1

CONGENITAL LUNG MALFORMATIONS

Federica Pederiva[1†], Steven S Rothenberg[2], Nigel Hall[3], Hanneke Ijsselstijn[4], Kenneth K Y Wong[5], Jan von der Thüsen[6], Pierluigi Ciet[7,8], Reuven Achiron[9], Adamo Pio d'Adamo[10,11] and J. Marco Schnater[12]

[1] Pediatric Surgery, Woman and Child Department, "F. Del Ponte" Hospital, ASST Settelaghi, Varese, Italy
[2] Department of Pediatric Surgery, Rocky Mountain Hospital for Children, Denver, Colorado, USA
[3] University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[4] Department of Pediatric Surgery and Intensive Care, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
[5] Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong, China
[6] Department of Pathology and Clinical Bioinformatics, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
[7] Departments of Radiology and Nuclear Medicine and Respiratory Medicine and Allergology, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands
[8] Department of Radiology, University of Cagliari, Cagliari, Italy
[9] Department of Obstetrics and Gynecology, Fetal Medicine Unit, The Chaim Sheba Medical Center Tel-Hashomer, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[10] Institute for Maternal and Child Health - IRCCS "Burlo Garofolo" - Trieste, Italy
[11] Department of Medical, Surgical and Health Sciences, University of Trieste, Trieste, Italy
[12] Department of Pediatric Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, The Netherlands

[†]e-mail: federica_pederiva@yahoo.it

Acknowledgements

The authors thank xxxxx

[Acknowledgements: Please use this section to acknowledge anyone important in the publication of this work who does not qualify for authorship or to declare relevant funding information. Please note that our general recommendation (see our acknowledgement guidance) is to acknowledge funding if the publication is in scope of the acknowledged grant and directly arises from the grant. In particular, grants that support data generation for distinct studies that are related in topic but that are not relevant for this specific publication should not be acknowledged. Therefore, for non-primary articles (reviews, perspectives etc), which report no new data, it is generally not best practice to acknowledge grant funding for projects just because they are related to the topic of the non-primary article.]

Competing interests

The authors declare no competing interests.

[Competing interests: Please declare financial and non-financial competing interests for all authors. Please refer to our competing interest policy for more information. Indicatively, the CI statement may include any stocks or shares in companies that may gain or lose financially through publication; consultation fees or other forms of remuneration (including reimbursements for attending symposia) from organizations that may gain or lose financially; patents or patent applications (awarded or pending) filed by the authors or their institutions whose value may be affected by publication. The declarations made in this section must match those in the submission system.]

Author contributions

Introduction (F.P. and J.M.S.); Epidemiology (F.P. and J.M.S.); Mechanism/pathophysiology (K.K.Y.W., A.P.D and F.P.); Diagnosis, screening and prevention (R.A., P.C.; F.P. and J. von der T.); Management (N.H, S.S.R, J.M.S. and F.P.); Quality of life (H.I. and N.H); Outlook **[Au: In EJP J. von der T. is marked as having contributed to the Outlook section. Please address this discrepancy.]** (F.P and A.P.D.).

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Congenital lung malformations (CLMs) are rare developmental anomalies of the lung, including congenital pulmonary airway malformations (CPAM), bronchopulmonary sequestration (BPS), congenital lobar overinflation, bronchogenic cyst (BC), and isolated congenital bronchial atresia (CBA). CLMs occur in 4 per 10,000 live births. Postnatal presentation ranges from an asymptomatic infant to respiratory failure. CLMs are typically diagnosed with antenatal ultrasonography and confirmed by chest computed tomography angiography in the first few months of life. Although surgical treatment is the gold standard for symptomatic CLMs, a consensus on asymptomatic cases has not been reached. Resection, either thoracoscopically **[Au: As this appears to be controversial among reviewers, or depending on the expertise available at the various medical centres across the globe, please consider reversing the order in which resection methods are introduced in the abstract.]** or through thoracotomy, minimizes risk of local morbidity, including recurrent infections and pneumothorax, and avoids the risk of malignancy that has been associated with CPAM, BPS, and BC **[Au: Edit OK?]**. However, some surgeons suggest expectant management, as the incidence of adverse outcomes, including malignancy, remains unknown. In either case, a planned follow up and a proper transition to adult care are needed. The biological mechanisms through which some CLMs may trigger malignant transformation, are under investigation. KRAS has already been confirmed to be somatically mutated in CPAM, and other genetic susceptibilities linked to tumor development have been explored. By summarizing current progress in CLM diagnosis, management, and molecular understanding we hope to highlight open questions that require urgent attention.

[H1] INTRODUCTION

Congenital lung malformations (CLMs) refer to a continuum of developmental disorders that involve the lung parenchyma, the tracheobronchial tree and, occasionally, the pulmonary vessels, or a combination of the above. At one end of the spectrum, congenital lobar overinflation (CLO; previously known as congenital lobar emphysema) represents abnormal lung supplied by normal vessels. At the other end of the spectrum, pulmonary arteriovenous malformations **[G]** are characterized by abnormal vessels within normal lung parenchyma [1].

This Primer focuses on the most common parenchymal and tracheobronchial anomalies: congenital pulmonary airway malformation (CPAM; previously known as congenital cystic adenomatoid malformation, CCAM); bronchopulmonary sequestration (BPS); CLO, and bronchogenic cyst (BC). We also discuss congenital bronchial atresia (CBA), which has been recognized as a separate CLM entity **[Au: Edit OK?]**. BPS can be intralobar (ILS) or extralobar (ELS). CPAM is further classified into five histological subtypes, defined by the suspected anatomical level of the airway they originate from [2,3] (**Figure 1**).

Of note, some researchers **[Au: only researchers, or clinicians too?]** consider all the CLMs under the umbrella of CPAM, but CPAM is only one of the CLM types, and adherence to the precise definition of each CLM is required when reporting new cases **[Au: Edit OK?]** .

CLMs arise during embryonic lung development (**Box 1**) as a result of an abnormal organogenesis or a dysregulation of cellular signaling within the epithelial-mesenchymal interaction **[G]** [4]. The timing of this dysregulation is likely to determine the type or subtype of CLM **[Au: I have removed reference to figure 1 from here, as the figure does not depict how the timing of malformations during embryogenesis determines CLM types or subtypes.]** .

[Au: Please add a sentence here to briefly describe the major symptoms/risks associated with CLMs, including respiratory distress at birth and risk of malignancy This will help the orientation of less familiar readers.] Professionals agree to surgically treat symptomatic

patients with CLMs, but there is an ongoing debate worldwide whether asymptomatic patients should be managed surgically or conservatively. The best way to address this controversy is to invest resources into researching the natural history of CLMs, the biological relationship between some CPAM, BPS, BC and malignancy, and potential drivers **[Au: Edit OK?]** of malignant transformation.. **[Au: I've removed the KRAS detail here, as this is better mentioned in the subsequent focused sections.]**

In addition, clinical professionals, surgeons and researchers continue to envision prognostic tools, standardize care, especially in asymptomatic cases, standardize respiratory and imaging follow up, provide transition of care into adulthood, and build a global registry **[Au: This sentence was edited to avoid repetition.]** .

This Primer describes the epidemiology and pathophysiology of CLMs as well as the progress in diagnosis and management, and the different viewpoints of pediatric and non-pediatric thoracic surgeons on CLM management .

[H1] EPIDEMIOLOGY

[H2] Demographics

CLMs have been estimated to comprise up to 18% of all congenital anomalies **[G]** [5]. Historically, the overall incidence of CLMs was estimated at ~0.5 to 1.5 per 10.000 live births but, in 2015, registry studies in the UK reported an incidence of around ~1 per 2,500 live births [6-9]**.** The apparent rising incidence of these malformations is probably a consequence of the widespread availability and the improved resolution of prenatal ultrasonographic screening, which have increased CLM detection, especially in high-income countries [8,10]. Due to a lack of global registries the exact number of patients with these rare malformations and possible regional differences remains unknown.

CPAM type 1 is the most common type of CPAMs, representing 50-70% of CPAM cases **[Au: Edit OK? Or is it the most common type of CLMs?]** [11]. CPAM type 2 underlies 15-30% of all CPAM cases [12], whereas CPAM type 3 represents 5-10% of CPAM. **[Au: Edit OK? Please add a reference on the incidence of CPAM type 3.]** The individual incidence of other CLMs remains unknown. **[Au: I moved this sentence here from below to improve the text flow.]**

Around 11.7% of patients with a CLM have an associated anomaly in other organs, but only 5-10% of them have an additional major malformation **[Au: Edit OK?]** [13]. Associated developmental defects in other organ systems may, therefore, stem from the same dysregulation in epithelial–mesenchymal interactions during embryonic development that causes CLMs. The most common associated malformations are congenital heart defects (32%) and gastrointestinal defects (18%) [14]. BC was found to have the highest proportion of associated anomalies (29%), particularly vascular malformations, followed by CPAM (12%), which was more frequently associated with congenital heart diseases and gastrointestinal malformations. A concurrent malformation existed in 10% of patients with BPS and in 9% of those with CLO, mainly gastrointestinal for BPS and cardiac for CLO [14]. Clinicians should be aware of these possible co-occurring anomalies and consider additional diagnostic imaging.

[H2] Risk factors

CLMs seem to occur sporadically and have not been associated with any karyotype anomalies **[Au: Is this edit correct? It might not be accurate to state that CLMs appear without karyotype anomalies in all of the cases. Please reference this statement.]** . Their formation has not been associated to maternal factors, such as race, age, or exposure to environmental factors **[Au: Please reference this statement.]** . No gender predilection has been demonstrated [15]. Risk factors for developing symptoms after birth **[Au: I've deleted this second part of this sentence, as risk of malformations is separately discussed below. OK?]** are not yet known. **[Au: What is the incidence of CLM symptoms at birth or later?]** Multicenter international

collaborations, including long term follow-up registries, and prospective trials, such as the CONNECT trial by the Collaborative Neonatal Network [16] **[Au: Deleted this part to avoid redundancy, as all of the above are also research studies. OK?]** will help understand the natural history of CLMs and how some of them (CPAM, BPS and BC) may be associated with malignant transformation. **[Au: Edited for conciseness.]**

[H3] Association of CLMs with lung cancer

[Au: Edit OK? I modified the heading level, placing it under the section on risk factors.]

The incidence of malignant degeneration in CLMs remains unknown. In 1983 [17], it was estimated to be 4%, and in 2010[18], the incidence of pleuropulmonary blastoma (PPB), specifically, was reported to be 2%. **[Au: Do these percentages (ie incidence of malignant degeneration) refer to all CLMs collectively or to CPAMs only? Please consider introducing PPB as the most common type of cancer that is associated with CLMs. What other cancer types are commonly associated with CLMs?]**

All CLMs, except for CLO and CBA, may be associated with a malignant lung lesion both in pediatric and adult patients [19]. PPB has been historically associated with CPAM, but it remains unclear whether the initially identified lesion was a CPAM preceding PPB or an unrecognized PPB [19]. **[Au: The highlighted sentence was moved here from below to avoid redundancy and improve the text flow. OK? See also previous comment about an earlier introduction of PPB and ensure consistency throughout the Primer as far as the definition of PPB as a CPAM type 4 (or not) is concerned.]** In earlier studies, CLOs in two children were associated with a PPB [20] and a rhabdomyosarcoma [21],respectively, and CLOs in ten adults , at that time diagnosed as congenical cystic emphysema, **[Au: Edit OK?]** were associated with bronchogenic carcinoma [22]; however, the histological definition of these CLOs might have been inaccurate **[Au: Edit OK?]** .

In the pediatric population, the CLM most frequently associated with a lung tumor is CPAM [19]; in adult patients, tumors co-occur mainly with CPAM or, to a similar extent, with BC [19]. **[Au: Edit OK?]** **[Au: What about BPS, which is mentioned elsewhere as also being associated to cancer?]** Biological research has so far focused mainly on malignancy biomarkers in CPAM, which is also the most frequent CLM **[Au: Edit OK?]** .

Similar to cancer cells, CPAM cells **[Au: Do you refer to epithelial cells here? Please specify.]** have a double proliferation index compared with normal cells and a lower susceptibility to apoptosis[23]. As CPAM is not inheritable and usually involves only one lung lobe, the mutations potentially linking CPAM with cancer are probably somatic and not germline. Despite this, the possibility of predisposing germline mutations has also been explored. De novo mutations in genes that encode proteins implicated in cancer, such as SMAD7 or KDM6A, have been found in 38.8% of patients with CPAM, providing some evidence to support prophylactic resection of CPAM [24]. **[Au: Edited for conciseness.]**

Moreover, among the 351 genes that were identified as differentially expressed in in paediatric macrocystic CPAM, microcystic CPAM, BPS, or hybrid lesions, compared with unaffected tissue of the resected lobe, genes in the Ras complex, PI3K-AKT-mTOR and mTOR signaling pathways, and Myc transcriptional targets were significantly enriched [25]. **[Au: Macrocystic, microcystic, hybrid (or giant) CPAM is only described later in the article. In addition, the highlighted text above and below relates more to mechanisms/pathophysiology and less so to epidemiology. Thus, I suggest moving it further down, to improve the text flow.]**

Moreover, genes involved in embryonic development and cell proliferation have been found to be differentially methylated in ELS samples (*HOX3B1*, *HOXD4*, *CTNNA1*, *NR2F2*, *HSF4*, *MEIS1*), in ILS samples (*HOXA3*, *HOXB1*, *TGFB1I1*, *BRD2*, *CTNNA1*, *CTSZ*, *GPR37L1*, *S100A13*; *TSPAN3*, *FOXP2*)[26], in CPAM type 1 lesions (PLD6, S100A13; MXS2 and TXNRD1), and in CPAM type 2 (ZFP57, and MEIS1). In CPAM type 3, differentially methylated regions were identified in *MSX2* and in an intergenic region involving a cis-regulatory element of *PITX2*, low methylation of which

has been associated with an increased risk of lung cancer progression [27], and of *ENPEP*, which is downregulated in lung adenocarcinoma [28].

[Au: I have moved a sentence referring to KRAS down into the mechanisms/pathophysiology section (highlighted in blue) to improve the text flow and avoid redundancy. OK?] [Au: I've removed a sentence here that was not directly related to the scope of the epidemiology section. OK?] Whereas a KRAS mutation confirms malignancy in adults with lung cancer, the clinical relevance of KRAS mutations in pediatric lung specimens still needs to be investigated. **[Au: The text highlighted in yellow does not fit within the scope of the epidemiology section. Please consider moving to the management section.]**

[Au: A sentence that was initially found here, referring to MCCs was not related to the scope of the epidemiology section. I have, thus, merged this sentence with the discussion on MCCs under the CPAM type 1 paragraph of mechanisms/pathophysiology (highlighted in blue).]

[Au: I have removed a part of text (highlighted in yellow in the tracked version of the edit) that does not fit within the scope of the epidemiology section.]

[Au: I removed the last paragraph of the section, as it was unrelated to the scope of the section and the article, and unreferenced.] [19]. **[Au: The initial first sentence of this subsection was moved further up to improve the text flow and avoid redundance.] [Au: I have deleted the discussion on CPAM type 4 and PPB from here, as it was redundant with the discussion under the paragraph on CPAM type 4, under the mechanisms/pathophysiology section.]**

[H1] MECHANISMS/PATHOPHYSIOLOGY

[H2] CPAM

[H3] CPAM pathogenesis

[Au: I have suggested adding a new level of subheadings, to break down the long text. OK?]

