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PEDIATRIC ONCOLOGIC IMAGING

Imaging of DICER1 syndrome

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Abstract

DICER1 syndrome is a highly pleiotropic tumor predisposition syndrome that has been increasingly recognized in the last 10 years. Diseases in the syndrome result from mutations in both copies of the gene *DICER1*, a highly conserved gene that is critically implicated in micro-ribonucleic acid (miRNA) biogenesis and hence modulation of messenger RNAs. In general, susceptible individuals carry an inherited germline mutation that disables one copy of *DICER1*; within tumors, a very characteristic second mutation alters function of the other gene copy. About 20 hamartomatous, hyperplastic or neoplastic conditions comprise DICER1 syndrome. Most are not life-threatening, but some are aggressive malignancies. There are many unaffected carriers because penetrance is generally low; however, clinically occult thyroid nodules and lung cysts are frequent. Rare diseases of early childhood were the first recognized conditions in DICER1 syndrome, while other conditions affect adolescents and adults. The hallmarks of DICER1 syndrome are certain rare tumors including pleuropulmonary blastoma; cystic nephroma; ovarian Sertoli–Leydig cell tumor; sarcomas of the cervix, kidneys and cerebrum; pituitary blastoma; ciliary body medulloepithelioma; and nasal chondromesenchymal hamartoma. Radiologists are often the first practitioners to observe these diverse manifestations and play a primary role in recognizing DICER1 syndrome.

Keywords Children · Computed tomography · DICER1 syndrome · Magnetic resonance imaging · Pleuropulmonary blastoma · Tumor predisposition · Ultrasound

Introduction

DICER1 syndrome is an autosomal-dominant tumor predisposition syndrome caused by mutations in the gene *DICER1*. The syndrome affects individuals from birth to approximately 50 years of age and features a unique constellation of hamartomatous, hyperplastic or neoplastic conditions of the head, neck, thorax, abdomen and pelvis. DICER1 syndrome includes common conditions such as multinodular goiter and several rare but distinct conditions including pleuropulmonary blastoma (PPB), cystic nephroma, ovarian Sertoli–Leydig cell tumor, pituitary blastoma, ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma and sarcomas of the cervix, kidneys and cerebrum.

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DICER1 syndrome

The rudiments of DICER1 syndrome were reported in 1996 [1] among 45 families in which a child had PPB, an early childhood embryonal lung tumor first described in 1988 [2]. In 12 of these families, the child with PPB or a family member had lung cysts, cystic nephroma, multinodular goiter, embryonal rhabdomyosarcoma or another case of PPB [1]. In 2009 and 2011, additional associated conditions were described [3, 4], and germline loss-of-function mutations in *DICER1* were reported in 11 of 11 prototypical families [5]. Many further investigations have extended the range of syndrome phenotypes and clarified the underlying molecular pathology. The clinical and molecular basics of DICER1 syndrome have been reviewed [6].

Table 1 DICER1 syndrome phenotypes, relative frequency, ages at presentation, mortality, syndrome specificity, *DICER1* mutation testing recommendation, and radiologic differential diagnosis

Phenotypes (abbreviation)	Age range in years (peak)	Mortality	Specificity for DICER1 syndrome	*DICER1* mutation testing indicated	Radiologic differential diagnosis
Most frequent phenotypes					
Pleuropulmonary blastoma (PPB)	0–8	10–50%	High	Yes	Cystic: congenital pulmonary airway malformation (CPAM), intrapulmonary bronchogenic cyst, pneumatocele, persistent pulmonary interstitial emphysema, pleuropulmonary synovial sarcoma
Type I (cystic)	(0–2)	~10%			
Type II (cystic and solid)	(1–5)	~30%			
Type III (solid)	(1.5–6)	~50%			Solid: sarcoma, inflammatory myofibroblastic tumor, infantile hemangioma, adenocarcinoma, nuclear-protein-in-testis (NUT) midline carcinoma
PPB Type Ir (cystic)	Any age	No	High	Yes	Same as Type I (cystic) PPB
Multinodular goiter	2–40 (10–25)	No	Low, unless familial or age <18 years	Possibly[a,b]	
Cystic nephroma	0–15 (0–4)	No	High	Yes	Cystic partially differentiated nephroblastoma, cystic Wilms tumor, segmental cystic renal dysplasia, localized cystic disease of the kidney
Ovarian Sertoli–Leydig cell tumors	2–40 (10–25)	<10%	High	Yes	Germ cell tumor, other sex cord–stromal tumor, epithelial tumor
Macrocephaly	Any age	No	Low	Possibly[a]	
Moderately frequent phenotypes					
Differentiated thyroid carcinoma	5–45 (10–30)	<5%	Low, unless age <18 years	Possibly[a,c]	Nodular hyperplasia, adenoma, other carcinoma
Cervix embryonal rhabdomyosarcoma	4–45 (10–20)	<10%	High	Yes	Adenocarcinoma, fibroepithelial polyp
Nasal chondromesenchymal hamartoma	5–25 (8–20)	No	Moderate	Yes	Inverted papilloma, chondrosarcoma, rhabdomyosarcoma, lymphoma, esthesioneuroblastoma, nasoethmoidal encephalocele, nasal glioma, NUT midline carcinoma
Rare phenotypes					
Pituitary blastoma	0–2	~50%	Very high	Yes	Craniopharyngioma, adenoma, germinoma
Pineoblastoma	2–25 (2–10)	~50%	Moderate	Possibly[a,d]	Germinoma, pineocytoma, pineal parenchymal tumor of intermediate differentiation, tectal glioma
Ciliary body medulloepithelioma	3–10	No	Moderate	Yes	Retinoblastoma, melanoma, juvenile xanthogranuloma, metastasis
Juvenile hamartomatous intestinal polyps	0–20 (0–4)	No	Low	Possibly[a]	Other polyposis syndromes (e.g., juvenile polyposis, Peutz–Jeghers syndrome, Cowden syndrome, familial adenomatous polyposis)
Anaplastic renal sarcoma	2–20	Unknown	High	Yes	Wilms tumor, renal cell carcinoma
Bladder embryonal rhabdomyosarcoma	0–12	<10%	Undetermined	Possibly[a]	Inflammatory myofibroblastic tumor, urothelial neoplasm, nephrogenic adenoma, pheochromocytoma, rhabdoid tumor
Wilms tumor	3–8	<10%	Low	Possibly[a]	Renal cell carcinoma, anaplastic sarcoma of kidney
Cerebral sarcoma	Undetermined	Unknown	Undetermined	Yes	Glioma, embryonal tumor, atypical teratoid rhabdoid tumor
Very rare phenotypes					
Mesenchymal hamartoma of the liver	0–8 (0–3)	No	Undetermined	Possibly[a]	Hemangioma, hepatoblastoma, undifferentiated embryonal sarcoma
Infantile cerebellar embryonal tumor	0–1	Unknown	High	Yes	Medulloblastoma, medulloepithelioma, atypical teratoid rhabdoid tumor
Ovarian embryonal rhabdomyosarcoma	Undetermined	Unknown	High	Yes	Germ cell tumor, sex cord–stromal tumor, epithelial tumor
Gynandroblastoma	Undetermined	Unknown	High	Yes	Other sex cord–stromal tumor, germ cell tumor, epithelial tumor
Cervix primitive neuroectodermal tumor (PNET)[e]	Undetermined	Unknown	Undetermined	Yes	Same as cervical embryonal rhabdomyosarcoma
Well-differentiated fetal adenocarcinoma	Undetermined	Unknown	Low	Possibly[a]	Other lung carcinoma

Table 1 (continued)

Phenotypes (abbreviation)	Age range in years (peak)	Mortality	Specificity for DICER1 syndrome	*DICER1* mutation testing indicated	Radiologic differential diagnosis
Uncertain association with *DICER1* mutation					
Congenital phthisis bulbi, pulmonary sequestration, neuroblastoma, thymoma, teratoma					

[a] "Yes" if the patient or other family members exhibit other DICER1 syndrome phenotypes

[b] "Yes" if familial or <18 years of age

[c] "Yes" if <18 years of age

[d] "Yes" if <10 years of age

[e] Cervical PNET might be a variant of cervical embryonal rhabdomyosarcoma

Adapted from Table 1 in reference [6], with permission

Table 1 presents the currently recognized DICER1 syndrome phenotypes, their relative frequencies and specificities for the syndrome, age of presentation, mortality and radiologic differential diagnoses. Even without a suggestive family history, the following conditions are sufficiently concerning to warrant evaluation for *DICER1* genetic testing: PPB, cystic nephroma, Sertoli–Leydig cell tumor, pituitary blastoma, ciliary body medulloepithelioma, embryonal rhabdomyosarcoma of uterine cervix or ovary, gynandroblastoma, anaplastic sarcoma of kidney, nasal chondromesenchymal hamartoma, cerebral sarcoma, infant cerebellar embryonal tumor, pineoblastoma diagnosed before age 10 years, differentiated thyroid carcinoma diagnosed before age 18 years, or multinodular goiter diagnosed before age 18 years.

Four recent publications address certain aspects of DICER1 syndrome imaging: imaging of primary childhood lung tumors [7], imaging of hereditary renal cystic disorders [8], imaging of DICER1 syndrome phenotypes observed at a single institution [9] and imaging of tumor predisposition syndromes including one DICER1 case [10]. No comprehensive review of the imaging of DICER1 syndrome phenotypes has been published to date.

