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Challenges with Congenital Lung Cysts: When to Consider *DICER1* Testing? A Narrative Review

Desafios com Cistos Pulmonares Congénitos: Quando Considerar o Teste *DICER1*? Uma Revisão Narrativa

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ABSTRACT

Congenital pulmonary airway malformations (CPAMs), according to the Stocker classification, comprise five types, two of which are non-cystic in nature (types 0 and 3) whereas the others present as cystic lung lesions (types 1, 2 and 4). While there is consensus that symptomatic lesions should be managed surgically, the asymptomatic cases are more problematic in terms of therapeutic intervention. The dilemma is further complicated by CPAM types 1 and 4 and their preneoplastic potential. In the case of CPAM type 1, there are reports of lipidic adenocarcinoma arising from the mucinous component. Type 4 has been equated to type I or cystic pleuropulmonary blastoma (PPB), a proposition that has been challenged in the past. Pleuropulmonary blastoma is associated with a heterozygous germline or somatic variants in *DICER1*. It was recognized that the earliest stage of the sarcomatous progression of PPB was a multicystic lesion in the periphery of the lung whose architectural features were identical to CPAM type 4. This narrative review addresses key aspects of the pathogenetic and diagnostic issues of type I PPB/CPAM type 4, as well as the association of *DICER1* and PPB, offering valuable insights for pediatricians and clinicians caring for young adults who are impacted by the presence of a germline *DICER1* variant.
Keywords: Child; Cystic Adenomatoid Malformation of Lung, Congenital; Germ-Line Mutation; Pulmonary Blastoma/genetics; Ribonuclease III/genetics

RESUMO

As malformações congénitas das vias aéreas pulmonares (MCVAP), segundo a classificação de Stocker, são representadas por cinco tipos, dos quais dois são de natureza não cística (tipos 0 e 3), enquanto os restantes apresentam-se como lesões pulmonares císticas (tipos 1, 2 e 4). Embora exista consenso quanto à abordagem cirúrgica das lesões sintomáticas, os casos assintomáticos colocam maiores dificuldades no que diz respeito à intervenção terapêutica. O dilema torna-se ainda mais complexo com as MCVAP tipos 1 e 4, devido ao seu potencial preneoplásico. No caso da MCVAP tipo 1, há relatos de adenocarcinoma lipídico originado a partir do componente mucinoso. A MCVAP tipo 4 foi equiparada ao blastoma pleuropulmonar (BPP) quístico ou tipo I, uma hipótese que já foi contestada no passado. O BPP está associado a variantes heterozigóticas germinativas ou somáticas no gene *DICER1*. Foi reconhecido que o estadio mais precoce da progressão sarcomatosa do BPP corresponde a uma lesão multicística localizada na periferia do pulmão, cujas características arquitectónicas são idênticas às da MCVAP tipo 4. Esta revisão narrativa aborda aspetos-chave das questões patogenéticas e de diagnóstico do BPP tipo I/MCVAP tipo 4, bem como a associação entre *DICER1* e BPP, oferecendo informações valiosas para especialistas em pediatria e clínicos que acompanham jovens adultos afetados pela presença de variantes germinativas no gene *DICER1*.
Palavras-chave: Blastoma Pulmonar/genética; Criança; Malformação Adenomatoide Quística Congénita do Pulmão; Mutação em Linhagem Germinativa; Ribonuclease III/genética

INTRODUCTION

Congenital pulmonary airway malformation (CPAM), formerly known as congenital cystic adenomatoid malformation, is a rare developmental anomaly of the lower respiratory tract, with an incidence rate ranging between 1:8300 - 35 000 newborns.[1-3] Currently, prenatal ultrasound and magnetic resonance imaging (MRI) enable the diagnosis and characterization of the lesion before birth.[4-6]

The original classification of CPAMs encompassed five distinctive types (types 0 to 4), based on histopathological features and their proposed site of origin along the tracheobronchial tree.[7-9] With the recognition that CPAM type 4 is, in fact, pleuropulmonary blastoma (PPB) type I/Ir, the level of concern has been heightened since the cystic stage has the potential to progress to the partially cystic and solid (PPB type II) or purely solid mass (PPB type III), which are highly aggressive neoplasms. Pleuropulmonary blastoma is the most common primary malignant neoplasm of the lung in childhood.[10-12]