CPAMs involve mainly proliferation of cells from the bronchial structures, but not from alveoli, presenting as cysts that are in direct communication with adjacent lung parenchyma. **[Au: Edit OK?]** CPAM usually affect one lobe, most commonly the lower ones, and multi-lobar or bilateral disease is less common [38]. There are several hypotheses about the mechanism of CPAM pathophysiology. One theory assumes that focal lung morphogenesis is interrupted during CPAM pathogenesis as a result of genetic defects that cause continuous expression of lung growth markers, such as SOX2 and thyroid transcription factor-1 (TTF1), together with a decreased expression of aldehyde dehydrogenase 1 family, member A1 (ALDH1A1) [39]. **[Au: Edited for style, OK?]** The obstructive hypothesis, which is based on histological studies, advocates that focal obstruction of the airway tree, such as a sort of bronchial stenosis,**[Au: Comma here OK, or after "peristalsis"?]** or an abnormal airway peristalsis might lead to a local increase of mediators that can trigger immune responses, such as fibroblast growth factor 10 (FGF10), interleukins and chemokines, , leading to the abnormalities **[Au: What sort of abnormalities? Do you mean cysts?]** of CPAM [40]. However, the timing of these events is poorly understood [41]. Other hypotheses on CPAM pathogenesis, include the disruptive spatial patterning of epithelial cells in cysts that resemble proximal airway structures, branching morphogenesis, and imbalance between cell cycle, cell proliferation and apoptosis (**Box 1**) [42,43].

In animal models, the FGF family of potent mitogens regulates cellular proliferation, migration and differentiation, with FGF7 and FGF10 being expressed in lung mesenchyme [44]. **[Au: The opening of this sentence was modified, as below rat and not mouse models are described. OK?]** Injection of FGF10 in fetal rat lungs resulted in formation of cystic lesions, which varied depending on the developmental stage and injection location [45]. However, no alteration of FGF10 expression

was found in fetal and postal-natal CPAM samples in humans, and this indicates that FGF10 overexpression may be a transient phenomenon during CPAM pathogenesis **[Au: Edit OK?]** [46]. Moreover, aberrant FGF expression or FGF protein mislocalization have been implicated in malignant transformation and metastasis **[Au: Do you mean in CPAM or generally? The link to CPAM is unclear.]** **[Au: I've removed mention of a link between FGF7, cancer and CPAM, as this had not clearly been explained.]** [50].Cystic lung lesions are also found in mice overexpressing Krueppel-like factor 5 (KLF5) [47] or Notch1 receptor[48], and in mice lacking expression of peroxisome proliferator-activated receptor gamma (PPARγ) [49].

[H3] Molecular classification of CPAM

[Au: New subheading introduced. OK? Please consider discussing molecular classification prior to mechanisms of CPAM pathogenesis, to improve the text flow.]

CPAM classification criteria have been redefined with the help of molecular biology. Acinar dysplasia is now the preferred term for the diffuse malformation previously described as CPAM type 0 **[Au: Please replace the term CPAM type 0 with acinar dysplasia throughout the text and the figures, if the latter is the preferred term.]** [36]. Acinar dysplasia is usually lethal and associated with mutations in genes that regulate embryonic development, cell proliferation and cell differentiation, including the genes encoding FGF10, FGFR2 and the transcription factor TBX4 [51,52]. **[Au: Where in the lungs does acinar dysplasia arise?]**

CPAM type 1 arises from the proximal bronchioles or distal bronchi (**Figure 1**). Mucinous cell clusters (MCCs) are pre-malignant or malignant cell clusters that occur in 75% of patients with CPAM type 1 **[Au: Edit OK? This information was moved here from the epidemiology section, where it was out of scope.]** (**Figure 2**), and are generally absent in CPAM types 2 and 3. MUC5AC has been identified as a valuable marker of MCCs [53], and mucinous proliferation tissue in CPAM type 1 sections have similar MUC5AC expression patterns as mucinous lung adenocarcinoma **[Au: Edit OK?]** . MCCs are thought to be a precursor reservoir for potential invasive mucinous adenocarcinomas. *KRAS*, one of the most mutated genes in lung cancer, has

been found to be mutated in both mucinous [29] and non-mucinous cells [30] of CPAM type 1, **[Au: The highlighted text was moved here from the previous section.]** Sequencing analyses revealed *KRAS* exon 2 mutations in MCCs from all 18 patients examined, irrespective of whether they were diagnosed with CPAM type 1, CPAM type 3, or CPAM with an intermediate morphology between 2 **[Au: between 1 and 2 or between 2 and 3? Please clarify.]** [29]. Furthermore, *KRAS* mutations were also found in 17 of the 25 CPAMs without MCC analyzed, and the p.G12D mutation was specifically correlated with type 1 morphology. **[Au: Edited for brevity, style and clarity. Please ensure that the intended meaning was maintained.]** . In patients harboring both CPAM type 1 and adenocarcinomas [31], both lesions can have the same *KRAS* mutations, which is an indication that mutated *KRAS* in CPAM may confer susceptibility to cancer. **[Au: Edited for conciseness and clarity. OK?] [Au: The parts highlighted in blue were moved here from the epidemiology section, to avoid redundancy and improve the text flow. OK?]**

CPAM type 2 lesions are believed to arise secondary to bronchial obstruction and may contain *KRAS* mutated cells **[Au: Edit OK?]** [30,41,54-56]. CPAM type 3 is believed to originate from acinar-like tissue **[G]** and has been associated with activating *KRAS* mutations or mutations in other genes involved in cell cycle regulation and growth; 50% of CPAM type 3 have a *KRAS* mutation, most commonly p.G12V. MCC are seen in 45% of CPAM type 3 and are often multifocal and have papillary or acinar architecture [57]. Overall, the formation of CPAMs type 1 and 3 seems to be driven by mosaic *KRAS* mutations arising in the lung epithelium early in development and places them within the growing cluster of mosaic RASopathies.

CPAM type 4 is now thought to represent type 1 PPB and should be diagnosed as such [33-36]. **[Au: Under the epidemiology section, it is stated that: "**It has been argued that CPAM type 4 is identical to PPB 1 [32], and should be considered a PPB, which is generally not diagnosed prenatally [33-36]. However, some studies suggest that a CPAM type 4 evolves into PPB through the acquisition of a somatic mutation in the DICER1 gene [34,37]." **This statement is also repeated at the end of this paragraph. Please revise the highlighted sentence for balance and consistency.]** A

pathognomonic molecular marker for PPB has not yet been discovered, but association with DICER1 germline mutation is found in up to 66% of PPBs. Some authors suggest a possible evolution of CPAM type 4 into PPB1 in case of acquisition of somatic mutations in the *Dicer1* gene [34,37]. In order to comprehensively elucidate the complex interplay between PPB and germline and somatic mutations in *DICER1*, initiatives such as the International PPB/DICER1 Registry and the DICER1-Related Pleuropulmonary Blastoma (PPB) Syndrome Study conducted by the National Cancer Institute are essential. **[Au: If you prefer, you may provide links to the above registry and study.]** These projects are extremely useful for characterizing the risk associated with pathogenic variants, for studying the clinical course of patients with these variants and, ultimately, for better management.

[H2] BPS

BPS is a hamartomatous mass of non-functioning lung tissue **[Au: Please reference this statement.]** , and the mechanisms involved in BPS formation generally remain unknown. High expression of Hoxb-5 gene **[Au: at what embryonic stage?]** , a Hox gene involved in normal lung development, might be involved in BPS pathogenesis [59]. **[Au: The highlighted sentence was moved here from below, to improve the text flow. Was this found in humans? If so, please adjust gene nomenclature to "HOXB5".]** BPS lesions are not in continuity with the tracheobronchial tree but supported by an aberrant systemic artery stemming from the thoracoabdominal aorta or, less commonly, from the gastric or splenic artery [41]. Intralobar sequestrations (ILS) , which appear within the visceral pleura, represent 75% of BPS lesions and are often localized in the lower lobes. **[Au: Edited for clarity. Please check that the intended meaning was maintained.]** Even though the abnormal lung parenchyma is non-aerated, some collateral ventilation is supported by the pores of Kohn **[G]** and channels of Lambert **[G]** of the adjacent lung tissue [41].Consequently, ILS are at increased risk of bacterial seeding and pneumonia or other complications [38]. ILS are usually fed by a single artery most commonly coming from the descending thoracic aorta and branching to the lower lobe after passing through the

inferior pulmonary ligament. Multiple arterial supply has been described in 16% of the cases [58].**[Au: You seem to mention arterial supply a few sentences above already. Please consolidate all info on this here and remove above.]** The venous drainage is most commonly to the left atrium through the pulmonary veins [58].**[Au: I've removed the more detailed description of uncommon drainage.]**

Extralobar sequestrations (ELS) correspond to a 25% of BPS lesions and are covered by a distinct pleura. ELS have one or, in 20% of the cases, more than one feeding artery, usually stemming from the thoracoabdominal aorta, and systemic venous drainage that is separated from normal lung parenchyma. In 80 % of cases, the systemic venous drainage occurs through the azygos or hemiazygos system, or through the vena cava to the right atrium [58]. **[Au: I've removed the descriptions of uncommon feeding and drainage here.]** Infections are less common in ELS as those are not connected with the tracheobronchial tree **[Au: Edit OK? Or do you mean in BPS in general. Is there any connection of ILS with the tracheobronchial tree? In the beginning of this section, it is stated that all BPS are not connected with the tracheobronchial tree. Please clarify.]** , and presenting symptoms of ELS are mainly associated with the abnormal systemic vascularization, which often leads to high-output congestive heart failure as a result of the right-to-left shunt, or to torsion of the vascular pedicle. ELS is usually found in the thoracic cavity, but it can also develop below the diaphragm in the abdomen, or within the diaphragm [41]. **[Au: The last sentence of this paragraph was moved further up (highlighted in yellow) to improve the text flow).**

Some ILS and ELS 'hybrid/mixed' lesions that rely on systemic blood supply share features of CPAM **[Au: Which features specifically? Do you mean, for example, proliferation of cells from the bronchial structures? MCCs? Please specify.]**[60,61]. Such lesions are histologically diagnosed as hybrid, both prenatally and in the pediatric population, and **[Au: Please move mention of the histological features of the hybrid lesions to the previous sentence, see also previous comment.]** , are distinct from acquired lesions diagnosed in adults following lower lobe infections that cause the cystic degeneration of the parenchyma and the proliferation of systemic

arteries entering the lung through the pulmonary ligament or across the pleura [58]. **[Au: Edited for clarity. Please check that the intended meaning has been maintained.]**

[H2] CLO

CLO is caused by a focal cartilaginous abnormality of the bronchial wall, which creates a valve effect after birth **[Au: Edit OK? Or is it only the overinflation that is caused after birth?]** and a consequent overinflation of a pulmonary lobe [62]. The bronchial narrowing may be caused by intrinsic factors, such as the absence of bronchial cartilage, bronchial stenosis **[Au: Do you mean congenital bronchial stenosis? Aren't 'bronchial narrowing' and 'bronchial stenosis' synonymous terms?]** or bronchomalacia **[G]** , or by an extrinsic cause, as a vascular sling **[G]** [63]. **[Au: What are the molecular mechanisms underlying the above causes, ie absence of bronchial cartilage or bronchomalacia, or vascular slings?]** In ~50% of patients, however, CLO is idiopathic, and a clear etiology cannot be identified [63]. The left upper lobe and the right middle lobe are most commonly affected by CLO.. **[Au: I have deleted a statement on prenatal diagnosis from here, as it also appears under the section on diagnosis. Please move reference 64 from here to the relevant part of the text under diagnosis.]** After birth, the progressive hyperinflation of the affected lobe may result in mediastinal shift **[G]** and consequent compression atelectasis of normal lung parenchyma [64]. Acute and rapidly worsening air trapping at birth, can lead to severe respiratory symptoms, and require emergency surgical procedure. In some cases, the hyperinflation of the lobe is slower and accounts for a delayed onset of respiratory symptoms within the first weeks of life [64]. However, some patients have minimal pulmonary symptoms or are completely asymptomatic, and are, therefore, managed with serial observation [38]. **[Au: Please remove the highlighted paragraph from here, as it is unrelated to mechanisms/pathophysiology and merge with the management section.]**

[H2] BC

BC is a unilocular malformation resulting from abnormal budding of the primitive ventral foregut. BCs contain cartilaginous tissue, smooth muscle, and bronchial glands, all lined by ciliated

columnar epithelium. Most BCs are localized in the mediastinum adjacent to the trachea or the mainstem bronchi (subcarinal space), but sometimes they can be intrapulmonary, or appear outside the chest, in the areas of the neck, the abdomen or the skin [38,65]. The pathophysiology of BC is still unknown. BC can be asymptomatic. Mediastinal BCs do not communicate with the tracheobronchial tree, but they contain mucus and may enlarge or compress the bronchi, causing dyspnea[65]. Intrapulmonary BCs are connected with the tracheobronchial tree and can lead to respiratory symptoms in newborns or in infants, or infection in children, as a result of air trapping [65].

[H2] CBA

CBA stems from a focal interruption of a lobar, segmental, or subsegmental bronchus, and is associated with the presence of a mucocele **[G]** and overinflation of the involved lung segment. The presence of the mucocele is pathognomonic and results from fluid **[Au: Do you mean accumulation of mucus?]** accumulation following airway obstruction [66]. CBAs are hypothesized to occur after the 16th week of gestation, probably due to intrauterine ischemia. The apicoposterior segmental bronchus of the left upper lobe seems to be most commonly affected by CBA [66]. Proximal CBA is located at the level of the mainstem, or the proximal lobar bronchi and it is almost always fatal during pregnancy or immediately after birth [62]. Peripheral CBA involves the segmental or subsegmental bronchi and may present as an isolated lesion[62].

In this Primer, we discuss peripheral CBA, which has also been associated with **[Au: Do you mean that CBA has been reported as secondary pathology in other prenatal lung malformations?]** other prenatal lung malformations, including CPAM, BPS, CLO [62], as part of the pathological spectrum of these CLMs.

[H1] DIAGNOSIS, SCREENING AND PREVENTION

[H2] Clinical presentation

Prenatally diagnosed CLMs have highly variable clinical presentation, ranging from lack of any symptoms to respiratory distress at birth **[Au: Edit OK?]** [15,38]. The latter is a rare event that occurs in <10% of patients mostly as a result of a mediastinal shift caused by a CLO or a giant CPAM **[Au: what is a giant CPAM? Is it just a 'large' CPAM? Otherwise, please consider introducing in the mechanisms/pathophysiology section. Does it classify under one of the five CPAM types discussed above?]** [15,38], and requires emergency surgery. Most commonly, however, children with prenatally diagnosed CLMs remain asymptomatic postnatally [67], and admission to an intensive care unit is not justified in an asymptomatic newborn[38].