Radiologists play a significant role in the care of children with DICER1 syndrome and might be the first to observe manifestations of the syndrome, some of which are clinically occult or noted incidentally while imaging for unrelated reasons (Fig. 1). Systematic family-based cohort surveys have shown that asymptomatic lung cysts detectable by CT and multinodular goiter detectable by ultrasonography are frequent [11–13]. In addition, radiologists are involved in tumor staging, therapy response assessment, relapse surveillance and screening of mutation carriers.

Although the penetrance for clinical expression of the full range of syndrome phenotypes is not well established, reports on the quantitative risks of certain phenotypes in mutation carriers are emerging [12, 13]. Most germline *DICER1* mutation carriers live generally healthy lives. In non-proband *DICER1* mutation carriers, the estimated ranges of cumulative neoplasm risk are 1–10% by age 10 years, 3–15% by age 20 years and 6–21% by age 40 years [13]. Mutation carriers who develop clinically overt disease tend to manifest one or two phenotypes in childhood or adolescence [11], with 22% of those with one neoplasm developing multiple neoplasms over time [13], and some individuals developing up to eight phenotypes [1, 14, 15]. Bilateral disease in the thyroid, lungs, kidneys or ovaries is not unusual. After 10 years of age, females are more affected than males because of gynecologic phenotypes and more frequent thyroid disease [13].

DICER1 function and mutations

DICER1 is a highly conserved gene encoding DICER1 enzyme. The enzyme cleaves precursors to produce mature micro-

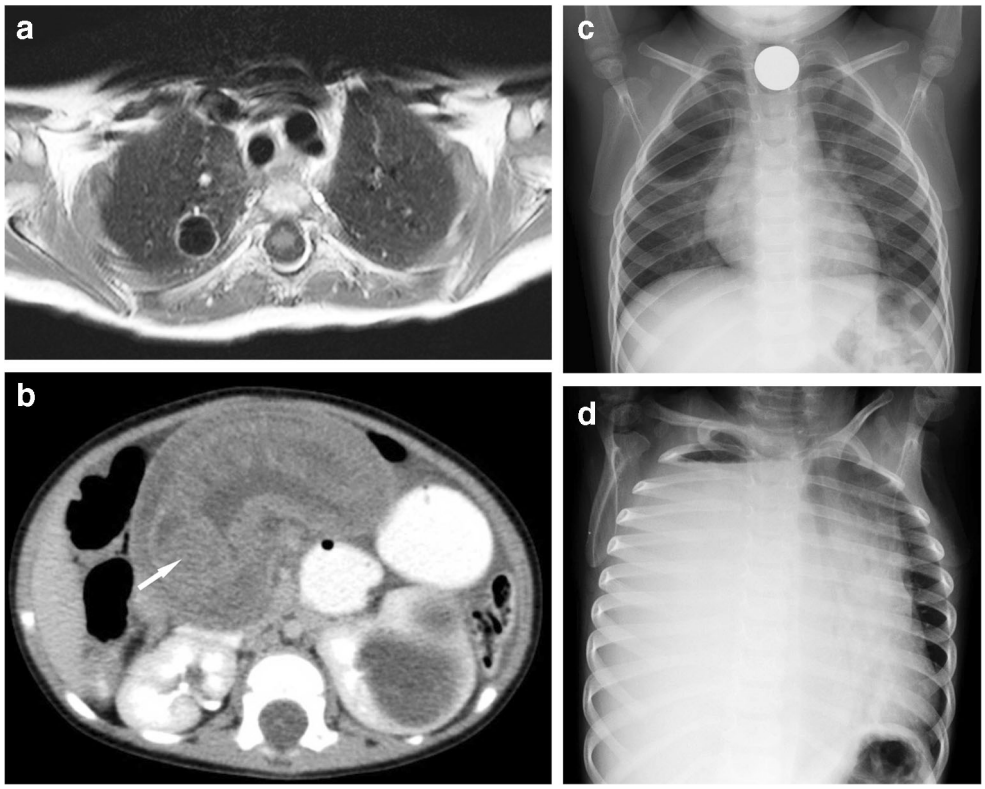

Fig. 1 Incidental observations of DICER1 syndrome phenotypes. **a** MRI in a 3-year-old boy being monitored for drop metastases from pineoblastoma diagnosed at age 2 years. Axial gadolinium-enhanced T1-weighted thoracic spine MR image reveals a thin-walled air-filled unilocular lung cyst of the right upper lobe. **b** CT in a 6-month-old boy with abdominal pain and distension. Axial contrast-enhanced abdominal CT image reveals a left renal cystic mass and a small bowel intussusception with an intraluminal polypoid mass (*arrow*). Subsequent left nephrectomy and bowel resection revealed a cystic nephroma of the left kidney and a juvenile hamartomatous polyp as lead point for the intussusception. **c, d** Anteroposterior (AP) chest radiograph in a 24-month-old girl for coin ingestion (**c**) shows a coin in the proximal esophagus and a right upper lobe lung cyst, considered a pneumatocele despite no history of pneumonia; image (**d**), in the same girl at age 30 months presenting for respiratory distress, shows near opacification of the right hemithorax and leftward mediastinal shift from mass effect. Resected right lung mass was a Type II pleuropulmonary blastoma (PPB). Images (**c**) and (**d**) courtesy of Kenneth Heym, MD

ribonucleic acids (miRNAs) that repress or silence expression of protein-coding messenger RNA [6]. Both benign and malignant DICER1 tumors usually result from a predisposing germline mutation in one copy of the *DICER1* gene and an acquired tumor-only mutation in the other copy. In a minority of cases, the first or second *DICER1* change is not a mutation but a partial or complete loss of *DICER1* genetic material affecting one allele.

Three categories of predisposing mutations (rarely, deletions or rearrangements) in *DICER1* are recognized: (1) a germline mutation inherited from one parent in the great majority of cases; (2) a de novo germline mutation in ~10%; and (3) mosaicism (a de novo early, post-zygotic mutation that is distributed unevenly among tissues of the developing fetus) in ~10% of cases [11, 16]. A predisposing mutation can occur virtually anywhere in the gene (Fig. 2) and usually disables function of that gene copy. The prevalence of loss-of-function germline *DICER1* mutations in the general population is estimated at 1 in 10,600 people [17].

A mutation in the second copy of *DICER1* is found in most tumors, whether malignant or benign. This second mutation yields a dysfunctional DICER1 protein that produces an abnormal mix of silencing miRNAs. This second somatic mutation very characteristically affects one of five specialized *DICER1* "hotspot" codons, resulting in altered cleavage activities of the protein [6] (Fig. 2). Instead of a second *DICER1* mutation, occasionally the molecular change in a tumor is loss of the second copy of *DICER1* (loss of heterozygosity) [11, 18–21] (Fig. 2). In children with more than one tumor, the genetic event in each tumor often involves a different hotspot, indicating that each tumor's genetic evolution is independent of the evolution in the child's other tumor(s) [11, 16, 22–24]. In children with mosaicism, the predisposing mutation often *directly* alters a *DICER1* hotspot codon; these children tend to develop many tumors [11, 15, 25].

A child with a *DICER1* mutation might develop a tumor *unrelated* to his or her predisposition; such a tumor would not have a second deleterious *DICER1* mutation, and the tumor would not be considered part of DICER1 syndrome [26]. On the other hand, a child who has no relevant family history and no known predisposition to DICER1 syndrome can develop

