tremendously in size, with smaller lesions likely representing a later error, or "hit" in embryologic development and sometimes referred to as "indeterminate" or "partial segmental" and having an arguably lower but unknown risk of associated anomalies.[61] In our literature review, segmental IH in LUMBAR were often extensive, involving all 3 defined regions, and more than one-third extended over one (or rarely both) lower limbs (**Figures 1**, A and B, **Figure 2**A). Unlike PHACE, where an arbitrary IH size criterion of > 5 cm in diameter was chosen,[62,63] we did not have sufficient evidence-based data to designate a minimum size criterion for LUMBAR. In a single prospective study of risk of spinal anomalies in children with lumbosacral IH, intraspinal abnormalities were detected in 21 of 41 participants who underwent magnetic resonance imaging (MRI) evaluation. The 21 infants with spinal anomalies had IH ranging in size from 4.6 cm^2 (~2.2 cm × 2.1 cm) to > 80 cm^2. As the investigators used an arbitrary lumbosacral IH size criterion of ≥ 2.5 cm in diameter, they could not comment on risk for smaller lesions.[64] Prospective studies are needed to determine whether a minimum size criterion for diagnosis can be established for LUMBAR and whether infants with partial segmental IH could meet criteria. Until then, it should be emphasized that IH morphology, for example, segmental patterning, is more important than size when determining risk for LUMBAR (**Figure 2**B).

Additionally, segmental IH in LUMBAR are often of "minimal or arrested growth" morphology (IH-MAG)[65] Typically, IH-MAG appears at birth or shortly thereafter as a telangiectatic patch that, over days to weeks, develops increased erythema and small erythematous papules, thin plaques, and/or swelling that are unique to IH (**Figures 1**, A and B, **Figure 2**, A-D, F). Newborns with segmental IH-MAG affecting the pelvic region have occasionally been misdiagnosed with diaper dermatitis, and the limb as reticulate ("lace-like") capillary malformation or cutis marmorata telangiectatica congenita. Despite the minimal proliferation of segmental IH-MAG, ulceration in this setting is described in nearly half of patients in our literature review and is often severe, sometimes requiring diverting colostomies to heal severe perianal ulceration.[30,66]

Among cutaneous indicators that confer an increased risk for spinal dysraphism, lumbosacral segmental IH has one of the highest risks, with a reported relative risk of 438.[64] Three subjects in our review described lumbosacral segmental IH with a small midline (centrally located within the IH) skin