Nearly half of the patients that are asymptomatic at birth develop symptoms in their first year of life, with a peak at a median age of two years [68]. Long-term follow up has revealed that most **[Au: Is it possible to provide a percentage here?]** infants with CLM develop symptoms [68,69]. The most common symptoms are respiratory infections, pneumonia, fever, chronic cough, pneumothorax, and respiratory distress. The incidence of respiratory infections in children with CLM is not clearly defined and varies **[Au: Do you mean varies across studies or across CLMs?]** between 5 and 86% [68,70,71] High-output cardiac failure is a rare complication resulting from large systemic feeding vessels[41]. **[Au: I have deleted the last sentence of this paragraph to improve the text flow and avoid redundancy, as it overlapped with information presented under the subsection on postnatal diagnosis.]**

[H2] Prenatal screening and diagnosis

[H3] Fetal ultrasonography

Although CPAM, BPS, CLO, BC, and CBA are distinct pathologies, their embryology and imaging phenotyping overlap [1], and they also share some common clinical and histological features **[Au: Edit OK?]** [61]. The prenatal diagnosis of CLMs relies on the cystic or solid appearance of space-occupying lesions within the fetal thorax, or the abnormal size of the lungs and consequent deviation of the heart from its normal 45-degree position (**Figure 3**). **[Au: I moved this sentence**

here from below to improve the text flow.] According to the Adzick classification for fetal ultrasonography **[Au: Edit OK?]** , CLMs are described as either macrocystic lesions that present as single or multiple cysts >5 mm, or microcystic lesions with solid appearance that feature cysts <5 mm[72].

CLMs are easily detected during routine prenatal ultrasonograpic examination at 18-22 weeks of gestation. The differential diagnosis includes congenital diaphragmatic hernia **[G]** , esophageal duplication **[G]**, foregut duplication cysts **[G]** and other thoracic masses, such as pericardial teratoma. **[Au: I moved this sentence here from below to improve the text flow. Please check this edit for accuracy – did you indeed mean differential diagnosis to CLMs or rather differential diagnosis to disappearance of the lesions?]** CLMs usually increase in size between 20 and 26 weeks of gestation before reaching a plateau by 29 weeks of gestation [73]. Later, the decrease in size of CLMs seems to be related not only to growth of the fetus but also to the transition from the canalicular to saccular stage of lung development (**Box 1**), with consequent changes in proliferation and apoptosis rates **[Au: Edit OK? Proliferation and apoptosis rates of what cells? Please specify]** [74]. CLMs become isoechoic to normal lung tissue late in gestation, and this can be mistakenly considered as disappearance of the lesions. For this reason, it is imperative to perform a CT scan after birth **[Au: Do you mean CT angiography, consistently with what is discussed in the next section?]** to exclude the presence of a CLM. **[Au: Edit OK? I suggest focusing on CT vs CR in the next section, on postnatal diagnosis.]** Amniocentesis is not recommended in pregnancies with a diagnosis of CLM if a solitary lung lesion is identified. A vaginal delivery at a local birthing center without neonatal intensive care or pediatric surgical support is safe for fetuses with small lung lesions [15].

CPAM and BPS are the two CLMs most commonly diagnosed in utero, as intrathoracic, usually unilateral, cystic, or solid masses [75]. CPAM is usually recognized at mid gestation as a multilocular lesion with cysts from few millimeters to 10-12 mm in size (macrocystic type), or as well-defined homogeneously hyperechogenic mass (microcystic type) [75]. In both cases, the heart is usually

pushed to the contralateral side [75]. BPS appears as a well-defined homogeneously hyperechogenic mass that is indistinguishable from the microcystic type of CPAM [75]. However, exploration with color Doppler ultrasonography can help identify any aberrant feeding artery arising from the aorta, and this is specific to BPS **[Au: Edit OK?]** . 3D and 4D ultrasonography may provide greater information regarding the spatial relationship, volume, and vascular feeding of both CLMs [76]. A giant CPAM can grow and cause mediastinal shift with consequent esophageal compression, pulmonary hypoplasia, polyhydramnios **[G]** and obstruction to venous return leading to hydrops [77] (Figure 3a). Thus, it is recommended to monitor CLM growth by serial calculation of CPAM volume ratio (CVR) [78] (**Figure 3**).

ILS hydrops may develop in the fetus **[Au: Edit OK?]** because of abnormal systemic arterial blood supply with increase of venous drainage via the pulmonary veins, leading to “left-to-left” shunting which sometimes results in high-output cardiac failure. It is therefore recommended to assess cardiac function **[Au: At what stage of gestation and how often?]** , for example based on Tricuspid annular plane systole excursion (TAPSE) **[G]**, to identify hemodynamic deterioration [79] (**Figure 3**).

CLO is identified only rarely via prenatal screening, mainly because of the phenotypic similarity to microcystic CPAM. **[Au: Edit OK?]** CLO appears in fetal ultrasonography **[Au: Edit OK?]** as uniformly enlarged lung **[Au: Does microcystic CPAM also appear as uniformly enlarged lung? This was not mentioned above.]** , mildly hyperechoic, without cysts or systemic arterial supply [76]. The identification of a tubular cystic hilar structure consistent with a dilated bronchus and prominent oblique lung fissure at 2D and 3D ultrasonography may hint towards the correct diagnosis [76] (**Figure 3**).

Mass size, rather than CLM type, is the major predictor of perinatal outcomes[15,80]. CVR, the ratio of the 3D size of the lesion to the fetal head circumference, is the most commonly used metric for CLM mass (Figure 3b) [81]. Risk of developing fetal hydrops is ~80% for fetuses with a CVR exceeding 1.6, and CVR increase during pregnancy **[Au: Edit OK?]** has been associated with

increased rates of prenatal intervention and adverse postnatal outcomes [82,83]. CVR has been associated with development of hydrops, neonatal respiratory distress (NRD), and increased rates of oxygen supplementation, mechanical ventilation, and resection at birth [15]. In addition, high first **[Au: Please clarify what is the first CVR value. Do you mean CVR at first diagnosis?]** or high maximum CVR values were predictive of risk for NRD for both term and preterm infants [84], but consensus on a precise cut-off value is lacking [85]. **[Au: Edited for brevity. OK?]** One cohort study showed that a CVR ≤0.39 measured between 25-30 weeks predicts a low probability of need for respiratory support at birth but does not rule out respiratory problems later on [86]. The low probability of NRD (<10%) for a maximum CVR <0.40 supports this cut-off value [84]. A CVR >0.84 seems to be a reliable predictor of respiratory morbidities, such as respiratory distress, recurrent infections, cough, and the need for surgical resection **[Au: Do you mean at birth or later in life?]** [87,88] (**Figure 3**).

[H3] Fetal MRI

The merit of MRI for the prenatal diagnosis of CLMs remains controversial [38]. MRI can be used to accurately assess the location, size, **[Au: Edit OK? Isn't 'extent' reflected by location and size only?]** mass effect **[G]** , and internal features **[Au: What internal features? Please provide some examples.]** of CLMs [89,90], and a one study has shown the superiority of MRI against ultrasonography **[Au: Edit OK?]** in identifying vascular supply [89]. However, in fetuses with small lung lesions, the limited additional information provided by prenatal MRI is not sufficient to amend management plans. For this reason, MRI is only selectively recommended, for example, when a lung lesion in not clearly defined at prenatal ultrasonography or in the presence of a large CLM. MRI might help to characterize the malformation or to prepare a treatment plan if prenatal management or early neonatal resection are needed [85,89].. In such cases, the best timing for fetal MRI is between the 24th to 30th week of gestation [91].

[H2] Postnatal diagnosis

[H3] Computer Tomography Angiography

Postnatal chest CTA at 2 months of age is essential for confirming prenatal diagnosis of CLMs (**Figure 4**) and for outlining a management plan. Chest CTA is the current gold standard for the postnatal evaluation of CLMs due to its ability to provide the highest spatial resolution and sensitivity [92,93]. The scan range of chest CTA should cover the anatomical area from the thoracic inlet to the mid-abdomen to enable full capture of the extent of any aberrant vasculature, which may arise or extend below the diaphragm [94]. The CTA protocol should be tailored to the patient's weight in accordance with the ALARA principle and include thyroid function monitoring to promptly detect any temporary thyroid dysfunction [98]. **[Au: This sentence was moved here from below, to improve the text flow. OK?]**

Third-generation CT scanners use a lower amount of radiation and have a rapid acquisition speed that overcomes the need for sedation [92]. They deliver diagnostic-quality images in >95% of patients [92,93], regardless of age or compliance with breathing instructions. Structured assessment of CTA results [95] can consistently provide precise information about the size, location, and other characteristics of CLMs [96] that are crucial for surgical planning **[Au: Please check the edits for accuracy.]** . Furthermore, CTA enables use of a quantitative scoring system **[Au: is this quantitative scoring system you are referring to here different from the structured assessment of CTA results referred to in the previous sentence? If possible, please consider merging the two sentences to avoid any redundancy.]** that provides objective data, to assess changes in size of CLMs or to determine indication to surgery [97].

[H3] Chest radiograph

CR is a first-line screening tool , being noninvasive and cost-effective. However, a a prenatally diagnosed CLM should never be ruled out in a newborn based on CR only, as CR fails to detect CLM in 50% of patients [99-101], and the information it provides fails to predict the potential onset of

symptoms or to inform the surgical plan [92] (**Figure 4**). **[Au: Edit OK?]** In pediatric patients **[Au: Edit OK?]** that present with recurrent infections in the same location but lack a prenatal diagnosis of CLM, certain radiographic features, such as persistent opacities or radiolucency, can raise suspicion for an underlying undiagnosed CLM [102]. In case of strong clinical suspicion of CLM, further imaging evaluation using cross-sectional techniques, such as CTA or MRI, is necessary to obtain a comprehensive and accurate diagnosis (**Figure 4 and 5**).

CR can also be applied to assess potential complications of CLM surgery, such as pneumothorax, bleeding, and infections[92]. In previously asymptomatic children with CLM that newly develop symptoms CR is often the first imaging modality used to evaluate the cause of these symptoms [92] and assess them as potential complications of BPS or CPAM, in the case of infections, and CLO or BC, in the case of progressive hyperinflation. **[Au: Edit OK?]**

[H3] Lung ultrasonography

Lung ultrasonography (LUS) has limited application in the detection of CLMs after birth, as ultrasound waves cannot penetrate normally aerated lungs and can only be used to image peripheral lung lesions **[Au: Edit OK?]** [92,103]. LUS can still be a cost-effective method for the diagnosis of complications in pediatric patients with respiratory distress [104] or infection, as the consolidation of the lung parenchyma in these patients makes the visualization of the CLM easier.**[Au: Edit OK?]**

[H3] MRI

Chest MRI has the potential to replace CTA for assessing CLMs in the future[90,105], especially in medical centers that have expertise in chest MRI techniques [90]. However, in current practice, surgical plans cannot be based entirely on MRI, as CTA provides superior quality images of lung parenchyma, especially in infants. In addition, sedation is required for infants and young children between 6 months and 5 years of age undergoing MRI[92,106]. **[Au: Edit OK?]**

Chest MRI protocols have the added advantage of not requiring use of contrast to visualize the vascular anomalies associated with CLMs [107]. In cases of CLMs with abnormal blood vessels, chest MRI can be combined with cardiac MRI to assess blood flow and shunting [92]. There are several clinical scenarios in which chest MRI may be used to assess CLMs, including follow-up of a previously identified CLM to avoid repeated exposure to radiation, evaluation of a mass in an atypical location, or complementary characterization when CTA is incomplete [90].

[H2] Histology

[Au: Do you rather mean histopathology?]

Histopathological assessment of lung tissue is necessary to confirm diagnosis of CLM and to identify the subtype of CLM.

[H3] CPAM

[Au: Please reference this subsection.]

CPAM type 1 appears as a cystic lung lesion, with cyst size ranging from <0.5 cm to >7 cm in greatest dimension. CPAM type 1 cysts are lined by ciliated cuboidal to stratified columnar epithelium, occasionally featuring cartilage in the cyst wall, and are interspersed within a lung parenchyma with enlarged and simplified alveoli. Multiple connections are observed between the thick cyst wall and adjacent alveolar wall, and epithelial complexity, including papillary projections, may occur. Some CPAM type 1 lesions **[Au: Edits OK?]** may have solid appearing areas with features of both type 1 and type 3 CPAM. In CPAM type 2, there are both identifiable cysts lined by ciliated columnar epithelium and mildly malformed alveolar type spaces. **[Au: This sentence was moved here to improve the text flow. Are the edits correct?]** Cysts can measure up to 2.5 cm in greatest dimension and are also interspersed within normal appearing lung parenchyma. Striated skeletal muscle occasionally appears in the septa between cysts. CPAM type 3 lesions have a solid, often lobulated appearance, and are well-demarcated from uninvolved lung

parenchyma. Cysts **[Au: Edit OK?]** mainly consist of small irregularly shaped airway spaces lined by ciliated cuboidal to columnar epithelium. Surrounding septa often appear thickened, with prominent mesenchyme and cuboidal epithelium.

[H3] BPS

BPS is defined by an anomalous systemic vascular supply and sequestration from the tracheobronchial tree. The systemic feeding vessel is usually identified only radiographically, but it may still be identifiable in intact gross specimens. **[Au: Edit OK?]** The BPS parenchyma has a variable macroscopic appearance, ranging from grossly normal to cystically altered[108]. Histologically, systemic artery branches may appear thickened with features that are characteristic of pulmonary hypertension in older patients [109]. All patientshave at least mild parenchymal maldevelopment with enlarged and simplified alveoli [60,61]. Pools of mucin and foamy intra-alveolar macrophages may suggest presence of mucostasis [110]. Foci of skeletal muscle may be seen in septa between larger cysts **[Au: Please reference.]**. Prominent lymphangiectasia is seen in a subset of extralobar bronchopulmonary sequestrations. **[Au: Please reference.]**

[H3] CLO

In CLO, tissue architecture is maintained, unlike in acquired emphysema. However, lack of acinar maturation with age and overinflated alveoli are seen. In many CLOs, there are normal numbers of radial alveoli at birth, but with acinar development arrested in the postpartum period. In the hypo-alveolar and poly-laveolar subtypes fewer or more than the expected number of alveoli are present, respectively[111].

[H3] BC

BC presents as a unilocular cyst filled with serous or mucinous material, lined by respiratory type epithelium, reminiscent of bronchial wall with variable amounts of seromucinous glands, cartilage,

and smooth muscle. **[Au: Please reference.]** Secondary changes related to previous infection or procedures may include acute and chronic inflammation with epithelial denudation or squamous metaplasia, and evidence of hemorrhage with cholesterol clefts and/or hemosiderophages, as well as variable fibrosis. **[Au: Please reference.]**

[H3] CBA

Surgical specimens of CBA have an atretic bronchus with distal pink hyperaerated lung with occasional subpleural blebs [112]. There is no proximal or central tracheal communication of the atretic bronchus, whereas distal to the atresia there is cystic dilatation of the bronchus, sometimes amounting to a mucocele, that contains plugs of desquamated tissue and mucus as an unvarying component[112]. The blind end of the proximal or distal bronchus is lined with bronchial epithelium without scar formation or granuloma [66]. Microscopic examination of the distal pulmonary parenchyma is essentially normal except for dilatation of alveoli and hypoplasia as evidenced by a reduced number of alveoli per unit area [112].

[H1] MANAGEMENT

[H2] In utero management

[H3] Maternal steroids

The first-line therapy for giant microcystic lesions (CVR>1.6) and hydrops or impending hydrops is maternal administration of two doses of systemic steroids [113].**[Au: We do not include dosing information in Primers, as these can change over time, so I have removed this here.)** This treatment is most effective before the 26th week of gestation. [114,115]. **[Au: Edit OK?]** It has been suggested that steroids act by speeding the passage from canalicular to saccular stage of lung development [38] (**Figure 3**). However, steroids show limited efficacy in fetuses with macrocystic lesions [116] **[Au: Edit OK?]**.