Given that PPB types I and Ir ("regressed type I") and CPAM often cannot be definitively distinguished from one another solely on clinical presentation and imaging, the associated risk of overt malignancy in childhood poses substantial challenges for the clinician in determining the optimal timing for surgical resection.[13,14] There is broad consensus that symptomatic cystic lung lesions should be surgically resected, typically shortly after birth.[1,15] However, the management of

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the asymptomatic cystic lesion remains an unresolved question, and the risks associated with surgical resection must be carefully weighed against those of conservative management.[16]

Pathogenic/likely pathogenic (P/LP) variants in the *DICER1* gene have been identified in over 70% of patients across all three types of PPB.[17-19] *DICER1* is inherited in an autosomal dominant pattern with variable penetrance and is linked to several other neoplastic and non-neoplastic conditions.[20,21] Identifying children with cystic lung lesions who have P/LP variants in the *DICER1* gene and are at an increased risk of developing malignant tumors is of critical importance, as it enables a more cautious and vigilant approach in managing the asymptomatic cystic lung lesion.[21-23]

Despite substantial scientific advancements and increasing clinical experience over the past two decades, significant controversy persists regarding the follow-up and genetic evaluation of asymptomatic cystic lung lesions including CPAM.[13] The aim of this narrative review is to synthesize current knowledge concerning the management of asymptomatic cystic lung lesions, the associated risk of PPB, and the indications for *DICER1* gene testing.

METHODS

A literature search until August 31st, 2025, was conducted in the PubMed database using the terms “congenital pulmonary airway malformation (CPAM)”, “congenital pulmonary cysts”, “pleuropulmonary blastoma (PPB)”, “DICER1”, and “infant”. The most recent and up-to-date articles published in leading English-language journals were considered.

Type I PPB/CPAM type 4

Type I PPB emerged from the study of 50 cases, which provided an important observation about this tumor and its morphologic evolution.[24] When PPB was first described, it was recognized as a solid, multipatterned primitive sarcoma occurring in children less than 10 years old at diagnosis with tumor-related death within two years of diagnosis.[25] However, the study also demonstrated that there was an earlier, purely cystic stage accompanied by a microscopic population of primitive small cells beneath the epithelial lining of the cysts; these small cells often had microscopic and immunophenotypic features of rhabdomyoblasts (Fig. 1A). This relationship between surface epithelium and rhabdomyoblasts known as a cambium layer was also recognized as a feature of the botryoid embryonal rhabdomyosarcoma. An intermediate morphologic stage was composed of residual cysts with the contiguous, solid sarcomatous component with overgrowth and replacement of the cystic foci; this penultimate stage was designated type II PPB and the purely solid tumor as type III PPB. The original series of 11 cases of PPB were all examples of the solid stage tumor (Fig. 1B).[24,25] The linkage of putative congenital cystic adenomatoid malformation and rhabdomyosarcoma was reported as early as 20 years before the description of the type I PPB.[24,26]

Congenital pulmonary airway malformation type 4 as a distinct entity from CPAM type 1 emerged from the review of cystic lung disease in infants and children.[8] This overview by Stocker addressed the issue of CPAM type 4 and cystic (type I) PPB with the acknowledgement of their shared multicystic features but emphasized the difference as the presence of “rhabdomyosarcoma beneath the cuboidal or columnar mucosa of the cyst wall” in the cystic PPB.[8] Stocker stated that “extreme care must be taken to not confuse a (malignant) PPB with a (benign) CPAM type 1 or 4.” Congenital pulmonary airway malformation 4 was described as “thin and uniform with a central region of loose and richly vascularized connective tissue” with a surface lining of type 2 pneumocytes.[8]

A detailed morphologic study of 51 cases of type I PPB revealed a spectrum of microscopic findings from the uniform presence of rhabdomyoblasts throughout the multicystic lesion to the very patchy, focal presence of rhabdomyoblasts whereas the remainder of the lesion was devoid of a primitive population of tumor cells.[12] In this study, we found multicystic lesions in *DICER1* family members, often older, with the architecture of type I PPB without rhabdomyoblasts or primitive CD56-positive small cells. From the latter observation, it was concluded that not all type I PPBs progress and may ‘regress’ with the designation of type Ir PPB, Fig. 1C. The potential difficulty in diagnosing CPAM type 4 was documented in individual case studies of rhabdomyosarcomas arising in CPAM type 4 or other congenital lung cysts.[27-30] Another report of type I and Ir PPB revealed the presence of *DICER1* changes in over 70% of both type I and Ir lesions.[23]

Pleuropulmonary blastoma has been demonstrated to have a strong association with P/LP variants in the *DICER1* gene.[31] These variants are also implicated in several other benign and malignant tumors, often but not always in the setting of hereditary cancer predispostion.[21]