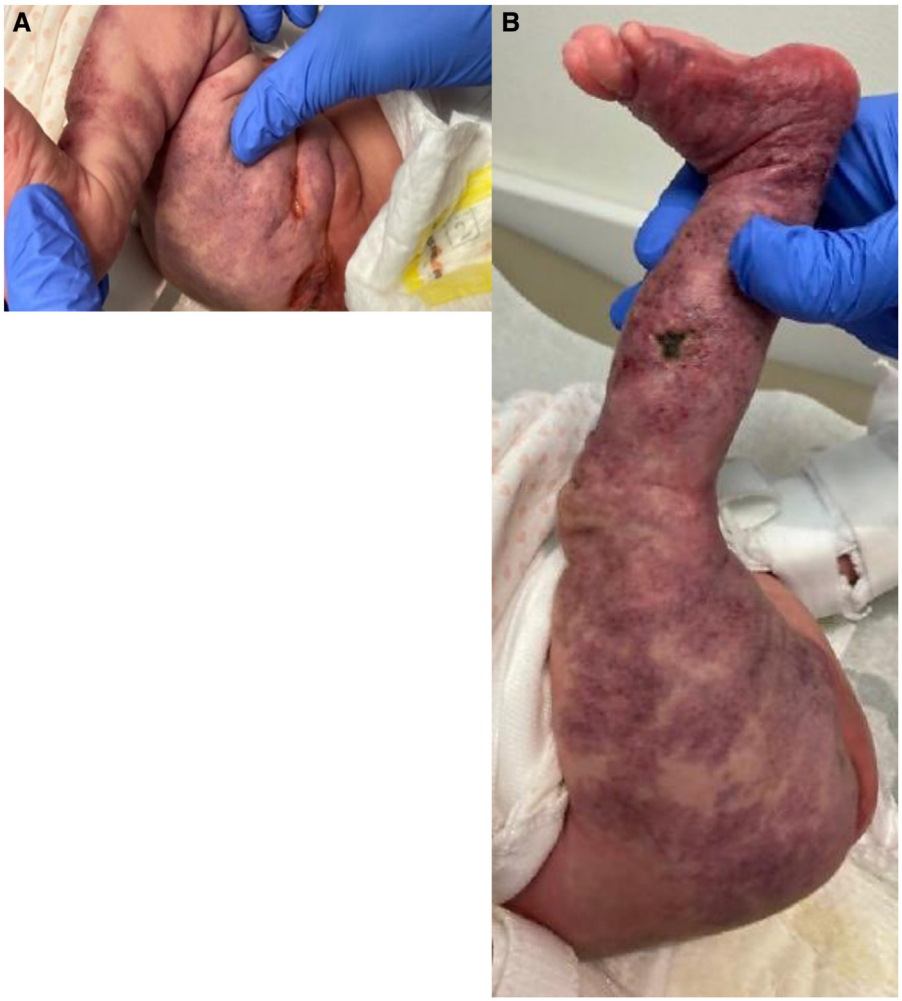

Figure 1. Segmental IH of minimal or arrested growth morphology (IH-MAG) with extensive, erythematous and telangiectatic patches affecting the right pelvic and sacrococcygeal regions plus lower limb (A) with necrotic ulceration of the lateral tibia (B).

defect covered with a transparent membrane, all of whom had associated spinal dysraphism.[14] This finding has been variably termed "meningocele manqué" in the neurosurgery literature,[67] and "aplasia cutis" in the dermatology literature, corresponding to group 4 (aplasia cutis overlying embryologic malformations) in Frieden's classification system[68,69] (**Figure 2**B). A variety of skin hamartomas have also been reported in association with LUMBAR, not only in the midline lumbosacral region but also within and outside midline of the sacrococcygeal and pelvic regions. Histologically, these hamartomas have variably demonstrated lipomatous, angiomatous, and/or skeletal tissues.[19,35,45,54,55] Since these skin hamartomas in published cases were always present with other major anomalies, they did not necessitate inclusion in the diagnostic criteria. An inferior umbilical raphe, a very rare cutaneous anomaly that presents as a midline linear scar extending inferiorly from the umbilicus, has been reported in 2 individuals with LUMBAR and is analogous to the superior umbilical raphe observed in PHACE syndrome.[8,56]

Urogenital and renal anomalies were present in approximately one-third and one-fifth of reported individuals, respectively. While reported, renal duplication, hypospadias, chordee, and penile torsion are all common to the pediatric population and occurred with other criteria, thus were excluded.

Although the original "M" in the LUMBAR acronym stood for "Myelopathy," this term describes signs of spinal cord dysfunction (sensorimotor loss, hypertonia, hyperreflexia, and abnormal spinal reflexes) from an array of spinal cord disorders and is inaccurate in the context of LUMBAR; we therefore recommend the alternate term "spinal cord Malformations." Otherwise, the acronym remains accurate as stands.

Closed congenital (dysraphic) spinal cord malformations, involving disordered early neural tube development, were by far the most common extracutaneous finding among reports of LUMBAR. These malformations are commonly associated with a tethered spinal cord (defined as a low-lying spinal cord/conus medullaris) that may result in sensorimotor deficits, bladder/bowel dysfunction, and orthopedic deformities