[H3] Thoracoamniotic shunts

When hydrops complicates a pregnancy with large lesions containing a dominant microcyst **[Au: Do you mean in the fetal lungs? Please specify.]** , the insertion of a thoracoamniotic shunt (TAS) (**Figure 3**) **[G]** has been demonstrated to decrease the mass **[Au: the mass of what? Please specify.]** , improving hydrops, and increasing fetal survival [113]. This ultrasonography-guided minimally invasive procedure can rely on double pigtail catheters to minimize dislodgement. However, it carries risk of premature preterm rupture of membranes, preterm labor, chorioamnionitis, shunt occlusion or dislodgment, and chest wall deformities [113].

[H3] Fetal surgery

The introduction of steroid therapy has considerably limited the need to recur to fetal surgery in case of severe hydrops before the third trimester [117]. Similarly, the indications for EXIT-to-resection **[Au: Please briefly explain the EXIT-to-resection procedure for the less familiar readers.]** management with the aim of creating space for the the lung to function postnatally**[Au: OK?]**, are very rare and considered for giant lesion with CVR >2 and persistent mediastinal shift [117].

[H3] Fetal management of BPS

Expectant management of fetuses with BPS and associated hydrops can lead to pulmonary hypoplasia and consequent poor prognosis [118,119]. However, the use of TAS has proved to help decreasing the hydrops, and neonatal death [38]. Laser coagulation of the feeding vessel contributes to decrease the malformation's volume [120] (**Figure 3**). A multicenter study [121] has demonstrated that laser ablation interrupting blood supply to the malformation helps to achieve better perinatal outcomes compared with TAS, including longer gestational age and less frequent postnatal surgery. **[Au: Edit OK?]**

[H2] Postnatal management

[Au: I suggest introducing a new level of subheadings here, to make the distinction between in utero and postnatal management clearer. OK?]

668

669 [H3] Management of asymptomatic CLMs.

670 **[Au: The heading and text of this section was edited to address concerns raised during the**
671 **second round of peer review. Please check all edits for accuracy, and consider moving this**
672 **subsection to the end of the section, after the discussion of surgical treatment.]**

673 Prenatally diagnosed CLMs that are symptomatic at birth or become symptomatic during the
674 neonatal period are managed with surgical resection. However, there is still an unresolved
675 controversy among pediatric surgeons about management of prenatally diagnosed CPAM, BPS,
676 or BC that are asymptomatic after birth. Most pediatric surgeons are still in favour of prophylactic
677 surgical resection of asymptomatic CLMs (**Figure 5**). However, some specialists consider
678 conservative (non-operative) management as an alternative to surgical resection, unless
679 symptoms and complications emerge [70,122,123].

680 Three lines of argumentation are used by clinicians favoring a conservative management
681 approach. First, it has been suggested that unnecessary surgery and general anaesthesia may
682 have negative effects on long-term neurodevelopment, and some potentially serious, or even life-
683 threatening complications, in infants [8,124-127]. Second, it has been argued that most asymptomatic
684 cases remain asymptomatic during childhood [70,71,133-135]. Third, professionals favoring the
685 conservative non-operative management consider the risk of malignancy as being small [17].

686 However, normal neurodevelopment outcomes have been demonstrated for children who undergo
687 surgical removal of a CLM in comparison with their healthy peers [132], and early prophylactic
688 elective surgery can facilitate compensatory lung growth [67].

689 Moreover, records of long term follow-up for emergence of symptoms later in life are lacking. Of
690 the few patients with CLMs that have been followed up until adulthood, an 80% have become
691 symptomatic and often present with acute onset of symptoms at diagnosis [136-139]. In addition, pre-
692 operative infections make surgery more challenging in patients presenting with symptoms later in
693 life **[Au: Edit OK?]** and increase the rate of conversion to thoracotomy [140].

Finally, even though the true incidence of malignancy in patients with CLMs remains unknown, lung cancer may appear at any age and is accompanied by nonspecific symptoms that may be missed **[Au: Edit OK?Please clarify the significance of symptoms being nonspecific]** [19], whereas radiological imaging fails to predict risk of malignancy or provide an early diagnosis of cancer[19]. **[Au: Edit OK?]**

The real conundrum in following a conservative approach is to design a clear follow up program for the patients in terms of frequency, duration, and methodology. Chest radiograph (CR) is inadequate to detect CLMs **[Au: How is this relevant for the management discussion, considering that it concerns management of asymptomatic but already diagnosed patients with CLMs? Would it be more fitting to note that CR is inadequate to detect any alterations in CLMs, including malignant transformation?]** [92]. Repeated exposure to chest CTA poses a risk of iatrogenic malignancy [141], precluding its adoption for radiological surveillance during childhood. In addition, long-term surveillance is challenging in terms of high cost, patient compliance, and transition of care with the involvement of adult thoracic surgeons and pulmonologists **[Au: Edited for clarity. OK?]** [77].

[H3] Surgical treatment

[Au: Please add an introductory sentence to this section, to present all surgical procedures currently available for CLM resection. Further below in the text, the procedures of segmentectomy, or pneumonectomy, are mentioned without having been introduced. In addition, please consider commenting on whether all surgical procedures discussed here are equally accessible to patients across the globe.] Thoracoscopic lobectomy in children for CLMs should be considered the standard of care [128,142-145], because it is a minimally invasive approach with improved visualization. The thoracoscopic approach, which has been proved to be feasible at any size and weight of the patients [128,129], has decreased the invasiveness of the surgical procedure, resulting in**[Au: OK?]** less pain, shorter hospital stay, and decreased long term morbidity, including a decreased risk of chest wall deformity, shoulder girdle weakness, and

scoliosis, in comparison with open thoracotomy [130,131]. Moreover, the magnification provided by thoracoscopy enables better visualization, especially of fissures and vessels [131]. **[Au: This text was moved here from above to improve the text flow. OK?]**

The timing of resection is debatable with some preferring earlier surgery, by 4 months of age (**Figure 5**), and some as late as 1 year of age, although delayed resection has not shown improved outcome [146]; in older infants, substantial adenopathy and inflammation in the fissures and around the pulmonary artery can lead to more difficult identification and safe division of these vessels (**Figure 4**). Data suggest earlier resection is associated with shorter operative times, hospital stays and reduced rates of inflammation in specimens [129,147-149]. This**[Au: What specifically?]** may also reduce the likelihood of pre-operative respiratory infections, which can distort tissue planes, create thick adhesions and complicate surgery, causing more frequent conversion from a minimally invasive approach to open surgery because of impaired visualization and difficult lung mobilization [140,150]. Moreover, the same patients with pulmonary infections before surgical treatment had increased incidence of post-surgery infections [140]

In asymptomatic CLO or CBA, there is agreement that no surgical treatment is required [151]. However, if CLO or CBA become symptomatic due to progressive air trapping of the affected lobe or infection, respectively, surgery is performed.

The last consideration is whether a lung-sparing approach is indicated in smaller lesions [152,153]. A sublobar anatomical resection is especially relevant if there is multi-lobar disease.

[H1] QUALITY OF LIFE

[Au: I have removed the subheading, as there was no second subsection .] So far, literature reviews on CLM outcomes **[Au: Edit OK?]** have mainly focused on patients having undergone surgery and, particularly, **[Au: Edit OK?]** on how the timing of partial lung resection can enhance compensatory lung growth [154-156]. Modalities in diagnostics and surgical techniques have changed

over time.**[Au: OK?]** The introduction of structural fetal ultrasonography that has led to an increased antenatal detection rate [9] and intensive care treatment, has helped improve survival rates of neonates with severe respiratory problems, and minimal access surgery has gained popularity [128]. Moreover, lung-sparing techniques have been introduced [157]. Thus, the data on long-term outcomes of children born in the past century can probably not be extrapolated to the cohort of neonates born with CLM during the past X years **[Au: If possible specify the time frame you are referring to here.]**. To optimize postnatal management and parental counselling, an international multicenter registry is important and initiatives for such a registry are underway [156].**[Au: OK?]**

Uniform data on pulmonary morbidities, which would be required for optimal counselling on growing up with CLM, are still lacking, especially data on general health, quality of life, and societal participation. **[Au: Edit OK?]** The focus is on **[Au: Do you mean the focus of the currently available data? Please specify.]** general outcomes, such as physical growth, disease-specific outcomes, such as respiratory tract infections, lung function and exercise tolerance, and treatment-related outcomes, such as musculoskeletal deformities.

Physical growth in infancy was found to be similar between infants who underwent surgical CLM resection and conservatively treated patients with asymptomatic CLM [158]. In a prospectively followed cohort of patients with resected CLM, weight-for-height was slightly below normal **[Au: Do you mean below average?]** at 2 years of age but within the normal range at 8 years of age [159]. **[Au: Edit OK?]** Similar observations were reported in an Italian cohort of patients with CLM who underwent surgery [160].

Susceptibility to respiratory tract infections was studied in a population-based cohort including 31 individuals with resected CLM that were born between 1991 and 2007[161]. Pneumonia and infections, including influenza, were more common in CLM-resected individuals than in the control cohort of 310 individuals of a population-based administrative data repository .

Small studies assessing lung function during infancy showed mild abnormalities in heterogeneous groups of patients with CLM, including reduced tidal volumes **[G]** [162,163], reduced lung compliance **[G]** [162], and increased airflow obstruction [158]. Interestingly, reduced lung compliance and airflow obstruction had also been reported in infants with CLM who did not undergo lung resection [158,162]. At school age, airflow obstruction mainly occurred in children who had undergone resection [159,164], although normal spirometry was reported in 76-86% of patients[165]. Exercise tolerance has been studied in only one group of eight-year-old participants of a structured longitudinal follow-up program. Reduced exercise tolerance was observed in 40% of children who underwent resection and in 28% of the non-surgery group [159]. Lobectomy had been performed in most of the operated patients, although pneumonectomy or segmentectomy **[G]** was done in few patients. The current results do not enable drawing any conclusion on the optimal surgical strategy for preservation of lung volumes, and functional MRI may be useful for further evaluation in the future [166]. Minimally invasive surgical techniques seem to have more favorable outcomes than thoracotomies in terms of lung function [167] and development of musculoskeletal deformities [168,169].

International collaboration and registries for CLMs and the various treatment modalities, complications, and outcomes are important to determine the long-term quality of life of patients with CLM.

[H1] OUTLOOK

[H2] Future perspectives in surgical treatment

[Au: Please consider adding an introductory sentence to this section, as it presently starts quite abruptly.] A combination of virtual reality (VR) and augmented reality (AR) with emerging artificial intelligence (AI) algorithms has been explored for the preoperative planning of pulmonary segmentectomy in adult patients [170]. In addition, a combination of VR and AI has also been used to preoperatively identify the exact vascular and bronchial anatomy and segmental borders **[Au:**

The highlighted sentence was moved here from below, to improve the text flow. OK?] in children with CLM[171]. However, although this approach could be used to remove gross disease, microscopic lesions might be left untreated, maintaining the risk of malignant transformation [19,172,173]. Unfortunately, current imaging modalities do not adequately distinguish between healthy and abnormal lung **[Au: Do you mean 'lung parenchyma'?]**, at least not at a microscopic level. Moreover, segmentectomy is burdened by a higher incidence of complications [174] **[Au: The highlighted sentence was moved here from below, to improve the text flow. OK?]**

Thus, VR- and AI-led anatomical segmentectomy could be considered as an approach only in cases where gross disease seems to be limited to a single segment. The resection must be based on segmental anatomy to try and ensure all affected tissue is removed, not a blind wedge resection using an endoscopic stapler. **[Au: I am not sure I understand this statement. Wouldn't resection based on anatomical segmentation be based on segmental anatomy anyway? Perhaps consider removing the highlighted sentence?]** that

Robotic surgery has been widely applied in adult patients, especially for urological and gynecological surgeries, but also in thoracic oncology [175]. The technical advantages over thoracoscopy include intuitive movements, more manipulative freedom, and high-definition stereoscopic vision. Moreover, similarly to thoracoscopy, robotic surgery has been associated with shorter hospital stay, quick restart of daily activities, and better cosmesis **[Au: Please reference this statement.]**. Although robotic surgery has been expanded to pediatric patients **[Au: Edit OK? Please reference this statement.]** , its uptake in younger infants, especially for procedures in the thorax, has been slow due to technical challenges . The reduced chest space of neonates **[Au: Edit OK?]** would call for a miniaturization of the devices **[Au: I've removed technical detail to maintain the focus on the key message. OK?]** and for a smaller distance between ports to decrease external cluttering [176,177]. So far, only a few series of pediatric robotic-assisted thoracic surgery have been reported[177,178], and even fewer infants with CLMs have undergone robotic-

assisted lobectomy [179]. Until a dramatic miniaturization of the devices is reached, robotic-assisted thoracic surgery won't be an option for small infants.

[H2] Association between CLMs and lung tumors

[Au: The heading of this section is almost identical as the heading of a subsection under epidemiology. Please merge the two parts of the text, keeping epidemiological information under the epidemiology section and moving the discussion relating to management under the management section. The 'Outlook' section should only highlight any open questions that will help resolve any controversies about the diagnosis and management of CLMs and improve disease management.]

However, the literature can give some perspective on the topic both in pediatric and adult patients with CLMs. In a recent systematic review, 76 children (<15 years) and 92 adults (≥15 years) with a CLM, CPAM, BPS, or BC, and an associated lung tumor were analyzed [19]. In children, more than half of the CLMs were associated to a PPB, followed by an adenocarcinoma in 27% of the cases.

Whether a congenital malformation preexisted, or the lesion was an unrecognized PPB from the beginning it is still under debate. **[Au: Please merge highlighted information with the relevant discussion and citation of reference 19 under the epidemiology section.]** It has been suggested that the cysts serve as a vehicle for the retention and persistence of unstable mesenchymal cells [180]. **[Au: What cysts are you referring to here? Please specify the relevance of unstable mesenchymal cells for malignant transformation and move this information under the mechanisms/pathophysiology section.]** Pulmonary cysts were identified radiographically in 38% of the children for years before making a definitive diagnosis **[Au: Diagnosis of CLM or of cancer? Please specify.]** [77]. The Pleuropulmonary Blastoma Registry has highlighted that 66% of PPBs were associated with lung cysts, either discovered at diagnosis or predating it [77]. **[Au: I suggest deleting this sentence to avoid repetition of what**

has been mentioned already above.] In either cases, prophylactic resection might protect the patients from developing a PPB or at least provide early resection of this malignant lesion [19,181]. Among adult patients, 43.5% of CLMs were associated with adenocarcinoma, 15.2% with squamous cell carcinoma, 7.6% with bronchial carcinoid. **[Au: Please move this information under the epidemiology section.]**

Second, CPAM, BPS, BC have been found to be associated with malignant lung lesions, confirming that these anomalies are more a continuum of developmental disorders than separate entities. On the other hand, even though some histological types of CLMs appear more often associated with specific types of lung tumors, a definitive pattern could not be described, challenging any speculation about considering some CLMs among CPAM, BPS, and BC "safer" than others and eligible for conservative treatment. Third, the onset of malignant transformation happens at any age starting from months of life up to elderly patients [19], making a lifelong follow up imperative in case of conservative treatment. Fourth, and closely related to the third issue, the interval of time between the first detection of a CLM and the discovery of an associated tumor is very variable. Fifth, all available radiological techniques may help in suspecting the diagnosis, but they fail to give a definitive confirmation of the presence or not of malignant transformation. Consistently, in all cases, both in children and adults, the diagnosis of association between the CLM and a lung tumor was made by the pathologist [19]. These data should be kept in mind when counselling the parents of an asymptomatic child with CPAM, BPS, or BC. **[Au: Please condense the discussion highlighted in yellow and move it under the management section.]**

[Au: Please provide two or three sentences that summarise the direction of the field overall in the next 10 to 20 years as a concluding remark.]