It is a rare pediatric sarcoma and its overall incidence rate remains low, with an estimated 25 to 50 new cases diagnosed annually in the United States.[32] Pleuropulmonary blastoma typically originates as a pulmonary cyst lined by epithelium and underlain by sarcomatous mesenchyme.[33] The disease progresses through well-defined stages – types I, Ir, II, and III – each correlated with the patient’s age at diagnosis and overall prognosis.[33]

Type I PPBs are purely cystic, usually multiloculated, air-filled lesions with thin septa. About one-third of all PPBs are diagnosed at this stage, with a median age of eight months, and 62% identified within the first year of life. They are typically unilateral, peripheral, unifocal, and larger than 5 cm, with a slight male predominance (55% - 57%).[33,34]

Type I PPBs may progress to type II or type III PPB, characterized by both cystic and solid components.[32,33] Type II PPBs are rarely diagnosed before 12 months of age (earliest at 4 months of age) and tend to present later than type I, with a median age of 35 months; 95% of cases are diagnosed by 6.8 years.[19,33] Alternatively, type I PPBs may regress to type Ir ("regressed type I"), accounting for approximately 23% of type I cases. These lesions retain the multilocular cystic architecture but lack primitive neoplastic cells.[33] Importantly, no deaths have been reported from progression of type Ir PPB, and such regression has not been observed in confirmed type II or III cases.[33,34]

Type III PPBs, in contrast, are entirely solid and typically diagnosed at a later age, with a median of 39 months.[19] The solid components of types II and III share similar histologic features, exhibiting a mixed sarcomatous pattern.[33]

Can CPAMs be distinguished from type I PPB based on clinical and imaging features?

An increasing number of CPAMs are diagnosed through prenatal ultrasound, and their clinical manifestations after birth can vary widely. CPAMs may decrease in size or even resolve during pregnancy, and prenatal ultrasound findings do not reliably predict the postnatal outcome.[35] Therefore, all infants diagnosed with CPAM prenatally should undergo postnatal evaluation.[35] A normal chest x-ray at birth does not rule out the persistence of CPAM, which may still be detected on computed tomography (CT).[35]

Approximately 75% of CPAMs are asymptomatic at birth. The minority of cases presenting with neonatal symptoms typically show varying degrees of respiratory distress, which correlates with the volume of the mass.[35-37] Computed tomography with contrast has superior resolution compared to MRI and is the preferred method for characterizing the mass.[4,38]

Distinguishing between type 1 CPAM and type 4 CPAM/PPB based on clinical features or imaging alone is challenging. However, certain features – such as rapid progression, pneumothorax, or a family history suggestive of *DICER1*-related conditions may favor a diagnosis of a neoplastic disease, even though it should be noted that PPB may be diagnosed in the absence of each of these findings.[12]

Radiologically, both CPAM and PPB can appear as multilocular cystic masses. Pleuropulmonary blastoma type I typically presents as a multicystic lesion with thin or slightly thickened septa and may show subtle contrast enhancement on CT without systemic vascular supply.[2,33] The presence of pneumothorax, or bilateral or multifocal cysts suggest PPB type I, although cystic PPB may also present as a small solitary unilocular lesion.[2] In contrast, CPAMs generally present with thin-walled cysts, often confined to a single lobe, and may exhibit systemic vascular involvement in hybrid lesions.[39]

A study involving 145 children (median age: 14 months) using CT found that a cyst larger than 7.9 cm in diameter, mediastinal shift, and pneumothorax were the key features of so-called type 4 CPAMs.[40] Another study identified factors favoring a CPAM diagnosis, including prenatal detection, systemic feeding vessel, asymptomatic presentation, and hyperinflated lung. On the other hand, bilateral or multisegmental involvement favored a diagnosis of PPB.[41]

While CPAMs tend to remain stable over time, PPB can show progressive changes.[33] Given the overlapping imaging features, a definitive diagnosis often requires histopathological confirmation following surgical resection.[2,33]

***DICER1*-related tumor predisposition**

DICER1-related tumor predisposition (OMIM 606241, 601200), is a rare hereditary condition that significantly increases the risk of developing various types of tumors, particularly during childhood and adolescence.[42,43] It is caused by pathogenic variants in the *DICER1* gene, located on chromosome 14q32.13, which plays a crucial role in regulating gene expression and controlling essential cellular processes such as growth and differentiation.[42-45]