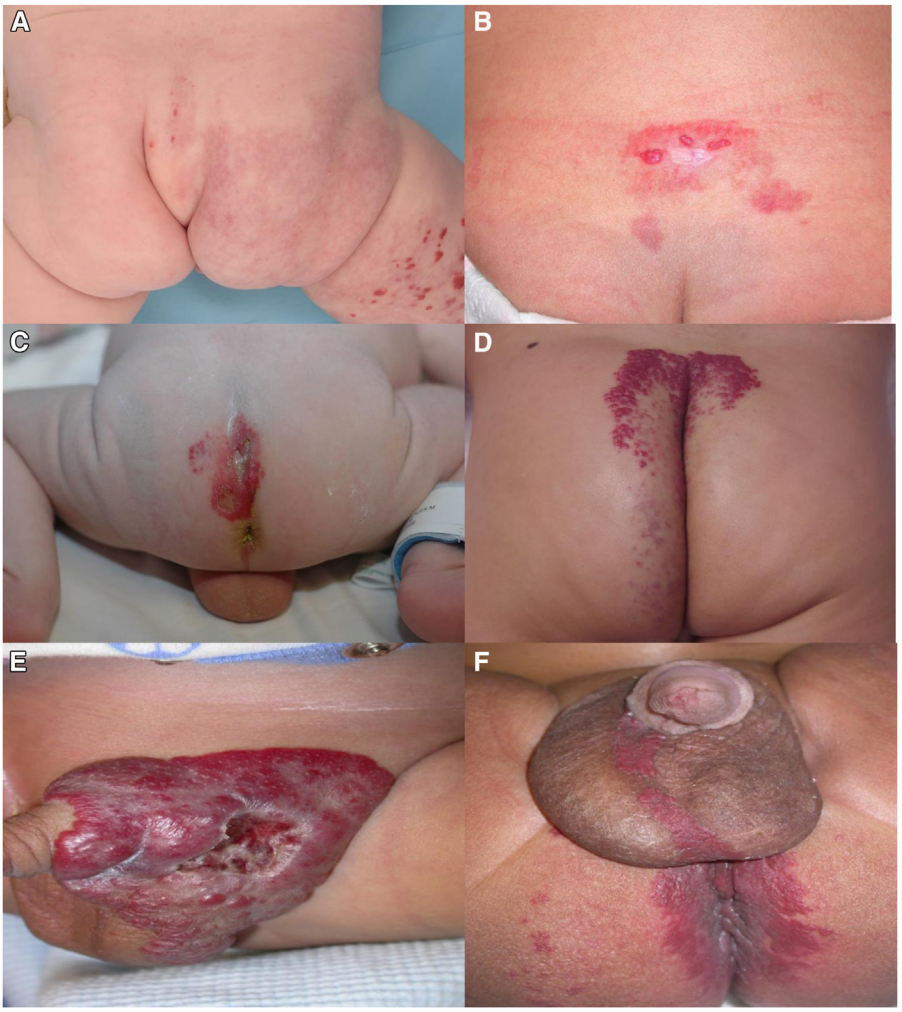

Figure 2. Composite A-F. (**A-B**) Lumbosacral Region. Defined as the region from the lower back to the top of the gluteal cleft. A: Segmental IH of minimal or arrested growth morphology, also affecting the sacrococcygeal region and right leg. The midline lumbosacral mass represents a lipomyelomeningocele. (**B**) Segmental IH of minimal or arrested growth morphology and a central atrophic scar known as "aplasia cutis" or "meningocele manque." (**C-D**) Sacrococcygeal Region. Defined as the intergluteal region from the top of the gluteal cleft to the palpable tip of the coccyx, including the buttocks and perianal skin. (**E-F**) Pelvic Region. Defined as the pubis/genitalia, and perineal skin between the genitals and anus.

of the legs and/or spine. Intraspinal lipomas and thickened and/or fat infiltrated filum terminale were most frequently seen in literature reports, with intraspinal IH and other dysraphic malformations being less common. "Spina bifida," noted in 10% of reported individuals, is unfortunately a confusing term used by some to refer broadly to all dysraphic malformations and by others to describe myelomeningocele. There was not enough clarity in the reports to allow us to further categorize these. Intraspinal IH was noted in 11 subjects, which histologically was often admixed with dural tissue, adipose tissue, and/or skeletal muscle. Intraspinal IH are very rare in general, but in one radiologic study were demonstrated in half of infants with IH affecting the lumbosacral cutaneous region.[36] An isolated syringomyelia (or syrinx), not associated with either a Chiari malformation or spinal cord neoplasm, was present in 10% of reported individuals. However, isolated syringomyelia has more frequently been reported as an incidental finding on MRI scans; its relationship with LUMBAR is therefore uncertain and requires further study.

Although the terms "imperforate," "anterior/anteriorly displaced," and "malpositioned" anus were commonly used in published reports of LUMBAR, updated colorectal definitions recently published in the pediatric surgery literature recommended abandoning these terms, which often actually represent perineal fistulas.[70] We thus used the preferred terms describing the location of the fistula (ex. "rectourethral fistula"), "anal or rectal stenosis," and "rectal atresia."

Bony defects were reported in approximately one-fifth of published reports; sacrococcygeal dysplasia was the most

frequent, and often coexists with underlying dysraphic malformations and presents with neurologic symptoms.[71] Scoliosis has also been rarely reported in LUMBAR.[1] Segmental IH extending over the leg were sometimes associated with limb atrophy, deformity, or leg length discrepancy, with some reports describing arterial anomalies of the affected limb. Such cases highlight the importance of following serial limb measurements and gait when the segmental IH affects the leg. Foot deformities, particularly talipes equinovarus (clubfoot), were also reported.