Commentato [A1]: Refers to deleted text

LEGEND FOR FIGURES.

Figure 1: Types of congenital lung malformations.

Abnormal organogenesis or dysregulation of cellular signaling within the epithelial-mesenchymal interaction during embryonic development might cause a congenital lung malformation (CLM). The timing of this dysregulation determines the type of CLM, which comprise five subtypes of congenital pulmonary airway malformations (CPAMs); bronchogenic cysts; bronchopulmonary sequestration, which can be intralobar or extralobar; congenital lobar overinflation; and congenital bronchial atresia. **[Au: Please add some additional information here to describe the figure in further detail. For example, please define and describe the five types of CPAM, the cellular/histological origin or timing of embryonic dysregulation associated with each of the CLMs. Furthermore, please clarify to the reader why Figure parts a and b are required; from the legend, it currently seems that all these CLMs are equivalent, but the Figure suggests otherwise by being split into two parts.]**

Figure 2: Histology of congenital pulmonary airway malformation type 1 (CPAM 1) with mucinous cell clusters.

Low power (**A**) and high power (**B**) micrographs of CPAM type I lesion demonstrating large cystic spaces (*) lined by non-atypical respiratory and cuboidal epithelium, surrounded by alveolar tissue with collapsed but apparently normal morphology, with focal proliferation of columnar mucinous cells (arrows). These mucinous proliferations, as well as the adjacent cystic spaces were shown to contain a KRAS exon 2: c.35G>A; p.G12D mutation by next generation sequencing.**[Au: Please provide the magnification values, and staining method.] [Au: We do not acknowledge provision of images if they have been provided by an author of the article, so I have removed.]**

Figure 3: Prenatal congenital lung malformation (CLM) diagnosis and management

a.**[Au: Please specify imaging technique for part a.]** Prenatal diagnosis of CLM relies on the size of the lungs and the identification of space-occupying lesions, either solid or cystic, within the fetal thorax. Congenital pulmonary airway malformation (CPAM) may present as either a multilocular lesion with cysts (macrocystic type), or as a well-defined homogeneously hyperechogenic mass (microcystic type). Bronchopulmonary sequestration (BPS) appears as a homogeneously hyperechogenic mass, indistinguishable from the microcystic type of CPAM. However, exploration with color Doppler ultrasonography should highlight an aberrant feeding artery arising from the aorta **[Au: Please indicate what parts of the figure show the aberrant feeding artery.]** . Congenital lobar overinflation (CLO) appears as uniformly enlarged lung, mildly hyperechoic, without cysts or systemic arterial supply, like microcystic CPAM. Both macrocystic CPAM and BPS can cause fetal hydrops, which would benefit from the insertion of a thoraco-amniotic shunt and from vascular laser ablation, respectively. **[Au: What about maternal steroids?]**

b. Illustrative diagram of CPAM volume ratio (CVR) and its calculation on prenatal ultrasonography images. CVR is a sonographic indicator of the mass volume normalized for gestational age to evaluate fetuses at risk of developing hydrops. **[Au: Please insert labels on the figure and update the figure legend to define the color code used for the arrows measuring the various dimensions used for CVR calculation.]**

_**[Au: We do not acknowledge provision of images if they have been provided by an author of the article, so I have removed.]**

Figure 4: Asymptomatic patient with CPAM becoming symptomatic.

A: Anterior Posterior chest radiograph at birth shows some radiolucent round abnormalities in the perihilar region of the right lung (arrow). **B**: Coronal lung window of chest Computer Tomography Angiography (CTA) at 6 months shows multicystic lesion (arrow), with cysts <2 cm surrounded by

low-density lung parenchyma, which is consistent with a congenital pulmonary airway malformation (CPAM) type 2. **C**: CTA at 5 years old of the same patient admitted with signs of pneumonia. The coronal CT reformat shows consolidation (arrow) of the lung parenchyma surrounding the cystic component of the CPAM. **[Au: We do not acknowledge provision of images if they have been provided by an author of the article, so I have removed.]**

Figure 5: Algorithm of postnatal diagnosis and surgical management in asymptomatic and symptomatic congenital lung malformations (CLM).

In asymptomatic prenatally detected CLM, the diagnosis must be confirmed with Computer Tomography Angiography (CTA) at 2 months. Asymptomatic congenital lobar overinflation (CLO) can be managed conservatively. However, if CLO becomes symptomatic due to progressive air trapping of the affected lobe, surgery is performed.**[Au:What about CBA that is mentioned in the Figure?]** By contrast, asymptomatic congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS), and bronchogenic cyst (BC) undergo elective surgery by 5-6 months of age **[Au: Please ensure consistency between the figure and the figure legend. Elective surgery by 4 or by 5-6 months?]** .

A symptomatic newborn needs emergency chest radiograph (CR) **[Au: Please check whether this is consistent with what is described in the main text.]** and CTA to confirm prenatal diagnosis, and in case of persistence of symptoms, undergoes emergency surgery.

In case of incidental detection of a previously undiagnosed CLM, a CTA is needed to confirm the diagnosis and elective surgery is planned. When a CLM is suspected in a symptomatic patient, CR and CTA are needed to confirm the diagnosis and surgery is planned as soon as possible.

Boxes

Box 1. Lung development

[Au: I've made some edits to shorten to get closer to the max word limit of Boxes.]

Lung development begins at 4 weeks of gestation and can be classified into five stages [182]:

Embryonic: Two lung buds appear as sacs of respiratory epithelial cells on the ventral part of the foregut [183]. Several genes are expressed at this stage: *Nkx2-1*, encoding TTF1, in the ventral wall, and *Sox2*, *Hox 5* and *Hoxb5* in the dorsal wall of the anterior foregut [42]. At 4-7 weeks, the lung buds extend and separate into branches creating the primitive bronchi **[Au: Please reference this statement.]** , while the pulmonary arteries develop from the 6th aortic arches and form a vascular plexus by growing into the mesenchyme [184]. Simultaneously, BMP4 and its antagonists Noggin, FGF10 and *Wnt* are expressed on mesenchyme [185,186].**[Au: Which Wnt are you referring to? Also, please use protein nomenclature for Wnt for cosnsitency.]** Dicer1, which encodes an endonuclease involved in the maturation process of siRNAs and miRNAs, generally influences embryonic development and normal cell physiology. [193]. Dicer1 inactivation in the lungs of mouse embryos shortly after the beginning of lung branching caused branching defects and prolonged ectopic cell death [194]. **[Au: I have moved the text part on Dicer 1 here from below, to improve the text flow. OK?]**

Pseudo-glandular: By the end of 7 weeks, repetitive sprouting forms pre-acinar airways. At 8-16 weeks, the primitive airway epithelium starts to grow and FGF10 regulates differentiation [184,187]. *Sox2* and *Sox9***[Au: Protein nomenclature?]** are the main transcription factors in lung progenitor cells for branching morphogenesis and cell differentiation [188,189].

Canalicular stage: At weeks 16-25, the blood–air barrier and the terminal bronchial branches take shape. At ~20 weeks, pulmonary epithelium cells differentiate into type I and type II pneumocytes, which are crucial to lung development [190]. The pulmonary vessels also begin to proliferate and develop the mesenchymal capillary network.

Saccular stage: This stage, starting at 24 **[Au: Above, it is stated that the canalicular stage ends at the 25th gestational week. Please check for consistency.]** weeks of gestation is the earliest period of lung viability and the formation of saccules on terminal airways. Surfactant production begins at ~26 weeks and primitive alveoli start to develop at 30 weeks [191,192].

Alveolar stage: This stage begins after birth and continues for 4-5 years with secondary septation in saccules. Alveolar ducts are divided into terminal alveoli and 85% of alveoli are formed after birth. The gas exchange surface area of the lung expands, and the thoracic growth carries on until adolescence.

[Au: This box contains a high level of technical detail, which is above the scope of Primers published in Nature Reviews Disease Primers. As this article contains eight display items in total, we suggest removing this box, which would be more suitable for the readership of a more specialized journal.]

Box 2. Adults with CLM [Au: Please cite this box in the main text.]

Most CLMs are diagnosed during pregnancy. However, some remain undetected in the prenatal period and in childhood and are discovered in adulthood. An insight into the management of adults with CLM might give the pediatric specialists a perspective of the possible future of children with CLMs treated conservatively.

Most adult patients with CLM (80%) complain about cough and respiratory infection as acute events or as recurrent symptoms throughout life; however, nearly 20% remain asymptomatic and the CLM is incidentally detected at screening imaging.**[Au: Or because of imaging for other reasons, as was stated above (now removed to avoid redundancy). Also, please reference.]** The presence of a CLM has been described in patients aged from 15 to 80 years. In all patients, a CR is performed as first line imaging and, in all cases, can reveal an infection, but fails to detect the CLM. A CTA is, therefore, always performed to define the diagnosis and plan the surgery [138]. Adult thoracic surgeons recommend surgical resection as treatment of choice in all adult patients with CLM **[Au: Edit OK?]** , even in asymptomatic cases, as they are concerned about the susceptibility to infections and the risk of malignant transformation, which has occurred in almost 10% of prenatally undiagnosed CLMs **[Au: Edit OK?]** described in literature [136,138]. Conservative treatment is offered only when surgery is not feasible together with the recommendation of annual CTA to monitor the CLM. **[Au: OK?]**

REFERENCES

1 Panicek, D. M. *et al.* The continuum of pulmonary developmental anomalies. *Radiographics* **7**, 747-772, doi:10.1148/radiographics.7.4.3448653 (1987).

2 Stocker, J. T., Madewell, J. E. & Drake, R. M. Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. *Hum Pathol* **8**, 155-171, doi:10.1016/s0046-8177(77)80078-6 (1977).

3 Alshamiri, K. M. & Abbod, H. B. Congenital cystic adenomatoid malformation. *Int J Pediatr Adolesc Med* **4**, 159-160, doi:10.1016/j.ijpam.2017.12.001 (2017).

4 Gupta, K. *et al.* Revisiting the histopathologic spectrum of congenital pulmonary developmental disorders. *Fetal Pediatr Pathol* **31**, 74-86, doi:10.3109/15513815.2011.650287 (2012).

5 Annunziata, F. *et al.* Congenital Lung Malformations: Unresolved Issues and Unanswered Questions. *Front Pediatr* **7**, 239, doi:10.3389/fped.2019.00239 (2019).

6 Laberge, J. M. *et al.* Outcome of the prenatally diagnosed congenital cystic adenomatoid lung malformation: a Canadian experience. *Fetal Diagn Ther* **16**, 178-186, doi:53905 [pii] 53905 (2001).

7 Gornall, A. S., Budd, J. L., Draper, E. S., Konje, J. C. & Kurinczuk, J. J. Congenital cystic adenomatoid malformation: accuracy of prenatal diagnosis, prevalence and outcome in a general population. *Prenat Diagn* **23**, 997-1002, doi:10.1002/pd.739 (2003).

8 Stocker, L. J., Wellesley, D. G., Stanton, M. P., Parasuraman, R. & Howe, D. T. The increasing incidence of foetal echogenic congenital lung malformations: an observational study. *Prenat Diagn* **35**, 148-153, doi:10.1002/pd.4507 (2015).

9 Lau, C. T., Kan, A., Shek, N., Tam, P. & Wong, K. K. Is congenital pulmonary airway malformation really a rare disease? Result of a prospective registry with universal antenatal screening program. *Pediatr Surg Int* **33**, 105-108, doi:10.1007/s00383-016-3991-1 (2017).

10 Thompson, A. J., Sidebotham, E. L., Chetcuti, P. A. J. & Crabbe, D. C. G. Prenatally diagnosed congenital lung malformations-A long-term outcome study. *Pediatr Pulmonol* **53**, 1442-1446, doi:10.1002/ppul.24119 (2018).

11 Sfakianaki, A. K. & Copel, J. A. Congenital cystic lesions of the lung: congenital cystic adenomatoid malformation and bronchopulmonary sequestration. *Rev Obstet Gynecol* **5**, 85-93 (2012).

12 Zobel, M., Gologorsky, R., Lee, H. & Vu, L. Congenital lung lesions. *Semin Pediatr Surg* **28**, 150821, doi:10.1053/j.sempedsurg.2019.07.004 (2019).

13 Moorthie, S. *et al.* Estimating the birth prevalence and pregnancy outcomes of congenital malformations worldwide. *J Community Genet* **9**, 387-396, doi:10.1007/s12687-018-0384-2 (2018).

14 Hermelijn, S. M. *et al.* Associated Anomalies in Congenital Lung Abnormalities: A 20-Year Experience. *Neonatology* **117**, 697-703, doi:10.1159/000509426 (2020).

15 Kunisaki, S. M. *et al.* Fetal Risk Stratification and Outcomes in Children with Prenatally Diagnosed Lung Malformations: Results from a Multi-Institutional Research Collaborative. *Ann Surg* **276**, e622-e630, doi:10.1097/SLA.0000000000004566 (2022).