Germline *DICER1* P/LP variants are associated with a heightened risk of developing PPB, pulmonary cysts, and several other neoplasms listed in Table 1.[22,23,42,46-48] Over 70% of children diagnosed with PPB (type I: 75%; type Ir: 83%; type II: 71%; type III: 77%) have a germline pathogenic variant in the *DICER1* gene.[18,19,42] Clinically significant PPB typically presents under the age of seven; however, rare cases have been reported in older children and, exceptionally, in one adult.[41] Most *DICER1*-associated tumors occur before the age of 40.[48]

Additional clinical features may include structural abnormalities of the kidneys and urinary collecting system.[42]

Germline *DICER1* mutations follow an autosomal dominant inheritance pattern (80% of cases); the remaining 20% arise *de novo*.[49] The penetrance for malignant tumors is relatively low, estimated at 10% - 15%, meaning that many individuals with the mutation will never develop a malignancy, however thyroid nodules and lung cysts are common.[50] In many of these cases, pulmonary 'cysts' found in adult relatives may actually represent regressed forms of PPB, such as type Ir

lesions.[51,52]

A more comprehensive overview of all tumor types associated with *DICER1* is available in the literature.[53]

When should *DICER1* testing be recommended in infants with pulmonary cysts?

Any patient diagnosed with PPB should be evaluated for possible *DICER1* variants.[54,55] When a pulmonary cyst is identified in a young child with a pathogenic germline *DICER1* variant or a family history of a *DICER1*-associated condition, it should be presumed to be type I or Ir PPB until proven otherwise.[53]

The International PPB Registry (https://www.ppbregistry.org/) has recently published detailed guidelines on *DICER1*-related genetic testing, organ-specific surveillance, and prenatal care.[52] *DICER1* testing should be performed in infants and children with bilateral, septated, or multiple lung cysts, as these findings are suggestive of PPB.[53,55]

A detailed family history should be obtained for all children with pulmonary cysts. It should be noted that some patients with PPB may not have easily identifiable variants on initial testing but may still have variants.[53] If tumor testing is negative or reveals only an RNase IIIb 'hotspot' variant, additional evaluation is warranted. Previous tests should be reviewed to confirm whether deletion/duplication analysis was conducted; if not, this testing should be carried out. Consideration should also be given to intronic testing, including splice site and/or RNA analysis.[53] Table 2 summarizes some of the situations in which *DICER1* gene testing should be strongly considered.[53-55]

Testing for *DICER1* is still justified in children with a small, asymptomatic, unifocal CPAM, without a family history suggestive of *DICER1*-related tumor predisposition, especially those who are under clinical surveillance and whose surgical resection is planned after four to six months of age since delaying resection increases the window during which a potential PPB could evolve. Knowing the child's *DICER1* status before the planned surgery allows clinicians to determine whether earlier intervention is warranted, ensures that the surveillance strategy during the wait period is appropriate, and provides critical risk information for both perioperative planning and family counseling. Therefore, *DICER1* testing adds important safety and management value, especially when surgery is intentionally postponed beyond the neonatal period.[53]

Given the autosomal dominant pattern of inheritance of P/LP variants, it is recommended to conduct at least site-specific genetic testing in all first-degree relatives.[53] Testing should be prioritized for children under the age of seven, as they are at the highest risk for any of the pathological types of PPB and young girls/women at risk for ovarian tumors. Second- and third-degree relatives may also benefit from testing; genetic counselling and cascade testing is strongly recommended.[53]

A third-trimester ultrasound is recommended when either parent carries a known germline *DICER1* mutation.[55] After birth, and ideally before three months of age, the infant should undergo genetic testing for the familial variant.[55] If the infant tests positive for a *DICER1* variant, a chest CT scan is advised at three months of age.[55] Chest x-rays are recommended every six months until age eight and every year until age 12. If the initial chest CT scan shows no evidence of cysts, a follow-up low-dose chest CT is recommended at around 2.5 years of age, just before the peak incidence of type II and type III PPB.[53] The primary aim of surveillance imaging in individuals with *DICER1* mutations is to detect PPB at its earliest, cystic, and most treatable stage, type I PPB. Five-year disease-free survival for type I is 90%.[18] In contrast, for type II and type III PPB, the five-year disease-free survival drops to 65.9% and 46.9% in local disease, with corresponding overall survival rates at 10 years of 74.2% and 57.1%.[19]

Both prenatal and pre-implantation genetic counselling are viable options for assessing the risk to an embryo or fetus when parents prefer not to wait until after birth. Those interested in pursuing these options should be referred to specialized prenatal genetics centers.[53]

Further discussion of the management of pulmonary cysts among individuals including adolescents with pathogenic germline DICER1 variants is beyond the scope of this review and is available through the International PPB Registry (www.PPBregistry.org) or in the European Very Rare Tumor Group guidelines (www.raretumors-children.eu).

A stepwise algorithm for CPAM/PPB evaluation and *DICER1* testing is summarized in Table 3.

CONCLUSION

The management of cystic lung lesions requires a careful and nuanced approach due to the potential risk of PPB, especially in the presence of *DICER1* P/LP variants. While symptomatic cystic lung lesions require early surgical intervention, the management of asymptomatic cases remains controversial, highlighting the importance of genetic testing and careful clinical decision-making. The identification of P/LP *DICER1* variants plays a potential role in determining the optimal management strategy, allowing clinicians to tailor their approach to each patient. Early detection of PPB through surveillance imaging significantly improves patient outcomes. Ultimately, personalized care, guided by genetic testing and careful clinical surveillance, is essential to improving the prognosis of infants with neonatal lung cysts.

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AUTHOR CONTRIBUTIONS

GR: Study design, literature search and review, writing and critical review of the manuscript.
LPD: Writing and critical review of the manuscript.
DRO: Critical review of the manuscript.
KAS: Literature review, critical review of the article.
All authors approved the final version to be published.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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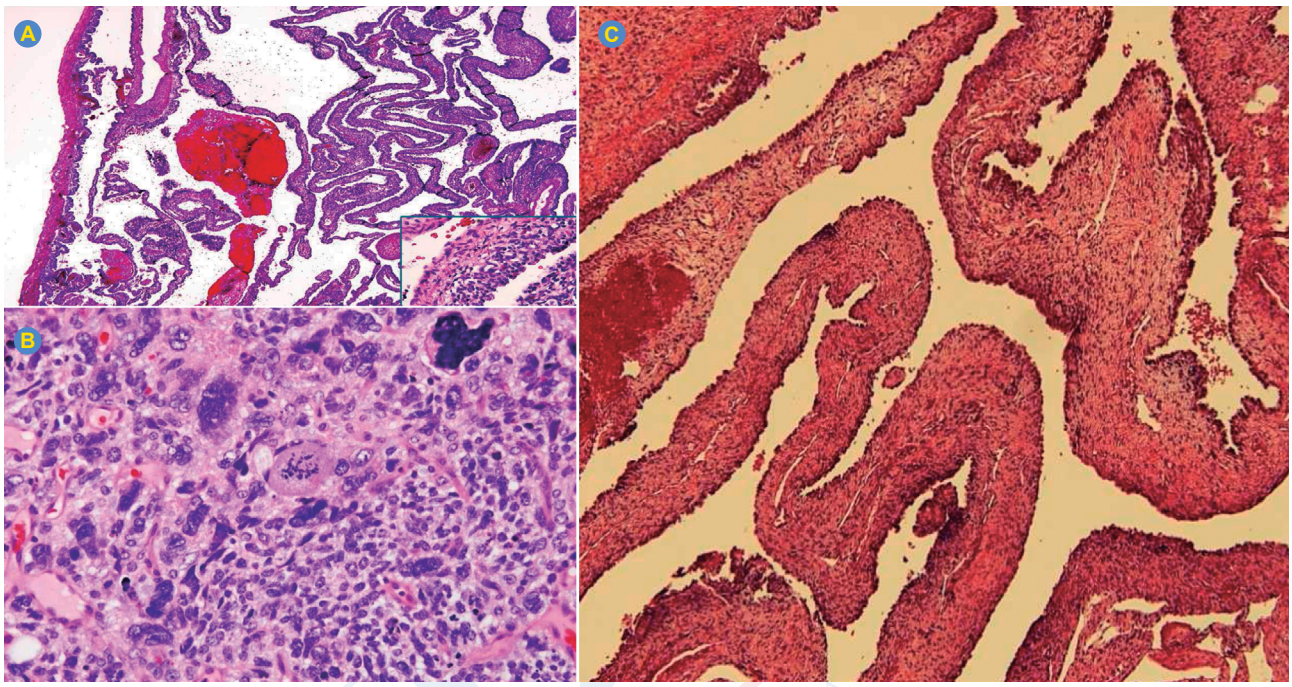

Figure 1 – (A) Pleuropulmonary blastoma type I showing the characteristic, multicystic architecture of the lesion in the lung periphery. Note the uniform cellularity of the septa and the presence of rhabdomyoblasts beneath the epithelial lining (inset). (B) Pleuropulmonary blastoma type III showing the marked anaplasia with a background of high-grade sarcoma. Many of the background cells were positive for desmin and myogenin. (C) Pleuropulmonary blastoma type Ir showing the similar multicystic architecture, but the stroma of the septa is hypocellular with a fibrous background. Note the absence of a primitive small cell population beneath the lining epithelium.

Table 1 – Features of *DICER1*-related tumor predisposition (adapted from references[18,19,42-45])

Features	**Percentage of individuals with a *DICER*1 germline pathogenic variant who exhibit the feature**
Pleuropulmonary blastoma	Lung cysts/type Ir PPB in 25% - 40%; PPB types I, II, and III in < 10%; over 75% of children with PPB had a *DICER1* germline pathogenic variant.
Multinodular goiter	32% of women; 13% of men (by age 20) 75% of women; 17% of men (by age 40)
Ovarian sex cord-stromal tumors	< 10% ~ 50% of persons with Sertoli-Leydig cell tumor and gynandroblastoma had a *DICER1* germline pathogenic variant[42]
Cystic nephroma	≤ 10%
Ciliary body medulloepithelioma	~ 3%
Differentiated thyroid carcinoma	Rare, 16- to 24-fold increased risk
Nasal chondromesenchymal hamartoma	Rare, ~ 1% of persons ascertained by family history (non-probands)
Other tumors: Embryonal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, CNS sarcomas, presacral malignant teratoid tumor, and other CNS embryonal tumors/embryonal tumor with multilayer rosettes-like	Rare
Multicystic hepatic lesions[43]	Very rare
Macrocephaly	~ 42%

CNS: central nervous system; PPB: pleuropulmonary blastoma

Table 2 – Situations involving neonatal pulmonary cysts for which *DICER1* gene testing should be performed

- When either parent carries a known germline *DICER1* mutation; generally after birth, and ideally before three months of age.[53]
- Children with a family history suggestive of *DICER1* tumor predisposition.[53]
- Infants and children with bilateral, septated, or multiple lung cysts, as these findings are suggestive of PPB.[53]
- In children who underwent resection of their CPAM and whose histological examination revealed a PPB.[52,53]
- Children with lung and renal cysts.[53]
- Testing should be considered for children with a unifocal CPAM, even without symptoms and in the absence of a family history suggestive of *DICER1*-related tumor predisposition, especially those who are under clinical surveillance and whose surgical resection is planned after four to six months of age as knowing the child's *DICER1* status before the planned surgery allows clinicians to determine whether earlier intervention is warranted.[53]

CPAM: congenital pulmonary airways malformation; PPB: pleuropulmonary blastoma

Table 3 – Stepwise algorithm for CPAM/PPB and *DICER1* testing

Step	Action/Assessment	Key points/Criteria
1. Prenatal findings	Detection of pulmonary cystic or solid lesions (US/fetal MRI)	Evaluate size, location, unifocal vs. multifocal, CPAM features
2. Postnatal work-up	Chest x-ray and/or CT; clinical monitoring	Identify suspicious features: large, septated, atypical cysts; progressive growth; symptoms
3. Features raising suspicion	Type 4 CPAM, multiple/bilateral cysts, symptomatic lesion, atypical histology; concurrent renal or other cystic lesions	Presume **Type I/Ir PPB** until excluded
4. Family history assessment	Detailed history of *DICER1*-related tumors	Positive history increases indication for genetic testing though family history may be negative even in the setting of a familial variant due to incomplete penetrance
5. *DICER1* testing criteria	**See Table 2**	If initial testing negative or only RNase IIIb hotspot variant, consider additional evaluation (deletion/duplication, intronic/splice site, RNA analysis)*
6. Surveillance cadence	Chest imaging and clinical follow-up	Chest x-ray every six months until 8 years, then yearly until 12 years; chest CT at three months if infant positive for a *DICER1* variant; low-dose CT ~ two and a half years if initial CT negative*
7. Surgical triggers	Significant symptoms, rapid growth, concerning radiology/histology	Multidisciplinary decision incorporating *DICER1* status

CPAM: congenital pulmonary airways malformation; CT: computed tomography; MRI: magnetic resonance image; RNase: ribonuclease; RNA: ribonucleic acid; US: ultrasound;
*: Please see reference[53] for additional surveillance guidelines