Arterial anomalies of the abdomen, pelvis or lower extremity were present in less than 10% of individuals, but this is likely an underestimate since few reports performed vascular-specific imaging, particularly when the segmental IH extended over the limb. The types of arterial anomalies described in LUMBAR mirror those seen in PHACE in which congenital vascular anomalies predominate and lead to progressive stenosis of medium-sized anomalous arteries and rarely to moyamoya disease and/or stroke.[72] Whether individuals with LUMBAR and arterial dysplasia are at risk for similar progressive arteriopathy is unknown. There are 2 reports of infants with extensive limb segmental IH and severe underlying arterial stenosis that required partial limb amputation due to vascular complications.[1,30] To our knowledge, there has been only one report of progressive arterial stenosis in LUMBAR, an infant with a lower limb segmental IH and abrupt tapering of her left superficial femoral artery with reconstitution from an anomalous dominant artery. The affected limb was atrophic, and during early childhood she had superficial erosions and white, atrophic, stellate scars, but was lost to long-term follow-up (Amy Nopper M.D., personal communication). It has been hypothesized that arterial dysplasia could play a role in both the limb atrophy and frequency of IH ulceration observed in LUMBAR.[1]

LUMBAR has substantial overlap with other early embryonic malformation syndromes of unknown pathogenesis including OEIS complex (omphalocele-exstrophy-imperforate anus-spinal anomalies, also known as cloacal exstrophy), Urorectal Septum Malformation Sequence (URSMS, also known as persistent cloaca) and MURCS association (Mullerian duct aplasia-renal anomalies-cervicothoracic somite dysplasia). Reports of LUMBAR with omphalocele,[30,73] bladder exstrophy,[8] persistent cloaca,[1] or other cloacal anomalies[1,46] along with renal, urinary, gastrointestinal, and skeletal/spinal malformations support the likelihood that LUMBAR, OEIS, URSMS, and MURCS represent a spectrum with shared pathogenesis, rather than separate disorders. Of these, only URSMS has been associated with rare reports of a genetic cause – CDX2.[74] Although the pathogenesis of LUMBAR is not understood, the observed malformations all originate during early embryogenesis and represent structures derived from the caudal cell mass from which arise the caudal notochord and neural tube, urogenital ridges and lower urogenital system, lower abdominal wall, and other lower body structures. During later stages of gastrulation, the caudal cell mass functions as a developmental field that is modulated by homeobox genes and a variety of other factors. Histopathologic studies in human embryos also support that OEIS is likely the result of a very early defect of insufficient cellular proliferation or deposition involving the caudal cell mass.[75-78] While defects of the caudal cell mass are prominent, several malformations such as renal agenesis or duplication, defects of lower body vasculogenesis, limb and foot deformities, and the open inferior umbilical (abdominal) raphe implicate other nearby embryonic structures. Similarly, the pathogenesis of PHACE syndrome is not understood.

Both OEIS and MURCS have been classified as Recurrent Constellations of Embryonic Malformations (RCEM), a group of caudal malformation disorders characterized by defined inclusion and exclusion criteria (**Figure 3**).[79] Both LUMBAR and PHACE meet all criteria except for increased reports in twins. Of note, while LUMBAR is associated with arterial anomalies, the defects observed do not derive from a single vascular territory, which would be an exclusion criterion for RCEM.

An association with twins and other multiple births has not been reported for LUMBAR or PHACE, as sufficient data to assess this are not available. We are aware of no reports of twins with LUMBAR. In the PHACE Syndrome International Clinical Registry, 11 of 193 (5.7%) were twins or other multiple births, a slightly greater but not statistically significant increase from the US prevalence of 3.5%. However, no data are available regarding zygosity in this cohort.[80]

We believe that LUMBAR and PHACE represent early embryonic malformation syndromes that, given the many embryonic structures involved, likely arise within the first 4 gestational weeks; a simultaneous impact on disparate structures at the time they are developing – generally 4-8 weeks – cannot be excluded. We also conclude that both LUMBAR and PHACE are RCEM syndromes, which for now should be classified as RCEM group 2 given the lack of twinning data.