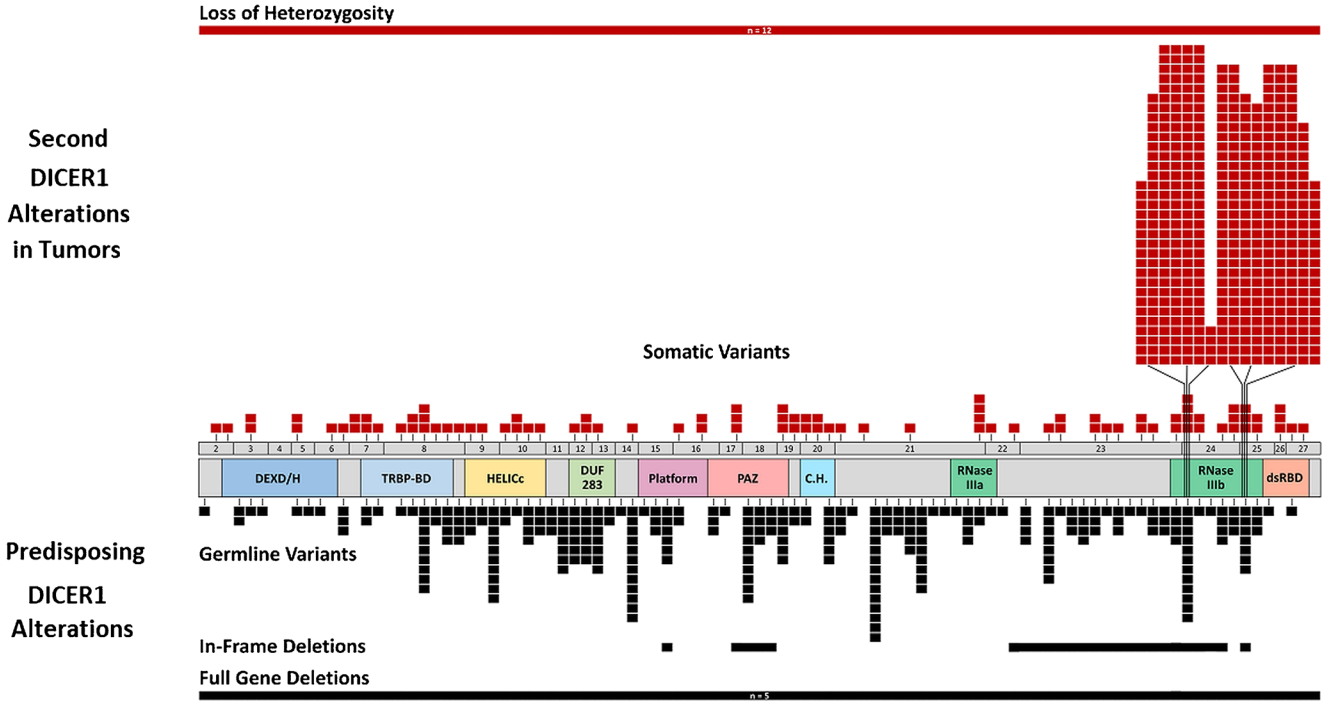

Fig. 2 Linear representation of DICER1 protein and its domains. Black squares below the protein diagram indicate the highly variable amino acid residues affected by 285 observed predisposing *DICER1* pathogenic variants (a variant in a family is counted once). Red squares above the diagram indicate amino acid residues affected by 535 observed somatic mutations, of which 435 affect five ribonuclease IIIb "hotspot" residues. Bars represent small and large deletions in *DICER1* as predisposing *DICER1* alterations or loss of heterozygosity as a somatic second event. Loss of heterozygosity is a more frequent second event than IIIb mutations in two syndrome phenotypes: pituitary blastoma and pineoblastoma. Diagram courtesy of Leanne de Kock

one tumor with two *DICER1* mutations. Following extensive investigation to rule out *DICER1* mutations elsewhere in the child, the child can be considered to have "tumor-restricted" DICER1 disease [11, 27]; the child does not have DICER1 syndrome and is not at risk for other DICER1 tumors or passing a *DICER1* abnormality to offspring. Verifying that mutations are restricted to one tumor requires extensive investigation but doing so greatly benefits the patient and family [26].

DICER1 syndrome phenotypes

Pleuropulmonary blastoma

Pleuropulmonary blastoma is the most common primary childhood lung malignancy and is the sentinel disease reported in early DICER1 syndrome families [1, 28]. Approximately 75% of PPB cases are associated with germline *DICER1* mutations, ~10% with mosaic mutations and ~10% with tumor-restricted mutations. Among germline mutations causing PPB, 87% are inherited and 13% de novo [11].

Among all *DICER1* mutation carriers, PPB is the most frequent serious neoplasm [13]. PPB presents in three primary manifestations along an age-related continuum: cystic Type I PPB in the youngest children including newborns, cystic/solid Type II PPB in older infants and young children, and solid Type III PPB in children up through age 6 years, with rare older exceptions [13, 29–31] (Table 1; Fig. 3).

Type I PPB cysts are an early malignancy characterized by an often-subtle population of sub-epithelial primitive mesenchymal cells. Type I PPB might be detected in utero or at birth [31, 32] (Fig. 4). Meticulous pathological examination is required to identify primitive cells indicative of Type I PPB in early childhood lung cysts to avoid an erroneous diagnosis of cystic congenital pulmonary airway malformation (CPAM).

The primitive cells in cystic PPB can coalesce into a "cambium layer" [33] and further sarcomatous overgrowth of this layer results in Types II or III PPB [3, 33, 34] (Fig. 3). Type II PPB is defined on pathological inspection by findings of grossly detectable solid nodules associated with a cyst. Large Type II tumors often contain intra-cystic botryoid masses (sarcoma botryoides), similar to the growth pattern of DICER1 syndrome tumors involving other hollow or fluid-filled structures (cervix/vagina, urinary bladder, nasal cavity, ocular globe), as discussed later. Type III PPB is solid with no cystic elements. It is generally thought that not every PPB follows a progression pattern of Types I to II to III. Some PPBs presumably develop directly as Types II or III.

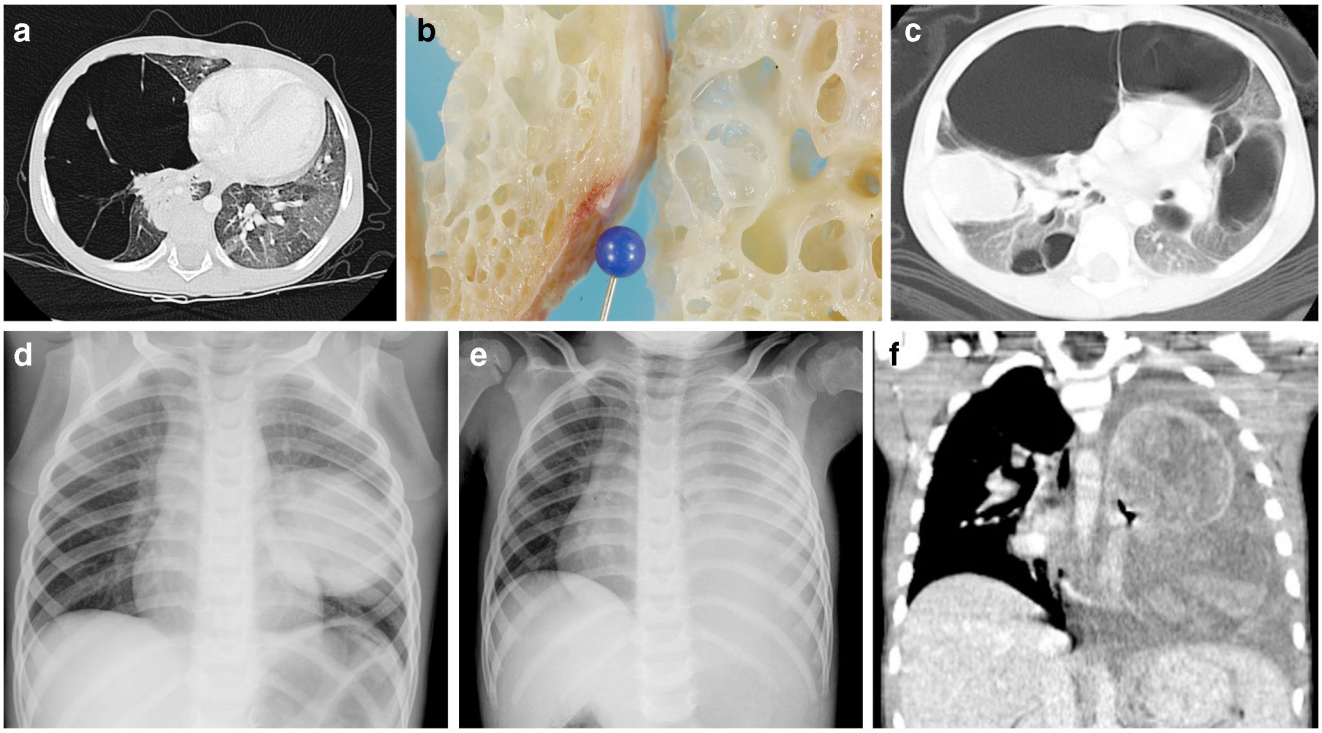

Fig. 3 Pleuropulmonary blastoma (PPB). **a** Type I PPB in a 3-month-old boy with respiratory distress. Axial chest CT image shows a thin-walled air-filled multilocular right lung cyst pathologically diagnosed as Type I PPB. A small septal nodule depicted within the cyst, suggesting Type II PPB, was mucus-filled rather than a solid tumor. **b** Type I PPB unfixed gross pathology specimen from a different case reveals a multiloculated cystic structure. Imaging typically does not fully depict the extensive septations. **c** Type II PPB in 25-month-old boy who had Type I PPB resected at 5 days of age. Axial chest CT image shows multiple bilateral thin-walled air-filled lung cysts and a nearly solid right lung mass pathologically diagnosed as Type II PPB (adapted from Fig. 2 from reference [6], with permission). **d–f** Type III PPB in a 3-year-old boy. Anteroposterior (AP) chest radiograph at the boy's presentation with cough and fever (**d**) was initially interpreted as showing a "round pneumonia"; (**e**) AP chest radiograph obtained 2 weeks later for increasing respiratory distress demonstrates a nearly opacified left hemithorax and rightward mediastinal shift; (**f**) coronal contrast-enhanced chest CT image shows a large heterogeneously enhancing left pulmonary mass with intratumoral hemorrhagic necrosis, left pleural effusion from tumor rupture into the pleural space, and rightward shift of the mediastinal structures from mass effect. Image (**b**) courtesy of Adrian Charles, MD, PhD

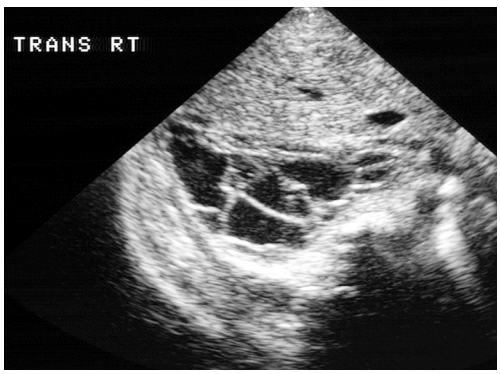

Fig. 4 Neonatal Type I pleuropulmonary blastoma (PPB). Transverse chest ultrasound image of a newborn boy of 41 2/7 weeks' gestational age with respiratory distress shows a fluid-filled, multilocular lung cyst of the right lower lobe. The mass was initially detected on a fetal ultrasound exam performed at 40 weeks' gestation for maternal size exceeding dates. The cyst was pathologically confirmed as a Type I PPB following resection on the second day of age. At 2 months of age, the boy was noted to have a 6-mm-diameter cyst of the left lung, and this cyst was pathologically confirmed as an additional Type I PPB following resection at 3 months of age

The solid portions of Types II and III PPBs are an aggressive mixed-pattern sarcoma, which can be fulminant [3]. Histological confirmation of the mixed pattern sarcoma requires an adequate biopsy sample, and surgical biopsies are preferred over image-guided percutaneous needle sampling. Five-year overall survival rates for Types I, II and III PPB are 91%, 71% and 53%, respectively [29]. Thus the age continuum of Types I, II and III PPB also represents a biological evolution and severity continuum. Because Type I PPB can evolve into Types II and III, early detection and surgical extirpation of cystic Type I PPB are considered advantageous [3, 34, 35].

Also recognized pathologically is cystic Type Ir (regressed) PPB, which is cystic PPB without primitive cells [33, 34] (Figs. 1 and 5). Lacking the primitive cells, Type Ir cysts are not thought to progress to Types II or III PPB. In non-proband *DICER1* mutation carriers, the prevalence of Type Ir cysts, which can be discovered at any age, is reported to be 27% [13]. Lung cysts detected by imaging in a *DICER1* mutation carrier can presumptively be considered Type Ir PPB after the

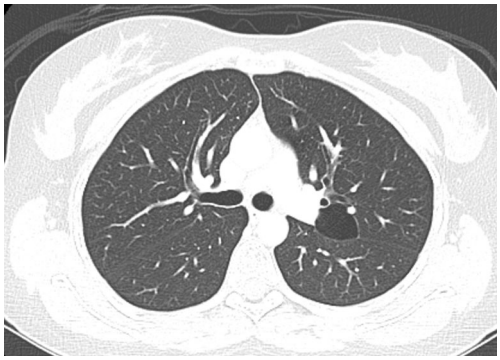

Fig. 5 Presumptive Type Ir pleuropulmonary blastoma (PPB). Axial chest CT image shows a small thin-walled air-filled unilocular lung cyst near the left hilum in a 17-year-old girl with a history of pineoblastoma (age 10 years), Sertoli–Leydig cell tumor (age 16 years) and cervical embryonal rhabdomyosarcoma (age 17 years). Image courtesy of Sharon Plon MD, PhD

age of about 8 years; however, progression of cystic disease after early childhood has rarely been reported [36].

On imaging, the cysts of Types I, Ir and II PPB are typically thin-walled and air-filled [3, 37] (Figs. 1, 3, 5 and 6). However, they contain fluid in the prenatal and early neonatal periods [31] (Fig. 4), and they are sometimes thick-walled, opacified or contain air-fluid levels when superinfected. Type I cysts might be unilocular or multilocular, and vary in size from subcentimeter to >10 cm diameter, involving nearly an entire hemithorax [37]. Cyst septations are typically delicate and not fully depicted on CT images compared to pathology specimens (Fig. 3). There are no systemic feeding vessels [37]. Spontaneous pneumothorax is reported in ~30% of cystic PPB [29] (Fig. 6). Cystic PPB is bilateral in ~20% of cases (Fig. 3), and ~35% of unilateral cases are multifocal [29].

Imaging of Type II PPB might reveal mural nodules or sarcoma botryoides (Fig. 6). Although the solid component might be occult on imaging and revealed only in the pathology specimen [30], a predominantly solid PPB with gross or microscopic cysts is also considered Type II (Fig. 3). Type III PPB is entirely solid with the exception of possible areas of liquefactive or hemorrhagic necrosis. Solid Type III PPB not infrequently involves an entire hemithorax, causing mediastinal shift, and a pleural effusion is present in ~50% of cases [29] (Fig. 3). A child with Types II or III PPB might present with fever, cough or malaise such that the corresponding opacity on a chest radiograph is often initially misdiagnosed as pneumonia (Fig. 3) and only revealed as a tumor on further studies after failure of antibiotic therapy.

Cystic PPB and CPAM are easily confused on imaging [3, 37, 38]. CPAM is estimated to be ~5–20 times more common than PPB [3] and is the presumptive diagnosis for most children undergoing surgery for lung cysts. In an asymptomatic child, imaging findings can be used to guide a decision to observe or resect a lung cyst. Multifocal or bilateral cysts, cyst complexity (septations or solid mural nodules), spontaneous pneumothorax, family history or incidental imaging observation of other DICER1 phenotypes favor PPB [3, 37, 38]. In contrast, prenatal detection in the mid-second trimester, presence of a systemic feeding vessel or a hyperinflated region favor CPAM [32, 37]. It should also be noted that type 4 CPAM and Type I PPB might be the same entity described under different rubrics [3, 33].

Several other conditions can mimic cystic PPB, with or without complicating pneumothorax. Heritable conditions with lung cysts include Cowden syndrome, Birt–Hogg–Dubé syndrome and, in some cases, lymphangioleiomyomatosis (tuberous sclerosis complex). Sporadic conditions with lung cysts include Langerhans cell histiocytosis, intrapulmonary bronchogenic cysts, pneumatoceles, persistent pulmonary interstitial emphysema, and pleuropulmonary synovial sarcoma.

In Cowden syndrome, a prototype PTEN (phosphate and tensin homolog) hamartoma syndrome, lung cysts,

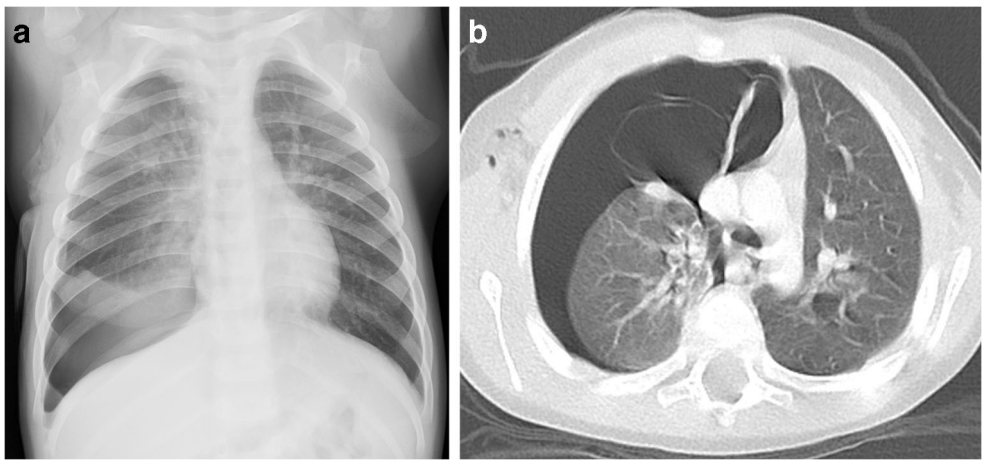

Fig. 6 Type II pleuropulmonary blastoma (PPB) with spontaneous pneumothorax. **a** Anteroposterior chest radiograph in a 2-year-old boy demonstrates a right-side pneumothorax that developed spontaneously and recurred after chest tube removal. **b** Axial chest CT image from the same patient depicts a thin-walled air-filled cyst with a small peripheral solid ccomponent (*arrow*) arising from the right lung. The cyst was biopsied but no neoplastic elements were identified. Follow-up imaging 7 months later showed persistence of a cystic lesion along the right lung and mediastinum. The lesion was subsequently resected, with pathological inspection revealing a Type II PPB

hamartomatous gastrointestinal polyps, multinodular goiter and follicular thyroid cancer might occur as in DICER1 syndrome, although the lung cysts in Cowden syndrome are noted in adulthood, and Cowden syndrome is characterized by mucocutaneous lesions and malignancies (breast, endometrial) that are not known to be associated with DICER1 syndrome [39]. Individuals with Birt–Hogg–Dubé syndrome caused by germline *FLCN* mutations develop lung cysts with a strong predilection for the lower medial lung zones and skin fibrofolliculomas at age 20 years or later, and manifest an elevated risk of renal oncocytomas and chromophobe renal cell carcinomas, unlike those with DICER1 syndrome [40]. Lymphangioleiomyomatosis and Langerhans cell histiocytosis (LCH) are additional conditions associated with lung cysts and spontaneous pneumothorax, but the cysts in these conditions are typically much more numerous than in DICER1 syndrome, are associated with tuberous sclerosis complex and occur almost exclusively in women of childbearing age in lymphangioleiomyomatosis [41], and are often accompanied by extrapulmonary (skin, liver or bone) involvement in LCH [42].

Intrapulmonary bronchogenic cysts typically contain mucinous or hemorrhagic fluid postnatally rather than air alone, and they are often symptomatic at diagnosis [43]. Pneumatoceles can be complicated by spontaneous pneumothorax but are typically sequela of infection, especially cavitary pneumonia, or a lung laceration [44]. Pulmonary interstitial emphysema typically presents on radiography as multiple tubular lucencies following barotrauma in a preterm infant and resolves over time but occasionally occurs in unventilated term infants and persists as a lung cyst with or without complicating pneumothorax [45]. Pleuropulmonary synovial sarcoma can present as a cystic lesion with pneumothorax, but this typically occurs in teen years or later and manifests in the *SYT/SSX* fusion gene [46].