16 Kersten, C. M. *et al.* COllaborative Neonatal Network for the first European CPAM Trial (CONNECT): a study protocol for a randomised controlled trial. *BMJ Open* **13**, e071989, doi:10.1136/bmjopen-2023-071989 (2023).
17 Hartman, G. E. & Shochat, S. J. Primary pulmonary neoplasms of childhood: a review. *Ann Thorac Surg* **36**, 108-119 (1983).
18 Nasr, A., Himidan, S., Pastor, A. C., Taylor, G. & Kim, P. C. Is congenital cystic adenomatoid malformation a premalignant lesion for pleuropulmonary blastoma? *J Pediatr Surg* **45**, 1086-1089, doi:S0022-3468(10)00186-7 [pii]
10.1016/j.jpedsurg.2010.02.067 (2010).
19 Casagrande, A. & Pederiva, F. Association between Congenital Lung Malformations and Lung Tumors in Children and Adults: A Systematic Review. *J Thorac Oncol* **11**, 1837-1845, doi:10.1016/j.jtho.2016.06.023 (2016).
20 Walsh, S., Wood, A. E. & Greally, P. Pleuropulmonary blastoma type I following resection of incidentally found congenital lobar emphysema. *Ir Med J* **102**, 230 (2009).
21 Bogers, A. J., Hazebroek, F. W., Molenaar, J. & Bos, E. Surgical treatment of congenital bronchopulmonary disease in children. *Eur J Cardiothorac Surg* **7**, 117-120 (1993).
22 Korol, E. The correlation of carcinoma and congenital cystic emphysema of the lungs; report of ten cases. *Dis Chest* **23**, 403-411, doi:10.1378/chest.23.4.403 (1953).
23 Cass, D. L. *et al.* Increased cell proliferation and decreased apoptosis characterize congenital cystic adenomatoid malformation of the lung. *J Pediatr Surg* **33**, 1043-1046; discussion 1047, doi:S0022-3468(98)90528-0 [pii] (1998).
24 Hsu, J. S. *et al.* Cancer gene mutations in congenital pulmonary airway malformation patients. *ERJ Open Res* **5**, doi:10.1183/23120541.00196-2018 (2019).
25 Swarr, D. T. *et al.* Novel Molecular and Phenotypic Insights into Congenital Lung Malformations. *Am J Respir Crit Care Med* **197**, 1328-1339, doi:10.1164/rccm.201706-1243OC (2018).
26 Patrizi, S., Pederiva, F. & d'Adamo, A. P. Whole-Genome Methylation Study of Congenital Lung Malformations in Children. *Front Oncol* **11**, 689833, doi:10.3389/fonc.2021.689833 (2021).
27 Luo, J. *et al.* PITX2 enhances progression of lung adenocarcinoma by transcriptionally regulating WNT3A and activating Wnt/beta-catenin signaling pathway. *Cancer Cell Int* **19**, 96, doi:10.1186/s12935-019-0800-7 (2019).
28 Goldstein, B., Trivedi, M. & Speth, R. C. Alterations in Gene Expression of Components of the Renin-Angiotensin System and Its Related Enzymes in Lung Cancer. *Lung Cancer Int* **2017**, 6914976, doi:10.1155/2017/6914976 (2017).
29 Nelson, N. D. *et al.* Defining the spatial landscape of KRAS mutated congenital pulmonary airway malformations: a distinct entity with a spectrum of histopathologic features. *Mod Pathol* **35**, 1870-1881, doi:10.1038/s41379-022-01129-0 (2022).
30 Hermelijn, S. M. *et al.* Early KRAS oncogenic driver mutations in nonmucinous tissue of congenital pulmonary airway malformations as an indicator of potential malignant behavior. *Hum Pathol* **103**, 95-106, doi:10.1016/j.humpath.2020.07.015 (2020).
31 Summers, R. J., Shehata, B. M., Bleacher, J. C., Stockwell, C. & Rapkin, L. Mucinous adenocarcinoma of the lung in association with congenital pulmonary airway malformation. *J Pediatr Surg* **45**, 2256-2259, doi:10.1016/j.jpedsurg.2010.07.008 (2010).

32 Dehner, L. P. *et al.* Type I Pleuropulmonary Blastoma versus Congenital Pulmonary Airway Malformation Type IV. *Neonatology* **111**, 76, doi:10.1159/000447992 (2017).

33 MacSweeney, F. *et al.* An assessment of the expanded classification of congenital cystic adenomatoid malformations and their relationship to malignant transformation. *Am J Surg Pathol* **27**, 1139-1146 (2003).

34 Brcic, L. *et al.* Pleuropulmonary blastoma type I might arise in congenital pulmonary airway malformation type 4 by acquiring a Dicer 1 mutation. *Virchows Arch* **477**, 375-382, doi:10.1007/s00428-020-02789-6 (2020).

35 Dehner, L. P. *et al.* Pleuropulmonary Blastoma: Evolution of an Entity as an Entry into a Familial Tumor Predisposition Syndrome. *Pediatr Dev Pathol* **18**, 504-511, doi:10.2350/15-10-1732-OA.1 (2015).

36 Dehner, L. P., Schultz, K. A. P. & Hill, D. A. Congenital Pulmonary Airway Malformations With a Reconsideration and Current Perspective on the Stocker Classification. *Pediatr Dev Pathol* **26**, 241-249, doi:10.1177/10935266221146823 (2023).

37 Messinger, Y. H. *et al.* Pleuropulmonary blastoma: a report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. *Cancer* **121**, 276-285, doi:10.1002/cncr.29032 (2015).

38 Kunisaki, S. M. Narrative review of congenital lung lesions. *Transl Pediatr* **10**, 1418-1431, doi:10.21037/tp-20-133 (2021).

39 Taylor, B., Rice, A., Nicholson, A. G., Hind, M. & Dean, C. H. Mechanism of lung development in the aetiology of adult congenital pulmonary airway malformations. *Thorax* **75**, 1001-1003, doi:10.1136/thoraxjnl-2020-214752 (2020).

40 Lezmi, G. *et al.* [Congenital cystic adenomatoid malformations of the lung: diagnosis, treatment, pathophysiological hypothesis]. *Rev Pneumol Clin* **69**, 190-197, doi:10.1016/j.pneumo.2013.06.001 (2013).

41 Langston, C. New concepts in the pathology of congenital lung malformations. *Semin Pediatr Surg* **12**, 17-37, doi:10.1053/spsu.2003.00001
S1055858603700043 [pii] (2003).

42 Correia-Pinto, J., Gonzaga, S., Huang, Y. & Rottier, R. Congenital lung lesions--underlying molecular mechanisms. *Semin Pediatr Surg* **19**, 171-179, doi:10.1053/j.sempedsurg.2010.03.003 (2010).

43 Doktor, F., Antounians, L., Lacher, M. & Zani, A. Congenital lung malformations: Dysregulated lung developmental processes and altered signaling pathways. *Semin Pediatr Surg* **31**, 151228, doi:10.1016/j.sempedsurg.2022.151228 (2022).

44 Warburton, D. *et al.* The molecular basis of lung morphogenesis. *Mech Dev* **92**, 55-81, doi:10.1016/s0925-4773(99)00325-1 (2000).

45 Leibel, S. L., McVicar, R. N., Winquist, A. M., Niles, W. D. & Snyder, E. Y. Generation of Complete Multi-Cell Type Lung Organoids From Human Embryonic and Patient-Specific Induced Pluripotent Stem Cells for Infectious Disease Modeling and Therapeutics Validation. *Curr Protoc Stem Cell Biol* **54**, e118, doi:10.1002/cpsc.118 (2020).

46 Gonzaga, S. *et al.* Cystic adenomatoid malformations are induced by localized FGF10 overexpression in fetal rat lung. *Am J Respir Cell Mol Biol* **39**, 346-355, doi:10.1165/rcmb.2007-0290OC (2008).

47 Wang, X. *et al.* Elevated Kruppel-like factor 5 expression in spatiotemporal mouse lungs is similar to human congenital cystic adenomatoid malformation of the lungs. *J Int Med Res* **46**, 2856-2865, doi:10.1177/0300060518774998 (2018).

48 Guseh, J. S. *et al.* Notch signaling promotes airway mucous metaplasia and inhibits alveolar development. *Development* **136**, 1751-1759, doi:10.1242/dev.029249 (2009).

49 Kim, J. H. *et al.* Lack of epithelial PPARgamma causes cystic adenomatoid malformations in mouse fetal lung. *Biochem Biophys Res Commun* **491**, 271-276, doi:10.1016/j.bbrc.2017.07.113 (2017).

50 Maretzky, T. *et al.* Migration of growth factor-stimulated epithelial and endothelial cells depends on EGFR transactivation by ADAM17. *Nat Commun* **2**, 229, doi:10.1038/ncomms1232 (2011).

51 Szafranski, P. *et al.* Phenotypic expansion of TBX4 mutations to include acinar dysplasia of the lungs. *Am J Med Genet A* **170**, 2440-2444, doi:10.1002/ajmg.a.37822 (2016).

52 Vincent, M. *et al.* Clinical, Histopathological, and Molecular Diagnostics in Lethal Lung Developmental Disorders. *Am J Respir Crit Care Med* **200**, 1093-1101, doi:10.1164/rccm.201903-0495TR (2019).

53 Rossi, G. *et al.* MUC5AC, cytokeratin 20 and HER2 expression and K-RAS mutations within mucinogenic growth in congenital pulmonary airway malformations. *Histopathology* **60**, 1133-1143, doi:10.1111/j.1365-2559.2011.04170.x (2012).

54 Imai, Y. & Mark, E. J. Cystic adenomatoid change is common to various forms of cystic lung diseases of children: a clinicopathologic analysis of 10 cases with emphasis on tracing the bronchial tree. *Arch Pathol Lab Med* **126**, 934-940, doi:10.5858/2002-126-0934-CACICT (2002).

55 Kunisaki, S. M. *et al.* Bronchial atresia: the hidden pathology within a spectrum of prenatally diagnosed lung masses. *J Pediatr Surg* **41**, 61-65; discussion 61-65, doi:10.1016/j.jpedsurg.2005.10.082 (2006).

56 Riedlinger, W. F. *et al.* Bronchial atresia is common to extralobar sequestration, intralobar sequestration, congenital cystic adenomatoid malformation, and lobar emphysema. *Pediatr Dev Pathol* **9**, 361-373, doi:10.2350/06-01-0023.1 (2006).

57 Nelson, N. D., Litzky, L. A., Peranteau, W. H. & Pogoriler, J. Mucinous Cell Clusters in Infantile Congenital Pulmonary Airway Malformations Mimic Adult Mucinous Adenocarcinoma But Are Not Associated With Poor Outcomes When Appropriately Resected. *Am J Surg Pathol* **44**, 1118-1129, doi:10.1097/PAS.0000000000001488 (2020).

58 Gabelloni, M., Faggioni, L., Accogli, S., Aringhieri, G. & Neri, E. Pulmonary sequestration: What the radiologist should know. *Clin Imaging* **73**, 61-72, doi:10.1016/j.clinimag.2020.11.040 (2021).

59 Volpe, M. V., Archavachotikul, K., Bhan, I., Lessin, M. S. & Nielsen, H. C. Association of bronchopulmonary sequestration with expression of the homeobox protein Hoxb-5. *J Pediatr Surg* **35**, 1817-1819, doi:10.1053/jpsu.2000.19266 (2000).

60 Conran, R. M. & Stocker, J. T. Extralobar sequestration with frequently associated congenital cystic adenomatoid malformation, type 2: report of 50 cases. *Pediatr Dev Pathol* **2**, 454-463, doi:98-88R [pii] (1999).

61 Cass, D. L. *et al.* Cystic lung lesions with systemic arterial blood supply: a hybrid of congenital cystic adenomatoid malformation and bronchopulmonary sequestration. *J Pediatr Surg* **32**, 986-990, doi:S0022-3468(97)90383-3 [pii] (1997).

62 Alamo, L., Vial, Y., Gengler, C. & Meuli, R. Imaging findings of bronchial atresia in fetuses, neonates and infants. *Pediatr Radiol* **46**, 383-390, doi:10.1007/s00247-015-3487-5 (2016).

63 Kravitz, R. M. Congenital malformations of the lung. *Pediatr Clin North Am* **41**, 453-472, doi:10.1016/s0031-3955(16)38765-x (1994).

64 Kunisaki, S. M. *et al.* Current operative management of congenital lobar emphysema in children: A report from the Midwest Pediatric Surgery Consortium. *J Pediatr Surg* **54**, 1138-1142, doi:10.1016/j.jpedsurg.2019.02.043 (2019).

65 Ortiz, R. J. *et al.* Bronchogenic Cyst: Lessons Learned in 20 Years of Experience at a Tertiary Pediatric Center. *J Pediatr Surg*, doi:10.1016/j.jpedsurg.2023.06.010 (2023).

66 Morikawa, N. *et al.* Congenital bronchial atresia in infants and children. *J Pediatr Surg* **40**, 1822-1826, doi:10.1016/j.jpedsurg.2005.08.021 (2005).

67 Tsai, A. Y. *et al.* Outcomes after postnatal resection of prenatally diagnosed asymptomatic cystic lung lesions. *J Pediatr Surg* **43**, 513-517, doi:S0022-3468(07)00831-7 [pii] 10.1016/j.jpedsurg.2007.10.032 (2008).

68 Wong, A., Vieten, D., Singh, S., Harvey, J. G. & Holland, A. J. Long-term outcome of asymptomatic patients with congenital cystic adenomatoid malformation. *Pediatr Surg Int* **25**, 479-485, doi:10.1007/s00383-009-2371-5 (2009).

69 Lujan, M. *et al.* Late-onset congenital cystic adenomatoid malformation of the lung. Embryology, clinical symptomatology, diagnostic procedures, therapeutic approach and clinical follow-up. *Respiration* **69**, 148-154, doi:10.1159/000056318 (2002).

70 Ng, C., Stanwell, J., Burge, D. M. & Stanton, M. P. Conservative management of antenatally diagnosed cystic lung malformations. *Arch Dis Child* **99**, 432-437, doi:10.1136/archdischild-2013-304048 (2014).

71 Criss, C. N. *et al.* Asymptomatic congenital lung malformations: Is nonoperative management a viable alternative? *J Pediatr Surg* **53**, 1092-1097, doi:10.1016/j.jpedsurg.2018.02.065 (2018).

72 Adzick, N. S. *et al.* Fetal cystic adenomatoid malformation: prenatal diagnosis and natural history. *J Pediatr Surg* **20**, 483-488, doi:S0022346885001038 [pii] (1985).

73 Kunisaki, S. M. *et al.* Large fetal congenital cystic adenomatoid malformations: growth trends and patient survival. *J Pediatr Surg* **42**, 404-410, doi:10.1016/j.jpedsurg.2006.10.014 (2007).

74 Macardle, C. A. *et al.* Surveillance of fetal lung lesions using the congenital pulmonary airway malformation volume ratio: natural history and outcomes. *Prenat Diagn* **36**, 282-289, doi:10.1002/pd.4761 (2016).

75 Monni, G. *et al.* Prenatal ultrasound diagnosis of congenital cystic adenomatoid malformation of the lung: a report of 26 cases and review of the literature. *Ultrasound Obstet Gynecol* **16**, 159-162, doi:10.1046/j.1469-0705.2000.00195.x (2000).

76 Achiron, R., Gindes, L., Zalel, Y., Lipitz, S. & Weisz, B. Three- and four-dimensional ultrasound: new methods for evaluating fetal thoracic anomalies. *Ultrasound Obstet Gynecol* **32**, 36-43, doi:10.1002/uog.5308 (2008).

77 Priest, J. R., Williams, G. M., Hill, D. A., Dehner, L. P. & Jaffe, A. Pulmonary cysts in early childhood and the risk of malignancy. *Pediatr Pulmonol* **44**, 14-30, doi:10.1002/ppul.20917 (2009).

78 Downard, C. D. *et al.* Treatment of congenital pulmonary airway malformations: a systematic review from the APSA outcomes and evidence based practice committee. *Pediatr Surg Int* **33**, 939-953, doi:10.1007/s00383-017-4098-z (2017).

79 Perlman, S. *et al.* The added value of f-TAPSE in the surveillance of pregnancies complicated by fetal and placental tumors. *Prenat Diagn* **37**, 788-792, doi:10.1002/pd.5087 (2017).

80 Girsen, A. I. *et al.* Prediction of neonatal respiratory distress in pregnancies complicated by fetal lung masses. *Prenat Diagn* **37**, 266-272, doi:10.1002/pd.5002 (2017).

81 Crombleholme, T. M. *et al.* Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. *J Pediatr Surg* **37**, 331-338, doi:10.1053/jpsu.2002.30832 (2002).

82 David, M., Lamas-Pinheiro, R. & Henriques-Coelho, T. Prenatal and Postnatal Management of Congenital Pulmonary Airway Malformation. *Neonatology* **110**, 101-115, doi:10.1159/000440894 (2016).

83 Kane, S. C., Ancona, E., Reidy, K. L. & Palma-Dias, R. The Utility of the Congenital Pulmonary Airway Malformation-Volume Ratio in the Assessment of Fetal Echogenic Lung Lesions: A Systematic Review. *Fetal Diagn Ther* **47**, 171-181, doi:10.1159/000502841 (2020).