The cutaneous location of the segmental IH is an important clue to the presence of underlying anomalies. In IH syndromes the IH and underlying anomalies are often ipsilateral and regional to each other, though this is not absolute. The true risk of spinal dysraphism or renal anomalies with a segmental IH isolated to the pelvic region (without lumbosacral involvement) is unknown, as is (conversely) the risk of pelvic or renal anomalies with a segmental IH isolated to the lumbosacral or sacrococcygeal regions. The literature is unclear as published cases generally report imaging that is incomplete, thus with abnormalities potentially undetected. A prospective study, in which all newborns with segmental IH of the lumbosacral, sacrococcygeal, or pelvic regions undergo complete imaging of the lumbosacral spine, pelvis, and kidneys, is needed to develop definitive screening guidelines.

Until then, we recommend spinal imaging be considered in all people with segmental IH involving the midline lumbosacral or sacrococcygeal regions, and pelvic-bladder ultrasound in all people with segmental IH involving the pelvic region. Pelvic-bladder ultrasound is also reasonable for individuals with lumbosacral or sacrococcygeal IH. Of note, ultrasound might also adequately assess LUMBAR-associated

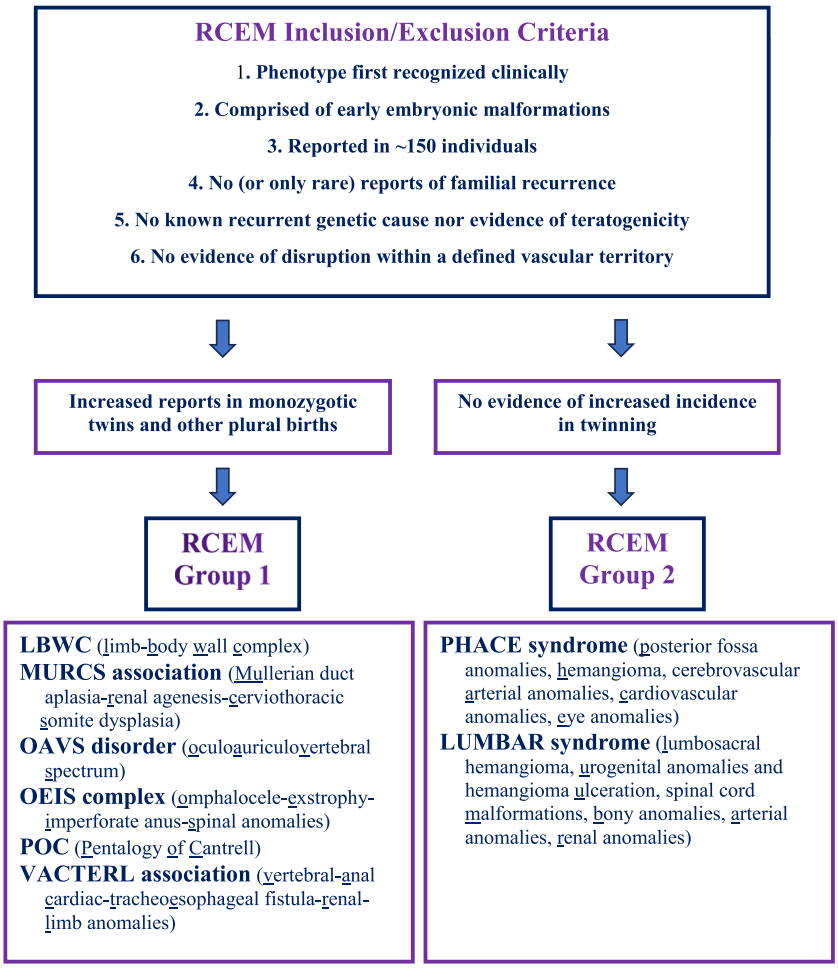

Figure 3. Recurrent constellations of embryonic malformations (RCEM)[78] groups 1 and 2.

bony defects of the lumbar, sacral, or coccygeal spine that are more visible on ultrasound than x-ray in newborns and infants.[81]

Spinal ultrasound may suffice to screen for spinal cord malformations in the first 3-4 months of life.[82] However, while lipomas are readily visualized, more subtle anomalies such as dermal sinus tracts or thick/fatty infiltrated filum terminale may be more difficult to detect.[83] After 3-4 months of age and progressive ossification of the posterior elements of the spine, the quality of ultrasound decreases, and spinal MRI becomes necessary. Spinal MRI is also recommended for infants less than 3-4 months of age who have more than one high-risk cutaneous finding (**Figure 3**B) or symptoms concerning for spinal dysraphism.[67,82,83]

It is important to recognize that regardless of the presence of a segmental IH, complex and syndromic malformations of the pelvic region, such as cloacal or anorectal malformations, are independently associated with spinal dysraphism. Given the association between spinal, genitourinary, anorectal, renal, and bony anomalies, complete imaging should be performed in any person who presents with a characteristic LUMBAR criterion regardless of segmental IH location, "atypical" morphology, or even the presence of a cutaneous IH.