While fetal and neonatal PPB is cystic, other fetal and neonatal lung tumors tend to be solid, including fetal lung interstitial tumor [47], congenital peribronchial myofibroblastic tumor [32], infant pulmonary teratoid tumor [48] and congenital hemangioma [49]. In older infants and children, the differential diagnostic considerations for a solid pleuropulmonary mass include Type II or Type III PPB, inflammatory myofibroblastic tumor, infantile hemangioma, nuclear-protein-in-testis (NUT) midline carcinoma, adenocarcinoma and sarcomas [7, 49].

Imaging is important for detecting complications of PPB. PPB can extend into the cardiac chambers and thoracic great vessels, and embolize during resection to cerebral and other arteries [50, 51]. Preoperative cardiovascular ultrasound can be considered but has not been widely utilized. The cerebrum is the most frequent site of distant PPB metastasis, occurring in 11% of all people diagnosed with Types II and III PPB [29]. Cerebral metastases are rare at PPB diagnosis and tend to occur within 30 months of PPB diagnosis, often without chest recurrence [29, 51]. Symptomatic cerebral metastases have been reported as soon as 6 weeks after a normal surveillance magnetic resonance (MR) exam [51], and a practical strategy for early detection of metastasis is problematic with such fulminant disease. Meningeal and spinal cord metastases are exceedingly rare [51]. Lytic bone metastases occur but are rare at diagnosis and thereafter [29].

Other thoracic conditions

One case each of well-differentiated fetal adenocarcinoma of lung [22] and pulmonary sequestration [52] has been reported in proven *DICER1* mutation carriers (Table 1). Adult-type biphasic pulmonary blastoma is distinctly different from PPB and not a phenotype of DICER1 syndrome, yet it can have tumor-related *DICER1* mutations [27].

Multinodular goiter and differentiated thyroid cancer

Multinodular goiter, including small US-detected thyroid nodules, is the most frequent and least specific phenotype in DICER1 syndrome [11, 12, 39, 53] (Table 1; Fig. 7). A systematic family-based cohort survey of *DICER1* mutation carriers revealed that multinodular goiter diagnoses begin in the first and second decades of life and that by age 40 years, 75% of women and 17% of men had multinodular goiter or thyroidectomy, compared to 8% of female and 0% of male genetically normal family controls [12]. Early onset multinodular goiter, especially if familial, or the coexistence of multinodular goiter and other syndrome phenotypes strongly suggest DICER1 syndrome [12, 54].

A unique contribution to the understanding of DICER1 syndrome has arisen from the study of multinodular goiter. Each individual hyperplastic thyroid nodule is likely to express a *different* hotspot change in *DICER1* from the hotspot changes in nearby nodules [55]. The clinical implication is that even after partial removal of the thyroid, additional genetic change can produce new nodules.

Differentiated thyroid carcinoma (papillary or follicular variants) also occurs in DICER1 syndrome [12, 56, 57] (Fig. 7). Differentiated thyroid carcinoma in DICER1 syndrome is diagnosed between ages 8 years and 43 years, with a 16- to 24-fold increase in risk compared with population controls [12]. Differentiated thyroid carcinoma in children younger than 18 years or differentiated thyroid carcinoma at any age with other syndrome phenotypes also strongly suggests DICER1 syndrome. Adult-onset differentiated thyroid carcinoma alone does not suggest DICER1 syndrome [58].

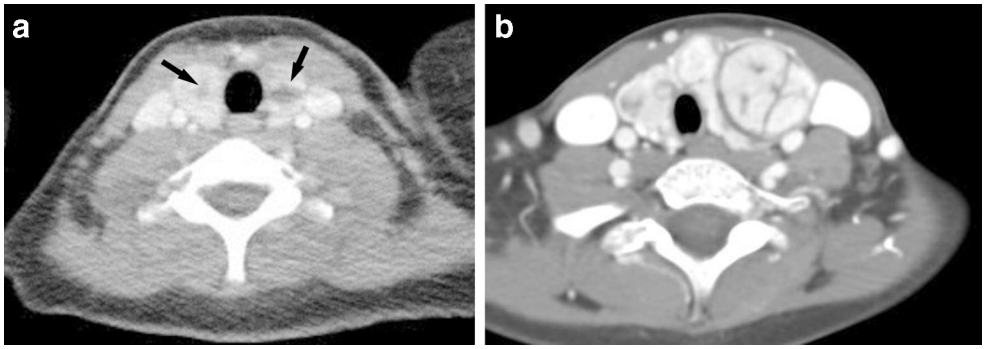

Fig. 7 Thyroid manifestations of DICER1 syndrome. **a** Multinodular goiter in a 13-year-old girl. Axial contrast-enhanced cervical CT image shows bilateral low-attenuation thyroid nodules (*arrows*), proved by needle biopsy to be hyperplastic nodules. The girl also had multiple Type Ir pleuropulmonary blastoma (PPB) lung cysts; her sister had bilateral Sertoli–Leydig cell tumors and multinodular goiter. **b** Differentiated (follicular variant of papillary) thyroid carcinoma in a 9-year-old girl who had Type III PPB at age 2 years. Axial contrast-enhanced cervical CT image reveals bilateral thyroid nodules, with a dominant left lobe nodule proved after thyroidectomy to be differentiated thyroid carcinoma. Image (**a**) courtesy of the family and Marci Lesperance, MD, and image (**b**) courtesy of B.-K. Park, MD

Ovarian Sertoli–Leydig cell tumors and other sex cord–stromal cell tumors

Ovarian Sertoli–Leydig cell tumor accounts for <1% of ovarian tumors but is highly characteristic of DICER1 syndrome [54, 59, 60] (Table 1). In 1974, the co-occurrence of Sertoli–Leydig cell tumor and multinodular goiter was observed by Jensen, Norris and Fraumeni [61] (OMIM 138800) and is now explained by *DICER1* mutations, as are bilateral and familial Sertoli–Leydig cell tumors [15, 62]. A *DICER1* hotspot change was found in 97% of 37 Sertoli–Leydig cell tumors in one study [63] and in 100% of 30 moderately and poorly differentiated Sertoli–Leydig cell tumors in another study [62]. Among 37 cases of Sertoli–Leydig cell tumor, 60% occurred in germline *DICER1* mutation carriers, and those with predisposing *DICER1* mutations had good overall and recurrence-free survival [63]. Sertoli–Leydig cell tumor associated with *DICER1* mutations can occur from early childhood to age 40+ years, with 75% of cases occurring before age 30 years [60, 64]. On imaging, Sertoli–Leydig cell tumor appearance is variable, ranging from a predominantly solid mass with small cysts to a multilocular cystic mass [65, 66] (Fig. 8). Metachronous Sertoli–Leydig cell tumors have been noted in individuals with predisposing *DICER1* mutations up to 14 years after initial diagnosis, which implies a need for prolonged surveillance, and the finding of a contralateral ovarian mass cannot be assumed to be a recurrence in an individual with *DICER1* mutation and a previously diagnosed ovarian Sertoli–Leydig cell tumor [63]. Ovarian sex cord–stromal tumors other than Sertoli–Leydig cell tumor, including juvenile granulosa cell tumor and gynandroblastoma, have also been reported in *DICER1* mutation carriers [60, 63], with the incidence of gynandroblastoma greatly increased in *DICER1* mutation carriers compared to the general population [13] (Table 1).

Kidney tumors

The kidney is frequently affected in DICER1 syndrome, with cystic nephroma and anaplastic sarcoma of kidney being the most closely associated conditions [13]. Nephromegaly, Beckwith–Wiedemann-like dysplasia and ill-defined maldevelopmental renal morphology have rarely been observed [15, 25]. A recent survey of *DICER1* mutation carriers

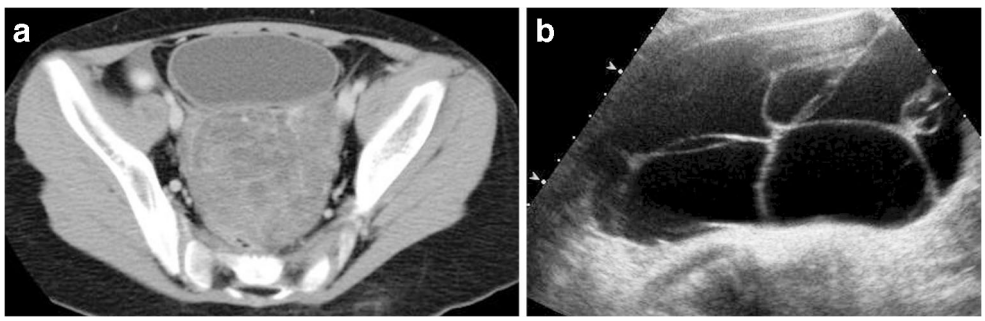

Fig. 8 Ovarian Sertoli–Leydig cell tumors. **a** Surveillance imaging in a 13-year-old girl following cystic nephroma resection. Axial contrast-enhanced CT image depicts a heterogeneous mixed solid–cystic retrovesicular mass arising from the left ovary (case is also discussed in reference [6]). **b** Amenorrhea and pelvic mass in a 16-year-old girl. Gray-scale abdominal US image demonstrates a multilocular cystic mass of the right ovary. Image (**a**) courtesy of the family and David Plager, MD

revealed renal structural abnormalities in 6%, including collecting system duplication, ureteropelvic junction obstruction, and incomplete renal rotation [67].

Cystic nephroma

Cystic nephroma is strongly associated with *DICER1* mutations [68–70] (Table 1). In a study of 20 cases of cystic nephroma, 15 had likely germline mutations and 18 had mutations altering hotspot codons [70]. Cystic nephroma primarily affects children younger than 4 years [68, 70], with rare later exceptions [24]. A condition similar to cystic nephroma that occurs in women older than 50 years is now considered separate from pediatric cystic nephroma [71, 72].

Prognosis following wedge resection or nephrectomy is generally excellent, although renal transplantation has rarely been required in the setting of bilateral nephrectomy for extensive masses [73]. On imaging, cystic nephroma manifests as a multilocular cystic renal mass (Fig. 9). Cystic nephroma, cystic partially differentiated nephroblastoma and cystic Wilms tumor can have similar imaging appearances [8, 74, 75], but a child with bilateral or multifocal complex renal cysts, other DICER1 syndrome manifestations or a positive family history is likely to have cystic nephroma. Non-neoplastic conditions that resemble cystic nephroma on imaging include segmental cystic renal dysplasia and localized cystic disease of the kidney [76]. The imaging features of acquired and heritable renal cystic conditions are reviewed elsewhere [8, 75].

Anaplastic sarcoma of kidney

Anaplastic sarcoma of kidney is a rare but important recent addition to DICER1 syndrome (Fig. 9), occurring at ~2–20 years old. First described in 2007 [77], this sarcoma was linked to *DICER1* mutations in 2014 [23, 70]. Some anaplastic sarcomas of kidney are closely related to cystic nephroma in that patients might have a history of cystic nephroma and remnants of cystic nephroma might be present microscopically in the anaplastic sarcoma of kidney [70]. Development of an anaplastic sarcoma of kidney was observed in a *DICER1* mutation carrier at the site of a cystic renal mass detected years earlier [23] (Fig. 9). In another *DICER1* mutation carrier, a large multiseptated cystic renal mass strongly suggestive of cystic nephroma harbored rare anaplastic nuclei and atypical mitoses (not consistent with cystic nephroma or cystic partially differentiated nephroblastoma), and the tumor was considered a nascent anaplastic sarcoma of kidney (cystic nephroma in transition to anaplastic sarcoma of kidney) [71, 78]. The evolution of cystic nephroma to anaplastic sarcoma of kidney is reminiscent of Type I PPB evolving to Types II or III PPB, although the evolution of cystic nephroma to anaplastic sarcoma of kidney is notably less frequent, and it is unclear whether the association between cystic nephroma and later anaplastic sarcoma of kidney suggests the need for extirpation of all cystic renal masses in *DICER1* mutation carriers.

Wilms tumor

Wilms tumor occurs with *DICER1* mutations but only very infrequently [4, 21, 52, 69, 70, 79, 80]. In the absence of personal or family history of associated phenotypes, a Wilms tumor diagnosis should not trigger suspicion of DICER1 syndrome. Cystic partially differentiated nephroblastoma is also not considered part of DICER1 syndrome [70].

Embryonal rhabdomyosarcoma

An embryonal rhabdomyosarcoma histological pattern is frequent in certain rare tumors related to *DICER1* mutations

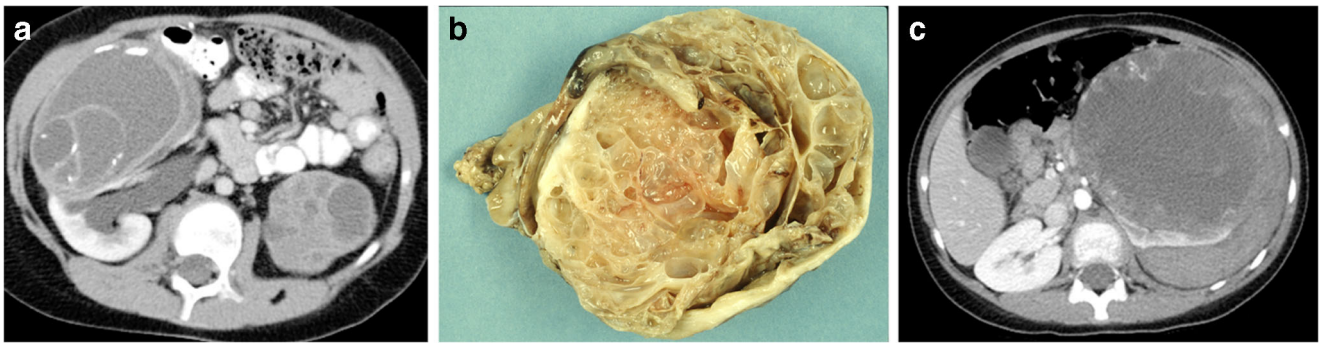

Fig. 9 Renal manifestations of DICER1 syndrome. **a** Cystic nephroma in a 6-month-old girl with abdominal distension. Axial contrast-enhanced abdominal CT shows bilateral multilocular renal cystic masses. **b** Gross pathology of a formalin-fixed cystic nephroma specimen. **c** Anaplastic sarcoma of kidney developing at age 8 years 9 months in a girl who had a renal cystic mass at the same site that was detected at age 10 months and exhibited growth and increased complexity by age 6 years. The girl also had Type I pleuropulmonary blastoma (PPB) at age 10 months. Axial contrast-enhanced abdominal CT image demonstrates a heterogeneously enhancing left renal mass with central hemorrhage or necrosis. Images courtesy of (**a**) family and David Plager, MD; (**b**) Adrian Charles, MD; and (**c**) Jeff Traubici, MD

detailed later in this paper. However, most childhood and adult embryonal rhabdomyosarcoma tumors are not related to *DICER1* mutations [81–83]. One alveolar rhabdomyosarcoma has been reported in a multinodular goiter kindred with a germline *DICER1* mutation, but alveolar rhabdomyosarcoma is not generally considered part of DICER1 syndrome [54].

Cervix embryonal rhabdomyosarcoma

Embryonal rhabdomyosarcoma of the uterine cervix is closely linked with *DICER1* mutations [52, 59, 81, 84–87] (Table 1). Cervical embryonal rhabdomyosarcoma typically affects adolescents but has been observed from infancy through the third–fourth decades of life. Vaginal spotting and a polypoid mass (sarcoma botryoides) protruding into the vagina are typical, and the tumor is occasionally visible at the introitus or is expelled (Fig. 10). Prognosis is favorable with most cases being localized.

An infant with polypoid cervical embryonal rhabdomyosarcoma containing a focus of primitive neuroectodermal tumor (PNET)-like elements has been reported without molecular information [86], and a cervical PNET–Ewing sarcoma, Sertoli–Leydig cell tumor and multinodular goiter occurred in one *DICER1* mutation carrier [52] (Table 1).

Bladder embryonal rhabdomyosarcoma

Bladder embryonal rhabdomyosarcoma with polypoid gross morphology (Fig. 11) has been observed in children with *DICER1* mutations from infancy through age 12 years [1, 11, 81, 88–90] (Table 1). Prognosis is consistent with the favorable outcome in sporadic bladder embryonal rhabdomyosarcoma. Other classic sites for early childhood embryonal rhabdomyosarcoma (vagina/vulva, orbit, parameninges, prostate and paratesticular tissues) have not been linked to DICER1 syndrome.

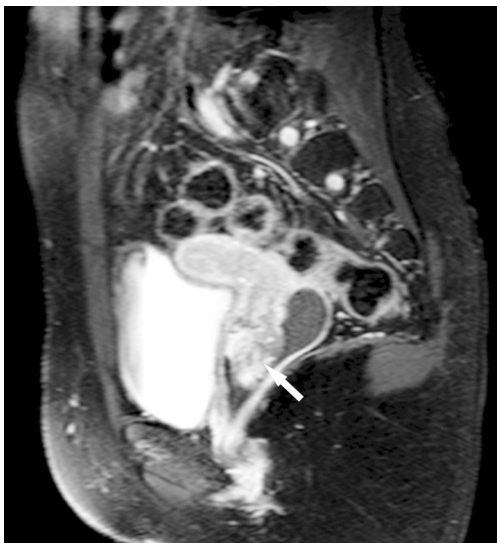

Fig. 10 Embryonal rhabdomyosarcoma (sarcoma botryoides) of the uterine cervix in a 17-year-old girl with vaginal bleeding. Sagittal gadolinium-enhanced T1-weighted fat-saturated MR image shows a polypoid mass of the uterine cervix protruding into the vaginal cavity (*arrow*). The girl had pineoblastoma at age 10 years, Sertoli–Leydig cell tumor at age 16 years and later presumed Type Ir pleuropulmonary blastoma (PPB) and pontine embryonal rhabdomyosarcoma at age 21 years. Same patient as in Fig. 5. Image courtesy of Sharon Plon MD, PhD

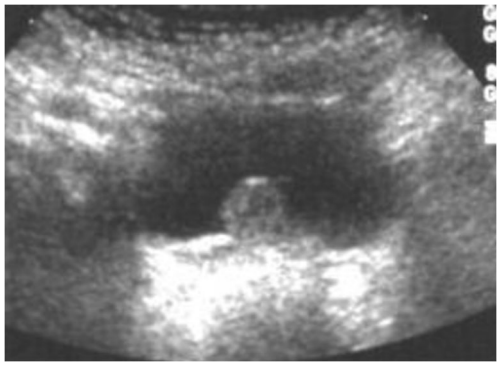

Fig. 11 Bladder embryonal rhabdomyosarcoma. Transverse gray-scale US image of the urinary bladder in a 5-month-old boy with concomitant Type I pleuropulmonary blastoma (PPB) shows an intraluminal polypoid mass, pathologically proved to be a bladder embryonal rhabdomyosarcoma

Ovarian embryonal rhabdomyosarcoma

Ovarian embryonal rhabdomyosarcoma and ovarian undifferentiated sarcoma have been associated with *DICER1* mutations [24, 91] (Table 1).

Cranial conditions

DICER1 syndrome presents the radiologist with a wide spectrum of cranial conditions: PPB metastasis to the cerebrum and meninges [29, 51], PPB tumor embolism with cerebral infarction, hemorrhage or tumor implantation [51], nasal chondromesenchymal hamartoma [92, 93], ciliary body medulloepithelioma [94], pituitary blastoma [20, 95], pineoblastoma [18, 19], cerebral sarcoma [1, 16, 96] and infantile cerebellar embryonal tumor [97].

Other central nervous system disease has been reported. In a child with a PPB who was shown to harbor tumor-restricted *DICER1* mutations, a choroid plexus papilloma was carefully determined not to be related to *DICER1* mutation [26, 98]. Other tumors reported without definitive evidence of DICER1 causation are medulloblastoma [1], intracranial medulloepithelioma [89], anaplastic meningeal sarcoma [18] and glioblastoma multiforme following radiation therapy for metastatic PPB [3]. The established primary cranial conditions associated with DICER1 syndrome are discussed next.

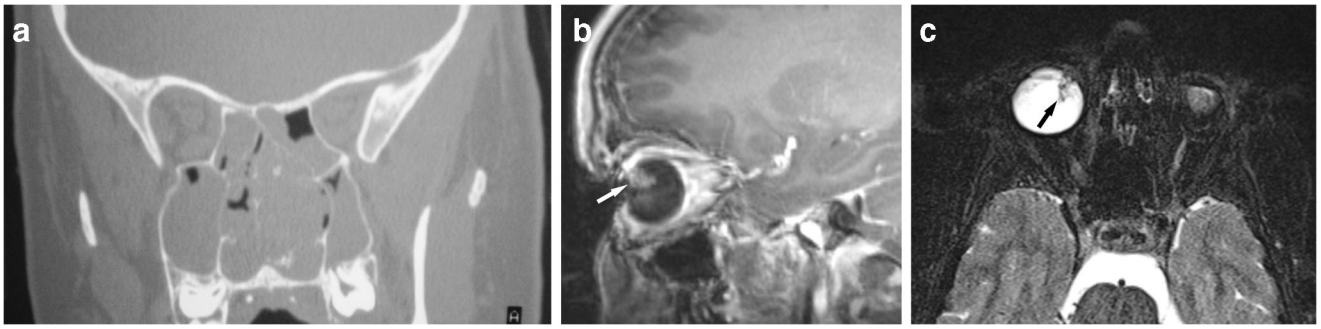

Fig. 12 Sinonasal and ocular manifestations of DICER1 syndrome. **a** Nasal chondromesenchymal hamartoma in a 15-year-old girl previously treated for pleuropulmonary blastoma (PPB) and Sertoli–Leydig cell tumor; the girl also had congenital phthisis bulbi. Coronal unenhanced facial CT image at bone windows shows a calcified soft-tissue mass expanding the left nasal cavity with remodeling and erosion of the middle and inferior turbinates. **b, c** Ciliary body medulloepithelioma in a 16-year-old girl: (**b**) Sagittal gadolinium-enhanced T1-weighted and (**c**) axial T2-weighted head MR images show an enhancing mass (*arrow*) extending posteriorly from the superomedial aspect of the ciliary body of the right globe. Image (**c**) also shows left prephthisis bulbi secondary to severe anterior segment dysgenesis noted at birth. Images (**b**) and (**c**) courtesy of the family and David Plager, MD

Nasal chondromesenchymal hamartoma

Nasal chondromesenchymal hamartoma is an unusual tumor linked in some cases to *DICER1* mutations [11, 15, 92, 93, 99, 100] that consists of a proliferation of mesenchymal tissues with spindle cell, cartilaginous and sometimes osseous elements and presents with nasal congestion, headache or tissue visible in the nares [101, 102] (Fig. 12). Nasal chondromesenchymal hamartoma related to DICER1 syndrome occurs generally at ages 5–25 years, whereas sporadic forms tend to occur before age 2 years [92]. Nasal chondromesenchymal hamartoma is benign but can be locally aggressive and erode through the sinonasal bones to extend into the sinus, orbital or intracranial cavities [99, 102]. CT and MR demonstrate a smoothly marginated, expansile intranasal mass that can be unilateral or bilateral. Although CT is superior for identifying bony erosion and intratumoral mineralization (Fig. 12), MR is better at depicting cyst-like myxoid stroma and extranasal extension. Although recurrence is possible after surgery, the prognosis is favorable [101].

Ciliary body medulloepithelioma

Ciliary body medulloepithelioma is a rare embryonal tumor of primitive epithelium in the anterior globe (Fig. 12). It is histologically classified as teratoid or non-teratoid, either of which can be benign or malignant. Several children with DICER1 syndrome and teratoid or non-teratoid ciliary body medulloepithelioma, ranging in age 3–10 years, have been reported [11, 14–16, 90, 94, 103, 104], and a recently published systematic family-based cohort study of the ocular phenotype of *DICER1* mutation carriers included incidental discovery of this tumor in two children [105]. Ciliary body medulloepithelioma presents with leukocoria, vision disturbance or ocular pain [94, 103, 106]. Consultation with ocular oncologists is recommended in suspected cases. Some children are managed without enucleation [14, 94]. On imaging, ciliary body medulloepithelioma typically appears as a solid or heterogeneous solid–cystic mass with marked contrast enhancement of the solid elements (Fig. 12). Compared to the vitreous humor, ciliary body medulloepithelioma tends to be hyperintense on unenhanced T1-weighted MR images and hypointense on T2-weighted MR images (Fig. 12). Mass effect on the lens, tractional retinal detachment, and subretinal hemorrhage might also be observed [103, 104, 106].

Pituitary blastoma

Pituitary blastoma is a rare tumor described by Scheithauer and colleagues [106, 107] in 2008 and 2012 and is essentially pathognomonic for DICER1 syndrome (Table 1). In a 2014 report of 13 pituitary blastoma cases, 11 of 11 adequately tested cases had germline or somatic *DICER1* mutations or loss of the normal allele [20]. Pituitary blastoma affects children younger than 24 months and characteristically presents with infant Cushing syndrome (Fig. 13), which is otherwise very rare. Ophthalmoplegia or signs of increased intracranial pressure might also be presenting signs. Whether pituitary blastoma is malignant or benign remains uncertain, but its location makes it life-threatening and approximately 50% of children with pituitary blastoma have died of the disease [20]. The imaging appearance ranges from a small solid mass within the pituitary to a large heterogeneous solid–cystic mass extending from the pituitary into the adjacent cisterns (Fig. 13).

Pineoblastoma

Pineoblastoma is an aggressive PNET of the pineal gland occurring infrequently in individuals or families with DICER1 disease (Table 1). Pineoblastoma presents with symptoms of increased intracranial pressure, gaze palsy or precocious puberty, and carries a poor prognosis [109]. Nine DICER1-

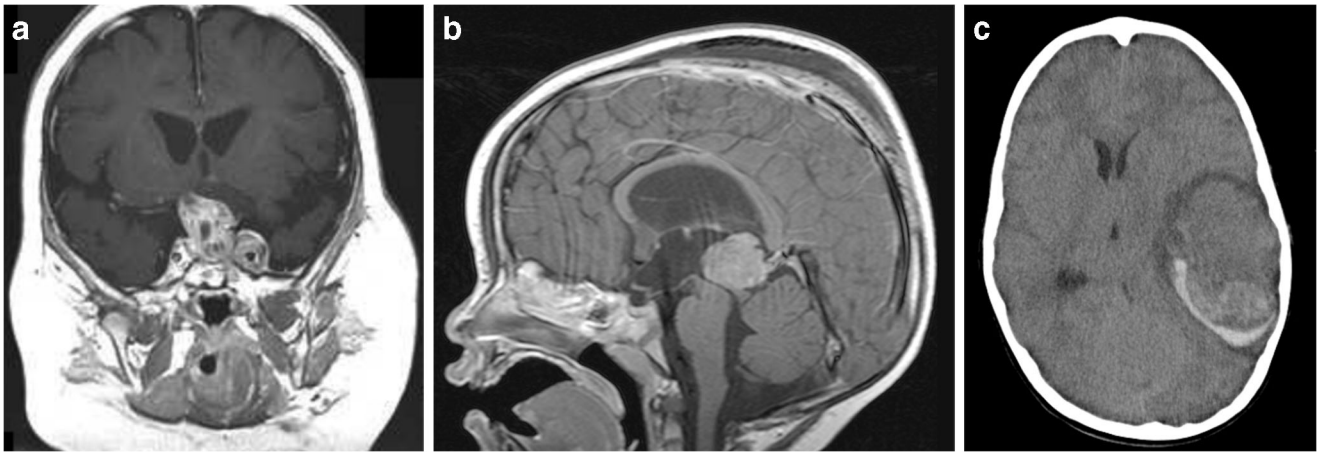

Fig. 13 Intracranial tumors in DICER1 syndrome. **a** Pituitary blastoma. Coronal gadolinium-enhanced T1-weighted head MR image in a 13-month-old boy with Cushing syndrome shows abundant facial fat and a heterogeneously enhancing pituitary mass extending into the suprasellar cistern. **b** Pineoblastoma**.** Midline sagittal gadolinium-enhanced T1-weighted head MR image in a 2-year-old boy shows a heterogeneously enhancing mass arising from the pineal gland and compressing the tectum and cerebral aqueduct. The boy also had a lung cyst (Fig. 1). **c** Cerebral sarcoma. Axial unenhanced head CT image reveals a left parietal cerebral mass with peritumoral edema, hemorrhage and rightward midline shift in a 4-year-old boy with ciliary body medulloepithelioma, multinodular goiter and presumptive Type Ir pleuropulmonary blastoma (PPB) (case also discussed in reference [15]). Image (**a**) courtesy of Heidi Traunecker, MD, and (**c**) courtesy of the family and of publisher John Wiley and Sons

related pineoblastoma cases have been reported [11, 14, 18, 19]. The limited data from these reports suggest that *DICER1* mutation is unlikely in adults with pineoblastoma and somewhat more likely in children. Pineoblastoma differs from other DICER1 phenotypes in that the second *DICER1* alteration is more often loss of the normal *DICER1* allele than mutations affecting hotspot codons [18, 19]. On imaging, pineoblastoma appears as a heterogeneous pineal mass that can cause obstructive hydrocephalus, infiltrate adjacent structures or disseminate through the cerebrospinal fluid [109] (Fig. 13).

Cerebral sarcoma

Cerebral sarcoma is a rare, recently recognized syndrome phenotype (Table 1). These tumors can be highly morbid, causing seizures, cerebral hemorrhage, edema and herniation [16] (Fig. 13). Cerebral sarcomas attributable to *DICER1* abnormalities were first noted in two children: a 4-year-old with a large deletion in chromosome 14 that encompassed the entire *DICER1* gene [16] and a 3-year-old whose cerebral tumor harbored two typical *DICER1* mutations [96]. Two additional cases without molecular confirmation are suggested in other reports [1, 18]. In a recent report that lacked complete clinical details and susceptibility information, tumor-based *DICER1* mutations affecting hotspots were noted in 21/22 cerebral sarcomas, most of which occurred in children [110]. Cerebral sarcomas in children are likely to be increasingly investigated for *DICER1* causation. Three additional young children, one of whom had neurofibromatosis type 1 (NF1), have recently been reported with DICER1-associated cerebral sarcomas with meningeal involvement [111]. A child with NF1 and PPB has also been reported [112], and an excess of malignant peripheral nerve sheath tumors observed in a study of *DICER1* mutation carriers is likely explained by the coexistence of NF1 in the two affected children [13].

Infantile cerebellar embryonal tumor

The spectrum of DICER1 syndrome was further expanded by the recent report of cerebellar embryonal tumors in two infants with germline and hotspot *DICER1* mutations [97] (Table 1). These tumors strongly resembled embryonal tumor with multilayered rosettes, but lacked the typical chromosome 19 microRNA cluster amplification. One of these tumors had sarcomatous elements, as is common in other tumors associated with DICER1 syndrome. These tumors appeared as enhancing midline posterior fossa masses on MR imaging [97].

Juvenile hamartomatous polyps

Gastrointestinal juvenile hamartomatous polyps occur in DICER1 syndrome (Table 1), as well as in other tumor predisposition syndromes such as Peutz-Jeghers and Cowden syndromes [113]. Juvenile hamartomatous polyps can occur from esophagus to rectum and can be asymptomatic or present with intussusception [11, 15, 73, 114, 115] (Fig. 1). Juvenile hamartomatous polyps might be especially frequent in very young children with mosaic *DICER1* mutations, who tend to develop many phenotypic conditions [11, 15].

Mesenchymal hamartoma of the liver

Mesenchymal hamartoma of the liver is the second most common benign liver tumor in children, after hemangioma, and

consists of disordered primitive mesenchymal tissue, cysts and hepatic parenchyma. Approximately 85% of cases present in the first 2 years of life. These lesions typically appear on imaging as a well-circumscribed multilocular cystic or mixed solid and cystic tumor, ranging from a few millimeters to many centimeters in dimension [116]. Chromosme 19q13 alterations resulting in aberrant activation of the chromosome 19 microRNA cluster (C19MC) and dysregulated microRNA profiles are often implicated in mesenchymal hamartoma of the liver. Two cases were recently reported — a child diagnosed at age 26 months with a mesenchymal harmatoma of the liver who lacked tumor C19MC activation but instead harbored a germline *DICER1* mutation and a somatic hotspot *DICER1* mutation; and a child with a liver lesion consistent with a mesenchymal hamartoma of the liver detected at age 9 months, a germline *DICER1* mutation and several DICER1 syndrome phenotypes (including Type I PPB, cystic nephroma and thyroid nodules). These cases suggest that mesenchymal hamartoma of the liver can be caused by *DICER1* mutations and is a phenotype of DICER1 syndrome [117]. The likelihood of either spontaneous regression or malignant transformation of unresected mesenchymal hamartoma of the liver to undifferentiated embryonal sarcoma of the liver in the setting of DICER1 syndrome, similar to the evolution of Type I PPB to Type Ir, II or III PPB, is currently unclear.

Other DICER1 syndrome phenotypes

Macrocephaly is a common finding in DICER1 syndrome, being reported in 42% of *DICER1* germline mutation carriers [118] (Table 1). Mosaic *DICER1* mutations have been reported with GLOW (global developmental delay, lung cysts, overgrowth and Wilms tumor) syndrome, which might be an unusual sub-type of DICER1 syndrome [25]. A case of congenital phthisis bulbi [99] and a case of prephthisis bulbi secondary to anterior segment dysgenesis [14] have been reported in children with DICER1 syndrome (Fig. 12), and a congenital globe lesion requiring enucleation at age 2 years is mentioned in a report of a woman with cervical embryonal rhabdomyosarcoma [119]. A pulmonary sequestration was observed in a known *DICER1* mutation carrier [52], and a Type I PPB was diagnosed in an extralobar sequestration in a child whose DICER1 status was not studied [120]. Further observations regarding pulmonary sequestration and DICER1 disease are needed.

Although neuroblastoma and medulloblastoma are mentioned in DICER1 kindred, confirming molecular data have not been reported [1, 4, 121]; furthermore, large series reveal that *DICER1* mutations contribute only rarely to neuroblastoma, if at all [13, 122], and not to medulloblastoma [123]. The observation of solitary cases of thymoma and malignant teratoma in a large cohort of *DICER1* mutation carriers is of uncertain significance [13]. Additional tumors reported but without molecular substantiation include paraspinal alveolar rhabdomyosarcoma [54], malignant fibrous histiocytoma (later considered pleiomorphic or leiomyosarcomatous sarcoma) [52], Hodgkin lymphoma [124] and synovial sarcoma [1]. No significant excess of certain common adult tumors (melanoma, breast or prostate cancer) was noted in a large cohort of *DICER1* mutation carriers [13].

Surveillance in DICER1 syndrome

Genetic testing for *DICER1* mutation carriers is available from commercial and research laboratories and is strongly encouraged along with genetic counseling in suspect families because of the syndrome's numerous and generally rare phenotypes, variable penetrance and severity, and wide age range of presentations (Table 1). Imaging surveillance might be used in an effort to detect clinically occult disease for early intervention, but this could alternately provide reassurance or provoke anxiety [125]. Except for resecting Type I PPB before progression to Types II or III PPB, a benefit of presymptomatic detection of DICER1 phenotypes has not been reported [35].

Proposed surveillance strategies for early disease detection in *DICER1* mutation carriers vary [13, 35, 126–130]. Devising an appropriate surveillance strategy requires consideration of the incidence, severity, progression rate and age range for each phenotype. A narrow approach advocates screening of *DICER1* mutation carriers for Type I PPB with chest CT in infancy before the peak incidence of Types II and III PPB so that resection can prevent progression [13, 35]. A broad approach involves annual chest CT to age 18 years, biannual abdominal/pelvic US to age 40 years, annual brain MR to age 25 years, and annual history and physical exam emphasizing thyroid palpation [128]. For each imaging modality (radiography, CT, MR, US), the diagnostic performance characteristics (sensitivity, specificity, predictive values), technique (contrast-enhanced vs. unenhanced; scan coverage), surveillance interval, need for sedation/anesthesia, risk of ionizing radiation, risk of contrast agent, and cost must be weighed [131]. The Image Gently (www.imagegently.org) and Image Wisely (www.imagewisely.org) programs should guide screening strategies. More intensive surveillance might be warranted for individuals with mosaicism because of their increased propensity to disease, while no screening might be needed for children proved to have tumor-restricted mutations [26, 130]. Recommended surveillance strategies organized by organ system and devised on the basis of expert consensus and literature review were recently published following an international symposium of DICER1 syndrome researchers [130]. However, the effectiveness of these recommendations remains to be validated, and because of the rarity of DICER1 syndrome, studies large enough to measure the benefit of

surveillance strategies are unlikely to be available soon. The effectiveness of certain surveillance strategies for DICER1 syndrome can be estimated by mathematical modeling, but this is a complex process that is limited by uncertainties in the assumptions used to inform the model [127].

Conclusion

A novel familial tumor syndrome encompassing PPB, cystic nephroma, embryonal rhabdomyosarcoma and multinodular goiter was recognized just more than 20 years ago. Systematic collection of patient and family data led to discovery of the causal *DICER1* mutations and many additional phenotypes. Mutations in *DICER1* predispose carriers to highly pleiotropic tumors of many organs, with the highest period of risk in childhood, yet extending into adulthood. Radiologists play a primary role in the diagnosis and management of DICER1 syndrome by recognizing the associated phenotypes and assisting in the surveillance of *DICER1* mutation carriers.

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Compliance with ethical standards

Conflicts of interest None

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