84 Delacourt, C. *et al.* Predicting the risk of respiratory distress in newborns with congenital pulmonary malformations. *Eur Respir J* **59**, doi:10.1183/13993003.00949-2021 (2022).

85 Gerall, C. *et al.* Prenatal ultrasound-and MRI-based imaging predictors of respiratory symptoms at birth for congenital lung malformations. *J Pediatr Surg* **58**, 420-426, doi:10.1016/j.jpedsurg.2022.08.026 (2023).

86 Peters, N. C. J. *et al.* Prediction of postnatal outcome in fetuses with congenital lung malformation: 2-year follow-up study. *Ultrasound Obstet Gynecol* **58**, 428-438, doi:10.1002/uog.23542 (2021).

87 Ehrenberg-Buchner, S. *et al.* Fetal lung lesions: can we start to breathe easier? *Am J Obstet Gynecol* **208**, 151 e151-157, doi:10.1016/j.ajog.2012.11.012 (2013).

88 Ruchonnet-Metrailler, I. *et al.* Neonatal outcomes of prenatally diagnosed congenital pulmonary malformations. *Pediatrics* **133**, e1285-1291, doi:10.1542/peds.2013-2986 (2014).

89 Mon, R. A. *et al.* Diagnostic accuracy of imaging studies in congenital lung malformations. *Arch Dis Child Fetal Neonatal Ed* **104**, F372-F377, doi:10.1136/archdischild-2018-314979 (2019).

90 Newman, B. Magnetic resonance imaging for congenital lung malformations. *Pediatr Radiol* **52**, 312-322, doi:10.1007/s00247-021-05018-7 (2022).

91 Wong, K. K. Y., Flake, A. W., Tibboel, D., Rottier, R. J. & Tam, P. K. H. Congenital pulmonary airway malformation: advances and controversies. *Lancet Child Adolesc Health* **2**, 290-297, doi:10.1016/S2352-4642(18)30035-X (2018).

92 Tivnan, P., Winant, A. J., Epelman, M. & Lee, E. Y. Pediatric Congenital Lung Malformations: Imaging Guidelines and Recommendations. *Radiol Clin North Am* **60**, 41-54, doi:10.1016/j.rcl.2021.08.002 (2022).

93 Style, C. C. *et al.* Accuracy of prenatal and postnatal imaging for management of congenital lung malformations. *J Pediatr Surg* **55**, 844-847, doi:10.1016/j.jpedsurg.2020.01.020 (2020).

94 Narayan, R. R. *et al.* Predicting Pathology From Imaging in Children Undergoing Resection of Congenital Lung Lesions. *J Surg Res* **236**, 68-73, doi:10.1016/j.jss.2018.10.042 (2019).

95 Hermelijn, S. M. *et al.* A clinical guideline for structured assessment of CT-imaging in congenital lung abnormalities. *Paediatr Respir Rev* **37**, 80-88, doi:10.1016/j.prrv.2019.12.004 (2021).

96 Kim, W. S. *et al.* Congenital cystic adenomatoid malformation of the lung: CT-pathologic correlation. *AJR Am J Roentgenol* **168**, 47-53, doi:10.2214/ajr.168.1.8976918 (1997).

97 Hermelijn, S. M. *et al.* Congenital lung abnormality quantification by computed tomography: The CLAQ method. *Pediatr Pulmonol* **55**, 3152-3161, doi:10.1002/ppul.25032 (2020).

98 Cheeney, S. H. E., Maloney, E. & Iyer, R. S. Safety considerations related to intravenous contrast agents in pediatric imaging. *Pediatr Radiol*, doi:10.1007/s00247-022-05470-z (2022).

99 Parikh, D. H. & Rasiah, S. V. Congenital lung lesions: Postnatal management and outcome. *Semin Pediatr Surg* **24**, 160-167, doi:10.1053/j.sempedsurg.2015.01.013 (2015).

100 Calvert, J. K. & Lakhoo, K. Antenatally suspected congenital cystic adenomatoid malformation of the lung: postnatal investigation and timing of surgery. *J Pediatr Surg* **42**, 411-414, doi:S0022-3468(06)00779-2 [pii]
10.1016/j.jpedsurg.2006.10.015 (2007).

101 Sauvat, F., Michel, J. L., Benachi, A., Emond, S. & Revillon, Y. Management of asymptomatic neonatal cystic adenomatoid malformations. *J Pediatr Surg* **38**, 548-552, doi:10.1053/jpsu.2003.50119 (2003).

102 El-Ali, A. M., Strubel, N. A. & Lala, S. V. Congenital lung lesions: a radiographic pattern approach. *Pediatr Radiol* **52**, 622-636, doi:10.1007/s00247-021-05210-9 (2022).

103 Merli, L. *et al.* Congenital lung malformations: a novel application for lung ultrasound? *J Ultrasound* **24**, 349-353, doi:10.1007/s40477-019-00406-0 (2021).

104 Quercia, M., Panza, R., Calderoni, G., Di Mauro, A. & Laforgia, N. Lung Ultrasound: A New Tool in the Management of Congenital Lung Malformation. *Am J Perinatol* **36**, S99-S105, doi:10.1055/s-0039-1692131 (2019).

105 Kellenberger, C. J. *et al.* Structural and perfusion magnetic resonance imaging of congenital lung malformations. *Pediatr Radiol* **50**, 1083-1094, doi:10.1007/s00247-020-04658-5 (2020).

106 Ciet, P. & Litmanovich, D. E. MR safety issues particular to women. *Magn Reson Imaging Clin N Am* **23**, 59-67, doi:10.1016/j.mric.2014.09.002 (2015).

107 Elders, B. *et al.* Congenital lung abnormalities on magnetic resonance imaging: the CLAM study. *Eur Radiol*, doi:10.1007/s00330-023-09458-7 (2023).

108 Fowler, D. J. & Gould, S. J. The pathology of congenital lung lesions. *Semin Pediatr Surg* **24**, 176-182, doi:10.1053/j.sempedsurg.2015.02.002 (2015).

109 Desai, S. *et al.* Secondary vascular changes in pulmonary sequestrations. *Histopathology* **57**, 121-127, doi:10.1111/j.1365-2559.2010.03586.x (2010).

110 Pogoriler, J., Swarr, D., Kreiger, P., Adzick, N. S. & Peranteau, W. Congenital Cystic Lung Lesions: Redefining the Natural Distribution of Subtypes and Assessing the Risk of Malignancy. *Am J Surg Pathol* **43**, 47-55, doi:10.1097/PAS.0000000000000992 (2019).

111 Mukhtar, S. & Trovela, D. A. V. in *StatPearls* (2022).

112 Schuster, S. R., Harris, G. B., Williams, A., Kirkpatrick, J. & Reid, L. Bronchial atresia: a recognizable entity in the pediatric age group. *J Pediatr Surg* **13**, 682-689, doi:10.1016/s0022-3468(78)80114-6 (1978).

113 Peranteau, W. H. *et al.* Effect of maternal betamethasone administration on prenatal congenital cystic adenomatoid malformation growth and fetal survival. *Fetal Diagn Ther* **22**, 365-371, doi:10.1159/000103298 (2007).

114 Muntean, A. *et al.* The long-term outcome following thoraco-amniotic shunting for congenital lung malformations. *J Pediatr Surg* **58**, 213-217, doi:10.1016/j.jpedsurg.2022.10.028 (2023).

115 Rosenblat, O. *et al.* In-utero treatment of prenatal thoracic abnormalities by thoraco-amniotic shunts, short and long term neuro developmental outcome: A single center experience. *J Pediatr Surg* **57**, 364-368, doi:10.1016/j.jpedsurg.2021.08.019 (2022).

116 Morris, L. M., Lim, F. Y., Livingston, J. C., Polzin, W. J. & Crombleholme, T. M. High-risk fetal congenital pulmonary airway malformations have a variable response to steroids. *J Pediatr Surg* **44**, 60-65, doi:10.1016/j.jpedsurg.2008.10.012 (2009).

117 Kunisaki, S. M. & Jennings, R. W. Fetal surgery. *J Intensive Care Med* **23**, 33-51, doi:10.1177/0885066607310240 (2008).

118 Bratu, I. *et al.* The multiple facets of pulmonary sequestration. *J Pediatr Surg* **36**, 784-790, doi:10.1053/jpsu.2001.22961 (2001).

119 da Silva, O. P., Ramanan, R., Romano, W., Bocking, A. & Evans, M. Nonimmune hydrops fetalis, pulmonary sequestration, and favorable neonatal outcome. *Obstet Gynecol* **88**, 681-683, doi:10.1016/0029-7844(96)00101-9 (1996).

120 Litwinska, M. *et al.* Management Options for Fetal Bronchopulmonary Sequestration. *J Clin Med* **11**, doi:10.3390/jcm11061724 (2022).

121 Mallmann, M. R. *et al.* Bronchopulmonary sequestration with massive pleural effusion: pleuroamniotic shunting vs intrafetal vascular laser ablation. *Ultrasound Obstet Gynecol* **44**, 441-446, doi:10.1002/uog.13304 (2014).

122 Aziz, D. *et al.* Perinatally diagnosed asymptomatic congenital cystic adenomatoid malformation: to resect or not? *J Pediatr Surg* **39**, 329-334; discussion 329-334, doi:S0022346803008790 [pii] (2004).

123 Chetcuti, P. A. & Crabbe, D. C. CAM lungs: the conservative approach. *Arch Dis Child Fetal Neonatal Ed* **91**, F463-464 (2006).

124 Hall, N. J., Chiu, P. P. & Langer, J. C. Morbidity after elective resection of prenatally diagnosed asymptomatic congenital pulmonary airway malformations. *Pediatr Pulmonol* **51**, 525-530, doi:10.1002/ppul.23255 (2016).

125 Aspirot, A. *et al.* A contemporary evaluation of surgical outcome in neonates and infants undergoing lung resection. *J Pediatr Surg* **43**, 508-512, doi:10.1016/j.jpedsurg.2007.10.031 (2008).

126 Rahman, N. & Lakhoo, K. Comparison between open and thoracoscopic resection of congenital lung lesions. *J Pediatr Surg* **44**, 333-336, doi:10.1016/j.jpedsurg.2008.10.081 (2009).

127 Bunduki, V. *et al.* Prognostic factors associated with congenital cystic adenomatoid malformation of the lung. *Prenat Diagn* **20**, 459-464, doi:10.1002/1097-0223(200006)20:6<459::aid-pd851>3.0.co;2-f (2000).

128 Rothenberg, S. S. Thoracoscopic Lobectomy in Infants and Children. *J Laparoendosc Adv Surg Tech A* **31**, 1157-1161, doi:10.1089/lap.2021.0454 (2021).

129 Rothenberg, S. S. *et al.* Thoracoscopic lobectomy in infants less than 10 kg with prenatally diagnosed cystic lung disease. *J Laparoendosc Adv Surg Tech A* **21**, 181-184, doi:10.1089/lap.2010.0138 (2011).

130 Lawal, T. A., Gosemann, J. H., Kuebler, J. F., Gluer, S. & Ure, B. M. Thoracoscopy versus thoracotomy improves midterm musculoskeletal status and cosmesis in infants and children. *Ann Thorac Surg* **87**, 224-228, doi:10.1016/j.athoracsur.2008.08.069 (2009).

131 Adams, S. *et al.* Does thoracoscopy have advantages over open surgery for asymptomatic congenital lung malformations? An analysis of 1626 resections. *J Pediatr Surg* **52**, 247-251, doi:10.1016/j.jpedsurg.2016.11.014 (2017).

132 Dossche, L. W. J. *et al.* Long-term neurodevelopment in children with resected congenital lung abnormalities. *Eur J Pediatr*, doi:10.1007/s00431-023-05054-5 (2023).

133 Robson, V. K., Shieh, H. F., Wilson, J. M. & Buchmiller, T. L. Non-operative management of extralobar pulmonary sequestration: a safe alternative to resection? *Pediatr Surg Int* **36**, 325-331, doi:10.1007/s00383-019-04590-2 (2020).

134 Cook, J., Chitty, L. S., De Coppi, P., Ashworth, M. & Wallis, C. The natural history of prenatally diagnosed congenital cystic lung lesions: long-term follow-up of 119 cases. *Arch Dis Child* **102**, 798-803, doi:10.1136/archdischild-2016-311233 (2017).

135 Karlsson, M., Conner, P., Ehren, H., Bitkover, C. & Burgos, C. M. The natural history of prenatally diagnosed congenital pulmonary airway malformations and bronchopulmonary sequestrations. *J Pediatr Surg* **57**, 282-287, doi:10.1016/j.jpedsurg.2022.03.021 (2022).

136 Duarte, J. C., Ferreira, P. G., Alfaro, T. M., Carvalho, L. & Ferreira, A. J. Cystic adenomatoid pulmonary malformation in adults: A retrospective study in a tertiary university hospital. *Rev Port Pneumol (2006)* **23**, 109-110, doi:10.1016/j.rppnen.2016.10.005 (2017).

137 Gorospe, L. *et al.* Cystic adenomatoid malformation of the lung in adult patients: clinicoradiological features and management. *Clin Imaging* **40**, 517-522, doi:10.1016/j.clinimag.2015.11.014 (2016).

138 Hamanaka, R., Yagasaki, H., Kohno, M., Masuda, R. & Iwazaki, M. Congenital cystic adenomatoid malformation in adults: Report of a case presenting with a recurrent pneumothorax and a literature review of 60 cases. *Respir Med Case Rep* **26**, 328-332, doi:10.1016/j.rmcr.2018.02.002 (2019).

139 Polaczek, M. *et al.* Clinical presentation and characteristics of 25 adult cases of pulmonary sequestration. *J Thorac Dis* **9**, 762-767, doi:10.21037/jtd.2017.03.107 (2017).

140 Elhattab, A. *et al.* Thoracoscopic surgery for congenital lung malformations: Does previous infection really matter? *J Pediatr Surg* **56**, 1982-1987, doi:10.1016/j.jpedsurg.2021.01.036 (2021).

141 Berrington de Gonzalez, A., Pasqual, E. & Veiga, L. Epidemiological studies of CT scans and cancer risk: the state of the science. *Br J Radiol* **94**, 20210471, doi:10.1259/bjr.20210471 (2021).

142 Rothenberg, S. S. First decade's experience with thoracoscopic lobectomy in infants and children. *J Pediatr Surg* **43**, 40-44; discussion 45, doi:10.1016/j.jpedsurg.2007.09.015 (2008).

143 Rothenberg, S. S. *et al.* Two decades of experience with thoracoscopic lobectomy in infants and children: standardizing techniques for advanced thoracoscopic surgery. *J Laparoendosc Adv Surg Tech A* **25**, 423-428, doi:10.1089/lap.2014.0350 (2015).

144 Cano, I., Anton-Pacheco, J. L., Garcia, A. & Rothenberg, S. Video-assisted thoracoscopic lobectomy in infants. *Eur J Cardiothorac Surg* **29**, 997-1000, doi:10.1016/j.ejcts.2005.12.060 (2006).

145 Bonnard, A. Thoracoscopic Lobectomy for Congenital Pulmonary Airway Malformation: Where Are We in 2019? *Eur J Pediatr Surg* **30**, 146-149, doi:10.1055/s-0040-1702221 (2020).

146 Kapralik, J., Wayne, C., Chan, E. & Nasr, A. Surgical versus conservative management of congenital pulmonary airway malformation in children: A systematic review and meta-analysis. *J Pediatr Surg* **51**, 508-512, doi:10.1016/j.jpedsurg.2015.11.022 (2016).