The true incidence and long-term risk of vascular anomalies in LUMBAR is unknown. We would thus recommend vascular-specific imaging (ultrasound with doppler or magnetic resonance angiography) on a case-by-case basis, but particularly if concerns arise on screening imaging or in the appropriate clinical context (limb atrophy or deformity, intractable skin ulceration, signs of cardiac overload).

There are several limitations to our work. While the Delphi is a superior consensus method, it is based on opinion rather than objective measures. Bias exists in whom we selected as "experts" to our PST and Delphi invitees, and the cases included in our literature review. We invited pediatric specialists for the Delphi from disciplines outside the field of vascular birthmarks, and while specialists were provided background information on LUMBAR, the majority were not LUMBAR experts. Furthermore, while we actively solicited Delphi participants from a wide range of pediatric disciplines and geographic locations, most respondents were US pediatric dermatologists familiar with IH syndromes.

We intended to make the diagnosis of LUMBAR more specific than sensitive, which could result in negative clinical implications if associated with delayed diagnosis. Unlike the diagnostic criteria for PHACE syndrome, we did not allow for a diagnosis of LUMBAR without the presence of a cutaneous segmental IH, to avoid confusion given the number of overlapping syndromes of caudal dysgenesis. We were unable to determine a minimum IH size criterion for diagnosis but emphasized the importance of segmental IH morphology as the most critical predictor of risk. Finally, without a genetic or other biomarker for LUMBAR, these criteria cannot be validated until tested against a broad spectrum of clinical presentations.

These diagnostic criteria will enhance clinical care by improving screening, detection, surveillance, and overall awareness of this neurocutaneous disorder. The criteria can be utilized by a wide variety of pediatric specialists. In addition, formal criteria will improve phenotypic uniformity among LUMBAR syndrome cohorts and aid in establishing a patient registry that allows investigators to document clinical features, long-term outcomes, and results of genetic sequencing in a standardized manner. Improved understanding of LUMBAR is also likely to improve understanding of other overlapping disorders of caudal dysgenesis, as well as PHACE syndrome. Finally, these criteria will serve as a launching point for prospective studies to refine screening and management guidelines. We acknowledge that this is a "living document" and it is our hope and expectation that these diagnostic criteria will be updated as new knowledge is acquired. ■

CRediT authorship contribution statement

Denise Metry: Writing – review & editing, Writing – original draft, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hillary L. Copp:** Writing – review & editing, Writing – original draft, Formal analysis. **Kristy L. Rialon:** Writing – review & editing, Writing – original draft, Formal analysis. **Ionela Iacobas:** Writing – review & editing, Formal analysis, Conceptualization. **Eulalia Baselga:** Writing – review & editing, Investigation, Formal analysis. **William B. Dobyns:** Writing – review & editing, Writing – original draft, Formal analysis. **Beth Drolet:** Writing – review & editing, Formal analysis. **Ilona J. Frieden:** Writing – review & editing, Writing – original draft, Formal analysis. **Maria Garzon:** Writing – review & editing, Writing – original draft, Formal analysis. **Anita Haggstrom:** Writing – review & editing, Writing – original draft, Formal analysis. **Darrell Hanson:** Writing – review & editing, Writing – original draft, Formal analysis. **Laura Hollenbach:** Writing – review & editing, Writing – original draft, Formal analysis. **Kim M. Keppler-Noreuil:** Writing – review & editing, Formal analysis. **Mohit Maheshwari:** Writing – review & editing, Writing – original draft, Formal analysis. **Dawn H. Siegel:** Writing – review & editing, Writing – original draft, Formal analysis. **Shamaila Waseem:** Writing – review & editing, Writing – original draft, Formal analysis. **Mark Dias:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of Competing Interest

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The authors declare no conflicts of interest

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