147 Duron, V. *et al.* Asymptomatic Congenital Lung Malformations: Timing of Resection Does Not Affect Adverse Surgical Outcomes. *Front Pediatr* **8**, 35, doi:10.3389/fped.2020.00035 (2020).

148 Esposito, C. *et al.* Thoracoscopic Management of Pediatric Patients with Congenital Lung Malformations: Results of a European Multicenter Survey. *J Laparoendosc Adv Surg Tech A* **31**, 355-362, doi:10.1089/lap.2020.0596 (2021).

149 Engall, N., Sethuraman, C., Wilkinson, D. J., Lansdale, N. & Peters, R. T. Does Timing of Resection Influence the Presence of Inflammation within Congenital Lung Malformations? *Eur J Pediatr Surg* **33**, 81-84, doi:10.1055/a-1957-6898 (2023).

150 Garrett-Cox, R., MacKinlay, G., Munro, F. & Aslam, A. Early experience of pediatric thoracoscopic lobectomy in the UK. *J Laparoendosc Adv Surg Tech A* **18**, 457-459, doi:10.1089/lap.2007.0038 (2008).

151 Mei-Zahav, M., Konen, O., Manson, D. & Langer, J. C. Is congenital lobar emphysema a surgical disease? *J Pediatr Surg* **41**, 1058-1061, doi:10.1016/j.jpedsurg.2006.02.011 (2006).

152 Bagrodia, N., Cassel, S., Liao, J., Pitcher, G. & Shilyansky, J. Segmental resection for the treatment of congenital pulmonary malformations. *J Pediatr Surg* **49**, 905-909, doi:10.1016/j.jpedsurg.2014.01.021 (2014).

153 Rothenberg, S. S. *et al.* Thoracoscopic segmentectomy for congenital and acquired pulmonary disease: a case for lung-sparing surgery. *J Laparoendosc Adv Surg Tech A* **24**, 50-54, doi:10.1089/lap.2013.0337 (2014).

154 Eber, E. Adult outcome of congenital lower respiratory tract malformations. *Swiss Med Wkly* **136**, 233-240, doi:10.4414/smw.2006.11164 (2006).

155 Davenport, M. & Eber, E. Long term respiratory outcomes of congenital thoracic malformations. *Semin Fetal Neonatal Med* **17**, 99-104, doi:10.1016/j.siny.2012.01.011 (2012).

156 Hall, N. J. & Stanton, M. P. Long-term outcomes of congenital lung malformations. *Semin Pediatr Surg* **26**, 311-316, doi:10.1053/j.sempedsurg.2017.09.001 (2017).

157 Lee, S., Kim, D. H. & Lee, S. K. Efficacy of segmental resection in patients with prenatally diagnosed congenital lung malformations. *Interact Cardiovasc Thorac Surg* **24**, 425-429, doi:10.1093/icvts/ivw408 (2017).

158 Spoel, M. *et al.* Lung function of infants with congenital lung lesions in the first year of life. *Neonatology* **103**, 60-66, doi:10.1159/000342224 (2013).

159 Hijkoop, A. *et al.* Lung function, exercise tolerance, and physical growth of children with congenital lung malformations at 8 years of age. *Pediatr Pulmonol* **54**, 1326-1334, doi:10.1002/ppul.24345 (2019).

160 Calzolari, F. *et al.* Outcome of infants operated on for congenital pulmonary malformations. *Pediatr Pulmonol* **51**, 1367-1372, doi:10.1002/ppul.23472 (2016).

161 Markel, M. *et al.* Congenital lung malformation patients experience respiratory infections after resection: A population-based cohort study. *J Pediatr Surg* **57**, 829-832, doi:10.1016/j.jpedsurg.2021.12.042 (2022).

162 Barikbin, P. *et al.* Postnatal lung function in congenital cystic adenomatoid malformation of the lung. *Ann Thorac Surg* **99**, 1164-1169, doi:10.1016/j.athoracsur.2014.11.018 (2015).

163 Huang, J. X., Hong, S. M., Hong, J. J., Chen, Q. & Cao, H. Medium-Term Pulmonary Function Test After Thoracoscopic Lobectomy and Segmentectomy for Congenital Lung Malformation: A Comparative Study With Normal Control. *Front Pediatr* **9**, 755328, doi:10.3389/fped.2021.755328 (2021).

164 Dincel, A. *et al.* Long-term respiratory outcomes of post-op congenital lung malformations. *Pediatr Int* **63**, 704-709, doi:10.1111/ped.14488 (2021).

165 Tocchioni, F. *et al.* Long-term lung function in children following lobectomy for congenital lung malformation. *J Pediatr Surg* **52**, 1891-1897, doi:10.1016/j.jpedsurg.2017.08.059 (2017).

166 Willers, C. *et al.* School-age structural and functional MRI and lung function in children following lung resection for congenital lung malformation in infancy. *Pediatr Radiol* **52**, 1255-1265, doi:10.1007/s00247-022-05317-7 (2022).

167 Lau, C. T., Wong, K. K. Y. & Tam, P. Medium Term Pulmonary Function Test After Thoracoscopic Lobectomy for Congenital Pulmonary Airway Malformation: A Comparative Study with Normal Control. *J Laparoendosc Adv Surg Tech A* **28**, 595-598, doi:10.1089/lap.2017.0276 (2018).

168 Albanese, C. T. & Rothenberg, S. S. Experience with 144 consecutive pediatric thoracoscopic lobectomies. *J Laparoendosc Adv Surg Tech A* **17**, 339-341, doi:10.1089/lap.2006.0184 (2007).

169 Lam, F. K. F., Lau, C. T., Yu, M. O. & Wong, K. K. Y. Comparison of thoracoscopy vs. thoracotomy on musculoskeletal outcomes of children with congenital pulmonary airway malformation (CPAM). *J Pediatr Surg* **56**, 1732-1736, doi:10.1016/j.jpedsurg.2021.01.028 (2021).

170 Sadeghi, A. H. *et al.* Virtual reality and artificial intelligence for 3-dimensional planning of lung segmentectomies. *JTCVS Tech* **7**, 309-321, doi:10.1016/j.xjtc.2021.03.016 (2021).

171 Bakhuis, W. *et al.* Preoperative visualization of congenital lung abnormalities: hybridizing artificial intelligence and virtual reality. *Eur J Cardiothorac Surg* **63**, doi:10.1093/ejcts/ezad014 (2022).

172 Sumner, T. E., Phelps, C. R., 2nd, Crowe, J. E., Poolos, S. P. & Shaffner, L. D. Pulmonary blastoma in a child. *AJR Am J Roentgenol* **133**, 147-148 (1979).

173 Papagiannopoulos, K. A., Sheppard, M., Bush, A. P. & Goldstraw, P. Pleuropulmonary blastoma: is prophylactic resection of congenital lung cysts effective? *Ann Thorac Surg* **72**, 604-605, doi:S0003-4975(00)02539-X [pii] (2001).

174 Laberge, J. M., Puligandla, P. & Flageole, H. Asymptomatic congenital lung malformations. *Semin Pediatr Surg* **14**, 16-33, doi:S1055858604000782 [pii] (2005).

175 Veronesi, G. *et al.* Report on First International Workshop on Robotic Surgery in Thoracic Oncology. *Front Oncol* **6**, 214, doi:10.3389/fonc.2016.00214 (2016).

176 Ballouhey, Q. *et al.* A comparison of robotic surgery in children weighing above and below 15.0 kg: size does not affect surgery success. *Surg Endosc* **29**, 2643-2650, doi:10.1007/s00464-014-3982-z (2015).

177 Durand, M. *et al.* Robotic lobectomy in children with severe bronchiectasis: A worthwhile new technology. *J Pediatr Surg* **56**, 1606-1610, doi:10.1016/j.jpedsurg.2020.11.009 (2021).

178 Ballouhey, Q. *et al.* Assessment of paediatric thoracic robotic surgery. *Interact Cardiovasc Thorac Surg* **20**, 300-303, doi:10.1093/icvts/ivu406 (2015).

179 Meehan, J. J., Phearman, L. & Sandler, A. Robotic pulmonary resections in children: series report and introduction of a new robotic instrument. *J Laparoendosc Adv Surg Tech A* **18**, 293-295, doi:10.1089/lap.2007.0078 (2008).

180 Ueda, K., Gruppo, R., Unger, F., Martin, L. & Bove, K. Rhabdomyosarcoma of lung arising in congenital cystic adenomatoid malformation. *Cancer* **40**, 383-388 (1977).

181 Kunisaki, S. M. *et al.* Pleuropulmonary Blastoma in Pediatric Lung Lesions. *Pediatrics* **147**, doi:10.1542/peds.2020-028357 (2021).

182 Herriges, M. & Morrisey, E. E. Lung development: orchestrating the generation and regeneration of a complex organ. *Development* **141**, 502-513, doi:10.1242/dev.098186 (2014).

183 Leblanc, C. *et al.* Congenital pulmonary airway malformations: state-of-the-art review for pediatrician's use. *Eur J Pediatr* **176**, 1559-1571, doi:10.1007/s00431-017-3032-7 (2017).

184 Mullassery, D. & Smith, N. P. Lung development. *Semin Pediatr Surg* **24**, 152-155, doi:10.1053/j.sempedsurg.2015.01.011 (2015).

185 Morrisey, E. E. & Hogan, B. L. Preparing for the first breath: genetic and cellular mechanisms in lung development. *Dev Cell* **18**, 8-23, doi:10.1016/j.devcel.2009.12.010 (2010).

186 Prince, L. S. FGF10 and Human Lung Disease Across the Life Spectrum. *Front Genet* **9**, 517, doi:10.3389/fgene.2018.00517 (2018).

187 Yuan, T., Volckaert, T., Chanda, D., Thannickal, V. J. & De Langhe, S. P. Fgf10 Signaling in Lung Development, Homeostasis, Disease, and Repair After Injury. *Front Genet* **9**, 418, doi:10.3389/fgene.2018.00418 (2018).

188 Yu, J. *et al.* Induced pluripotent stem cell lines derived from human somatic cells. *Science* **318**, 1917-1920, doi:10.1126/science.1151526 (2007).
189 Danopoulos, S. *et al.* Discordant roles for FGF ligands in lung branching morphogenesis between human and mouse. *J Pathol* **247**, 254-265, doi:10.1002/path.5188 (2019).
190 Otto-Verberne, C. J., Ten Have-Opbroek, A. A., Balkema, J. J. & Franken, C. Detection of the type II cell or its precursor before week 20 of human gestation, using antibodies against surfactant-associated proteins. *Anat Embryol (Berl)* **178**, 29-39, doi:10.1007/BF00305011 (1988).
191 Liggins, G. C. The role of cortisol in preparing the fetus for birth. *Reprod Fertil Dev* **6**, 141-150, doi:10.1071/rd9940141 (1994).
192 Jobe, A. H. & Ikegami, M. Lung development and function in preterm infants in the surfactant treatment era. *Annu Rev Physiol* **62**, 825-846, doi:10.1146/annurev.physiol.62.1.825 (2000).
193 Bernstein, E. *et al.* Dicer is essential for mouse development. *Nat Genet* **35**, 215-217, doi:10.1038/ng1253 (2003).
194 Harris, K. S., Zhang, Z., McManus, M. T., Harfe, B. D. & Sun, X. Dicer function is essential for lung epithelium morphogenesis. *Proc Natl Acad Sci U S A* **103**, 2208-2213, doi:10.1073/pnas.0510839103 (2006).
195 Yoshida, K. *et al.* Feasibility of using a vessel sealing system in a human pulmonary lobectomy: a retrospective comparison of this procedure with or without a vessel sealing system. *Ann Thorac Cardiovasc Surg* **20**, 353-358, doi:10.5761/atcs.oa.13-00014 (2014).
196 Lai, S. W. & Rothenberg, S. S. Culture of safety and error traps in pediatric thoracoscopy. *Semin Pediatr Surg* **28**, 178-182, doi:10.1053/j.sempedsurg.2019.04.021 (2019).
197 Murakami, H. *et al.* Does fissure status affect the outcome of thoracoscopic pulmonary lobectomy? *Pediatr Surg Int* **36**, 57-61, doi:10.1007/s00383-019-04577-z (2020).
198 Huang, J. X., Chen, Q., Hong, S. M., Hong, J. J. & Cao, H. Effects of pulmonary fissure completeness on major outcomes in children after video-assisted thoracoscopic congenital lung malformation lobectomy. *BMC Pediatr* **22**, 462, doi:10.1186/s12887-022-03527-4 (2022).

Highlighted References

[Au: Please list here the references that are particularly worth reading (5-10 of the total), please provide a single bold sentence that indicates the significance of the work.]

Commentato [A2]: The guidance says 5-10% but that can be a lot of individual references, so I usually ask for 5-10 individual ones.

Glossary

[Au: Please provide definitions for some newly suggested glossary terms (if you agree) and check terms that have been removed as they no longer appear in the main text.]

Pulmonary arteriovenous malformations:

Epithelial-mesenchymal interaction: a series of programmed, sequential and reciprocal communications between the epithelium and the mesenchyme with its heterotypic cell population that result in the differentiation of one or both cell populations.

Congenital anomalies: structural or functional anomalies occurring during intrauterine life, and affecting 3-6% of global live births (WHO definition)**[Au: Please reference.]**

Congenital diaphragmatic hernia: is a defect in the diaphragm causing the herniation of abdominal contents into the thoracic cavity, resulting in lung hypoplasia and altered pulmonary vascular development.

Esophageal atresia: is a rare congenital malformation characterized by an interruption in the continuity of the esophagus, with or without persistent communication with the trachea.

Hydrops: abnormal interstitial fluid collection in two or more compartments of the fetal body

Acinar-like tissue: A tissue composed of polarized epithelial cells rich in rough endoplasmic reticulum and characterized by an abundance of secretory zymogen granules.

Acinar dysplasia: A rare malformation characterized by growth arrest of the lower respiratory tract and complete absence of gas exchanging units, resulting in critical respiratory insufficiency at birth.

Pores of Kohn: Small communications between adjacent pulmonary alveoli that provide a collateral pathway for aeration.

Channels of Lambert: Microscopic collateral airways between the distal bronchiolar tree and adjacent alveoli.

Bronchomalacia:

Vascular sling:

Mediastinal shift: The deviation of the mediastinal structures towards one side of the chest cavity

Mucocele:

Esophageal duplication: separate masses along or in continuity with the native esophagus

Foregut duplication cysts: benign developmental anomalies that contain foregut derivatives

Polydramnios: a condition that occurs when too much amniotic fluid builds up during pregnancy**[Au: What effect does this have? Please briefly add.]**

Mass effect:

Thoraco-amniotic shunt: The shunt drains fluid from the lung into the amniotic sac.**[Au: Please check wording here and amend.]** treat pleural effusion, i.e. in congenital pulmonary airway malformations (CPAMs)

Tricuspid annular plane systole excursion (TAPSE): is a scoring system used with non-invasive Doppler echocardiography to determine right ventricular function.

[Au: This term was removed, as it no longer appears in the text. OK?]
[Au: This term was removed, as it no longer appears in the text. OK?]

[Au: This term was removed, as it no longer appears in the text. OK?]
Tidal volumes: is the amount of air that moves in or out of the lungs with each respiratory cycle

Lung compliance: a measure of the expansion of the lung,

Segmentectomy: