Chapter 9
DICER1 Syndrome

William D. Foulkes, Leanne de Kock, and John R. Priest

Abstract DICER1 syndrome, known previously as the pleuropulmonary blastoma—familial tumor dysplasia syndrome (OMIM #601200, #138800, #180295), was first described clinically in 1996. In 2009, heterozygous pathogenic variants in *DICER1* (OMIM *606241) were found to cause the syndrome now referred to as DICER1 syndrome; since then, numerous investigations have revealed that more than 25–30 phenotypes comprise DICER1 syndrome. The phenotypes are mostly rare to ultra-rare malignant and benign proliferative lesions, which occur from birth through ages 30–40 years. DICER1 syndrome is notably pleiotropic, but the most frequent and distinctive disorders are pleuropulmonary blastoma, cystic nephroma, and ovarian Sertoli-Leydig cell tumors, yet each has disease penetrance under 10%. In contrast, multinodular goiter, the least specific DICER1 phenotype, has penetrance approaching 75% in females and 20% in males. Other rare and highly characteristic conditions include pituitary blastoma, embryonal rhabdomyosarcoma of the uterine cervix, anaplastic renal sarcoma, as well as rare ocular and sinonasal tumors. Numerous reports of unusual rhabdomyosarcomatous tumors in young

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individuals, arising in the brain or in abdominal spaces, have *DICER1* variants as the cause and reveal similar and characteristic histopathology. Conditions such as pineoblastoma, Wilms tumor, and juvenile hamartomatous intestinal polyps may also occur but do not on their own suggest DICER1 syndrome.

The predisposing *DICER1* alterations are typically pathogenic loss-of-function variants in the germline. Termination and frameshift variants are common, but large and small deletions are also seen; mosaicism also causes DICER1 syndrome. In addition, most DICER1-related tumors harbor a highly characteristic somatic mutation in the second *DICER1* allele impairing DICER1 protein's RNase IIIb endonuclease function, which normally cleaves precursor microRNAs to their mature length. MicroRNAs function by targeted silencing and/or post-transcriptional degradation of specific messenger RNAs. Thus, *DICER1* has emerged as an unusual tumor suppressor gene: the first molecular "hit" cripples one allele completely, whereas the somatic second "hit" is a single base substitution leading to an amino acid change in the RNase IIIb cleavage domain. This impairs the function of the protein, without overall protein loss, leading to unbalanced microRNA products.

Keywords DICER1 · Pleuropulmonary blastoma · Embryonal tumors · MicroRNA · Pediatric cancer · Development · Sertoli-Leydig cell tumor · Cystic nephroma · Multinodular goiter · Pituitary blastoma · Pineoblastoma · Anaplastic sarcoma of the kidney

9.1 Introduction

Heterozygous pathogenic variants in the critical microRNA (miRNA) processing gene *DICER1*, located at chromosome 14q32.13, underlie the distinctive DICER1 syndrome—a childhood tumor and dysplasia syndrome recognized in recent years [1–5]. Such variants are present most often in the germline and are usually inherited [6]. Deletions of *DICER1* and mosaicism also cause the syndrome [7–10]. Approximately 25–30 phenotypes have been reported to date (Fig. 9.1, Table 9.1); rare phenotypes will continue to be identified. Mesenchymal proliferations, both malignant and benign, are typical. Pleuropulmonary blastoma (PPB), an early childhood sarcoma of lung and pleura, is the hallmark disease [11, 12], along with several other characteristic conditions, such as ovarian Sertoli-Leydig cell tumors, cystic nephroma, and rhabdomyosarcoma of the uterine cervix (Fig. 9.1, Table 9.1). DICER1-related sarcomas in diverse anatomic sites including cerebrum, kidneys, pelvis, and other sites are also characteristic of DICER1 disease and remarkably similar pathologically to PPB as discussed below (Fig. 9.1, Table 9.1) [13–17].

DICER1 syndrome exhibits marked pleiotropy and has low penetrance, generally less than 10% for any phenotype other than multinodular goiter (MNG) and

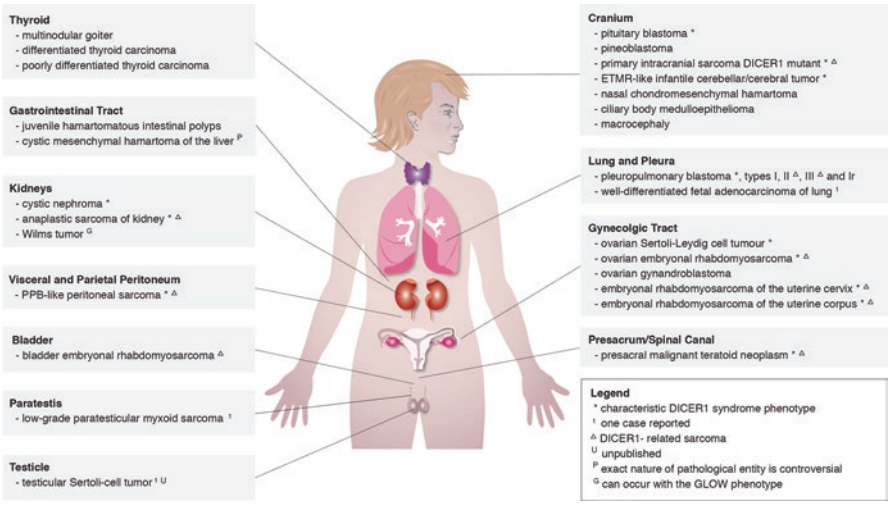

Fig. 9.1 DICER1 syndrome phenotype. Diseases recognized in *DICER1* variant carriers and in kindred clinically manifesting the DICER1 syndrome. Germline and somatic *DICER1* alterations have been demonstrated in each condition. This is an update and re-organization of a previously published figure [190]. Abbreviations: ETMR embryonal tumor with multilayered rosettes; PPB - pleuropulmonary blastoma

occult lung cysts. Detailed studies of affected cohorts have revealed that clinically or radiographically detected thyroid nodules affect three-quarters of females and up to 17% of males carrying pathogenic variants by age 40 years [18]. Similarly, occult often small lung cysts detectable by computed tomography are found in 25–30% of carriers [19]. The gynecologic manifestations and greater frequency of MNG in females compared to males result in higher overall penetrance in females. Bilateral disease in paired organs is not unusual. As shown in Table 9.1, some diseases in the syndrome have highly focused ages of presentation.

The typically adult-onset cancers found in certain other childhood and adolescent tumor predisposition syndromes, such as the Li-Fraumeni syndrome, do not appear to be part of the DICER1 complex. No evidence has emerged to date that DICER1 syndrome is more or less prevalent in any ethnic or racial group. There is also no evidence to date that *DICER1* variant carriers are prone to developing second malignant neoplasms as a result of cancer therapies such as alkylating agents or therapeutic radiation. The *possible* exception to this, discussed later in this chapter, is development of thyroid carcinoma as a result of intensive multimodal therapies such as stem cell transplant for a serious DICER1 disease or as a result of high cumulative diagnostic radiation exposures from chest computed tomography, as often occurs following a PPB diagnosis.

DICER1 is a cytoplasmic endoribonuclease III which cleaves hairpin precursor pre-miRNAs, produced in the cell nucleus by similar enzymes such as DROSHA (RNASEN) and DGCR8 (PASHA), into mature, non-coding regulatory miRNAs comprised of ~23 base pairs. As part of the RNA-induced silencing complex,

Table 9.1 DICER1 syndrome phenotypes and their typical ages of presentation, specificity for DICER1 syndrome, and biologic behavior

Phenotype[a]	Typical ages of presentation m, months y, years	Characteristic of DICER1 syndrome and genetic testing indicated	Typical biologic behavior B, benign M, malignant U, uncertain biologic behavior [hc] high cure potential [mc] moderate cure potential [lc] low cure potential [uncertain] uncertain prognosis
Lung and pleura diseases			
Pleuropulmonary blastoma			
Type I (cystic)	0–2y	Yes	M[hc]
Type II (cystic/solid)[b]	6 m–4 y	Yes	M[mc]
Type III (solid)[b]	1–6 y	Yes	M[mc]
Type Ir (cystic)	Any age	Yes	B
Well-differentiated fetal adenocarcinoma of the lung	Not established	No	M[hc]
Thyroid disease			
Multinodular goiter	3–any	No	B
Differentiated thyroid carcinoma	8–any	No	M[hc]
Poorly differentiated thyroid carcinoma	Not established	Yes	M[hc]
Renal disease			
Cystic nephroma	0–48 m	Yes	B
Anaplastic sarcoma of the kidney[b]	1–20 y	Yes	M[mc]
Wilms tumor	1–10 y	No	M[mc]
Gastrointestinal disease			
Juvenile hamartomatous polyps	0–20 y	No	B
Cystic mesenchymal hamartoma of the liver[c]	0–4 y[d]	No	B
Cranial disease			
Pituitary blastoma	0–24 m	Yes	U[mc]
Pineoblastoma	2–20 y	Only if <10 y	M[mc]
Primary cerebral sarcoma—*DICER1* mutant[b]	1–20 y[d]	Yes	M[mc]
ETMR-like infantile cerebral/cerebellar embryonal tumor	<36 m	Yes	M[lc]
Nasal chondromesenchymal hamartoma	6–20 y	No	B

(continued)

Table 9.1 (continued)

Phenotype[a]	Typical ages of presentation m, months y, years	Characteristic of DICER1 syndrome and genetic testing indicated	Typical biologic behavior B, benign M, malignant U, uncertain biologic behavior [hc] high cure potential [mc] moderate cure potential [lc] low cure potential [uncertain] uncertain prognosis
Ciliary body medulloepithelioma	3–10 y	No	B, rare $M^{uncertain}$
Gynecologic diseases			
Ovarian Sertoli-Leydig cell tumor	2–50+ y[e]	Yes	M^{hc}
Ovarian gynandroblastoma	10–25 y[d]	Yes	M^{hc}
Ovarian rhabdomyoblastic sarcoma[b]	5–15 y[d]	Yes	$M^{uncertain}$
ERMS of the uterine cervix[b]	5–25 y	Yes	M^{hc}
ERMS of the uterine corpus[b]	10–25 y[d]	Yes	M^{hc}
PPB-like sarcoma of peritoneum including fallopian tube serosa[b]	10–20 y[d]	Yes	M^{mc}
Bladder diseases			
ERMS bladder[b]	3–15 y[d]	No	M^{hc}
Pelvic/abdominal cavity and serosal diseases			
Presacral malignant teratoid tumor[b]	<5 y[d]	Yes	$M^{uncertain}$
PPB-like peritoneal sarcoma[b]	3–15 y[d]	Yes	M^{mc}
Non-proliferative manifestations of DICER1 syndrome			
Macrocephaly	Any	No	Not applicable
Dental dysmorphologies	Any	No	Not applicable
Ocular abnormalities	Any	No	Not applicable
Kidney and collecting system dysmorphologies	Any	No	Not applicable
"GLOW" phenotype			
Includes several manifestations including global developmental delay, overgrowth, lung cysts, Wilms tumor, and other findings. See references [20, 36, 37]			

Abbreviations: *ERMS* embryonal rhabdomyosarcoma; *PPB* pleuropulmonary blastoma
[a]Nomenclature to describe rare and recently reported phenotypes subject to change, especially for DICER1-related sarcomas in unusual sites
[b]DICER1-related sarcoma
[c]Exact nature of pathological entity is controversial
[d]Age range approximated when few cases known
[e]95% diagnosed under age 40 years [191]

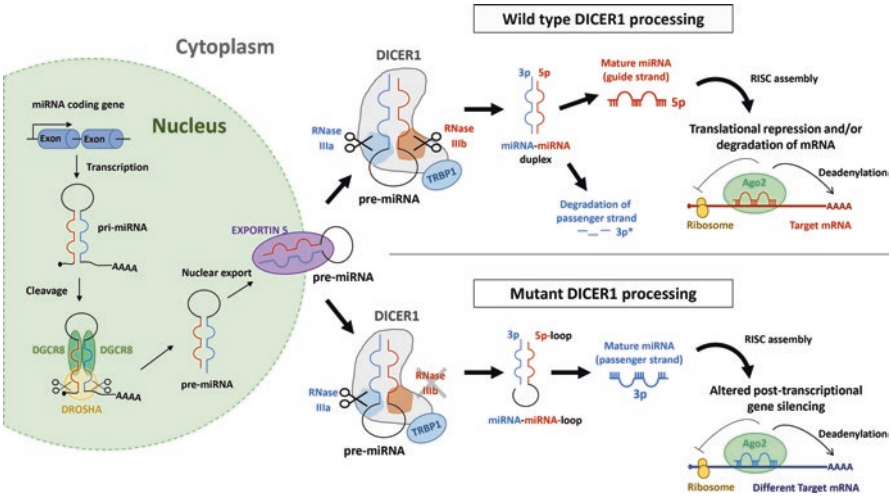

Fig. 9.2 Canonical pathway of miRNA biogenesis. Most miRNA genes are transcribed by RNA polymerase II in the nucleus. Then, primary miRNAs (pri-miRNAs) are cleaved by the microprocessor complex, formed by DROSHA and DGCR8, into precursor miRNAs (pre-miRNA), which are subsequently exported to the cytoplasm by Exportin 5. In the cytoplasm, DICER1 cleaves pre-miRNAs into mature microRNAs (3p-5p duplex). The 5p strand is derived from the 5′ end of the pre-miRNA hairpin, while the 3p strand originates from the 3′ end. The resulting miRNA-miRNA duplex is unwound by a helicase, and while the passenger strand is cleaved and degraded, the guide strand (usually the 5p) is loaded onto the miRNA-induced silencing complex (miRISC) to target mRNAs for post-transcriptional gene silencing [wild-type DICER1 panel]. However, in cells expressing a mutant DICER1 that lacks a functional RNase IIIb catalytic domain, the maturation of 5p strand is impeded, whereas the 3p strand is properly processed. Therefore, only the 3p strand will be loaded into miRISC to target mRNAs [mutant DICER1 panel]

DICER1, mature miRNAs, and other co-factors target specific messenger RNAs for post-transcriptional downregulation, thereby modulating cellular protein production [1]. A schematic figure of the miRNA biogenesis pathway is shown in Fig. 9.2. DICER1 is comprised of numerous domains (Fig. 9.3) including helicase, PAZ, and RNase III domains. As illustrated in Fig. 9.3, the ~254 reported distinct predisposing *DICER1* alterations (pathogenic variants including large and small deletions) occur throughout the gene. Most are loss-of-function variants, and are inherited rather than de novo [6]. Mosaicism appears to cause 4–5% of syndrome cases [7, 8, 20].

In addition to a primary *DICER1* alteration disabling one allele, most tumors in the syndrome exhibit a highly distinctive somatic change in the second *DICER1* allele affecting a narrow set of RNase IIIb metal-ion binding sites of DICER1 protein (Fig. 9.3) [21–28]. The somatic alterations are termed "hotspot" mutations. The RNase IIIb change caused by a hotspot mutation neither fully abrogates DICER1 function nor results in loss of the protein but instead alters the proportions of 3′- (3p) and 5′-derived (5p) miRNAs produced by the protein [1, 29, 30] (Fig. 9.2).

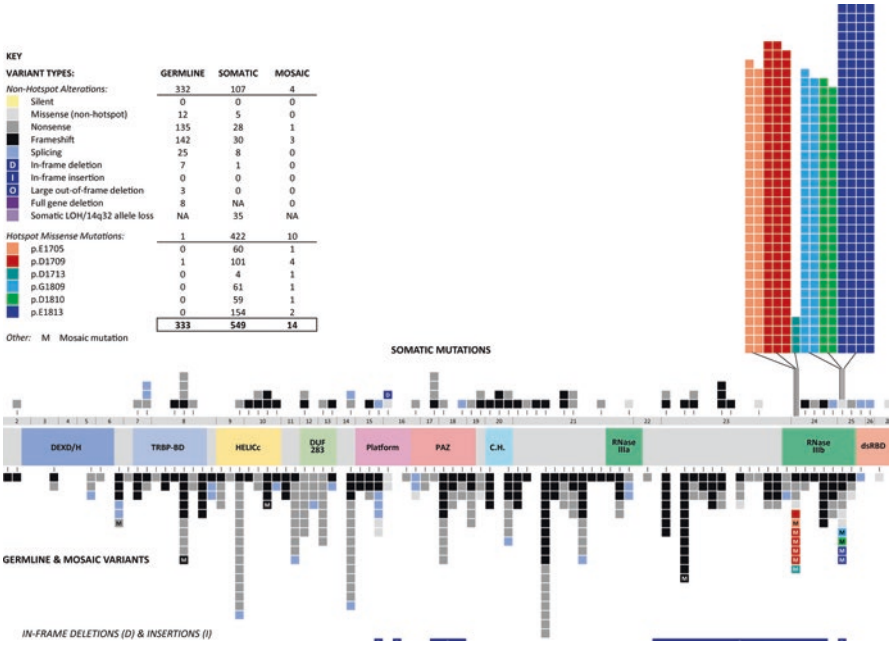

Fig. 9.3 Germline and somatic variants in *DICER1*. Plotted along the length of the unfolded DICER1 protein are all pathogenic and likely pathogenic *DICER1* alterations published prior to June 2020. Germline variants are plotted once per family (unique per family, UPF). A total of 333 UPF germline variants and 14 mosaic variants are plotted below the protein. The 549 confirmed-somatic events are plotted above the protein, except for the 35 confirmed-somatic allele loss events that are shown at the bottom of the figure. DICER1 domains are defined as follows: *DExD/H* DExD/H box helicase domain; *TRBP-BD* trans-activating response RNA-binding protein binding domain; *HELICc* helicase conserved C-terminal domain; *DUF283* domain of unknown function; Platform, platform domain; *PAZ* polyubiquitin-associated zinc finger domain; *c.h.* connector helix; *RNase IIIa* ribonuclease IIIa domain; *RNase IIIb* ribonuclease IIIb domain; *dsRBD* double-stranded RNA-binding domain. Abbreviations: *LOH* loss of heterozygosity; *NA* not applicable. This is an update of a previously published figure [6]

Instead of a somatic RNase IIIb mutation, loss of heterozygosity (LOH) of the wild-type *DICER1* allele is found in some syndrome tumors (in pineoblastoma particularly and in pituitary blastoma) [31]. Because several tumors in DICER1 syndrome occur in relatively tightly defined age ranges in young children (Table 9.1), it appears as if *DICER1* and miRNAs have critical time- and tissue-specific effects on development of certain organs. Examples of this phenomenon are PPB in children under age 6 years, cystic nephroma in children under age 4 years, and pituitary blastoma in children under age 2 years.

Reports to date suggest genotype-phenotype correlations in DICER1 syndrome only for unusual and specific gene alterations. Compared to loss-of-function (LOF) variant carriers, children with mosaic RNase IIIb mutations are diagnosed at significantly younger ages and develop more diseases per affected individual [7, 8]. The

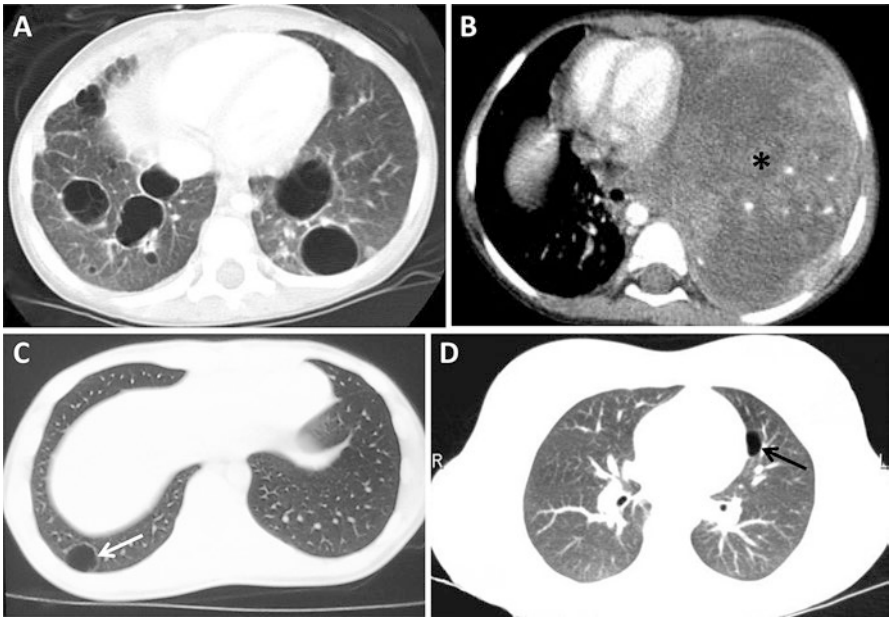

Fig. 9.4 Pleuropulmonary blastoma. (**a**) An axial chest computed tomography (CT) image of a child with a mosaic RNase IIIb hotspot predisposing *DICER1* alteration showing numerous large and small air-filled cysts in the right and left lungs. The patient was subsequently diagnosed with bowel polyps at age 9 months, PPB Type II at 2.1 years, nasal chondromesenchymal hamartoma at 8 years, and metastases of PPB to the brain at ages 2.1 years, 3.1 years, 10.5 years, and 10.9 years. (**b**) An axial chest CT image with black asterisk indicating Type III PPB filling the hemithorax. (**c** and **d**) Axial chest CT images in which small arrows identify occult air-filled lung cyst in variant carriers, which likely represent Type Ir PPB. Patient C developed an esophageal juvenile hamartomatous polyp and multinodular goiter and has a family history of DICER1 syndrome. Patient D was diagnosed with multinodular goiter at age 12 years and had an older sister with DICER1 syndrome, which occasioned chest imaging. (Images courtesy of Barbara Pasini, M.D. [C] and the patient [D])

triad in very young infants of lung cysts, renal cysts, and small bowel polyps may suggest mosaicism [7, 8, 32–35]. Furthermore, these children appear to have unusually abundant lung cysts, often in many if not all lobes bilaterally [20, 22, 32] (Fig. 9.4a). In addition, a very rare complex phenotype of DICER1 syndrome, termed "GLOW," has been identified in two children with mosaic RNase IIIb mutations and one child with a germline RNase IIIa variant (Table 9.1) [20, 36, 37]; GLOW signifies global developmental delays, lung cysts, regional somatic overgrowths including macrocephaly, and Wilms tumor, in addition to other findings.

Biallelic *DICER1* tumor-only alterations in DICER1 syndrome-associated tumors have also been reported [7, 38]. Detailed studies must prove the limited nature of the variants, yet their elucidation is of great benefit to patient and family [38]; because the genetic alteration is restricted to the tumor, such cases are not considered to involve the child or family with DICER1 syndrome.

The DICER1 syndrome should be strongly considered in a child or family with even one of the highly distinctive diseases (Fig. 9.1, Table 9.1) or, because of the syndrome's pleiotropy and low penetrance, in a child or kindred with any combination of the related diseases.

The recent wide utilization of genetic sequencing of many human tumors has revealed that *somatic* mutations in the family of miRNA processing genes (*DROSHA*, *DGCR8*, *DICER1*, *XPO5*, and *TARBP2*) play a role in human neoplasia [39–41]. A pathogenic variant in *DGCR8* is the only other reported heritable alteration in an miRNA biogenesis gene associated with tumor development; individuals in three generations of one kindred were affected by MNG and schwannomatosis [42]. In addition, childhood tumors similar to DICER1-related tumors are associated with miRNA disturbances not linked to miRNA biogenesis. Specifically, amplification of the chromosome 19 microcluster (*C19MC*: chr19q13.41 miRNA cluster), amplification of the *miR-17-92* miRNA cluster on chromosome 13 (also known as *MIR17HG*), and *DICER1* alterations cause similar-appearing aggressive early childhood central nervous system tumors termed embryonal tumors with multilayered rosettes, which include tumors previously labeled ependymoblastoma or medulloepithelioma [43, 44]. Both *DICER1* alterations and *C19MC* amplification are associated with similar childhood cystic hepatic mesenchymal lesions [45–47].

We do not discuss in this chapter those diseases in which exclusively somatic *DICER1* mutations are implicated. *DICER1* mutations in the broadest sense have been reviewed elsewhere [6].

9.2 DICER1-Related Sarcomas

In 1988, PPB became the first and remains the hallmark malignant mesenchymal tumor in DICER1 syndrome, but now a wide anatomic distribution of pathologically similar sarcomas is recognized as a characteristic syndrome phenotype [12]. These DICER1-related sarcomas arise in the lung and pleura, cerebrum, cerebellum, kidney, ovary, uterus, and bladder. In addition, similar DICER1-related sarcomas arise in less well-defined abdominal and pelvic sites apparently in visceral and parietal serosa (fallopian tube, presacrum) [13–17]. Unfortunately, as tumors with similar histologies have been identified in various sites, their naming has been diverse and obscures the striking pathological similarities [48]. The DICER1-related sarcomas are identified in Table 9.1 and Fig. 9.1 and are discussed below. In viscera with a lumen (e.g., vagina, bladder, lung cyst), DICER1-related sarcomas characteristically form the grape-like clusters of sarcoma botryoides.

Even before these tumors could be unified by *DICER1* causation, their histologic similarity to PPB was recognized. Pathologists have remarked that some of these tumors could be considered PPB except that they did not arise in the lung [49]. Although not every DICER1-related sarcoma expresses all characteristic pathologic elements, the features include cyst formation, subtle subepithelial malignant mesenchymal cells (small blue cells which may condense into subepithelial "cambium"

layers), malignant stromal and spindle cell areas, skeletal muscle differentiation or de-differentiation with rhabdomyoblastic or embryonal rhabdomyoblastic areas (with myogenin- and myoD-positive immunostaining), blastema, areas of sometimes striking anaplasia, primitive or overt and sometimes malignant cartilaginous and rarely osteoid differentiation, and, very rarely, primitive neuroectodermal elements. Notably absent in these tumors is any epithelial differentiation.

Specific phenotypes are discussed below based on body region as in Fig. 9.1.

9.3 Chest

9.3.1 Pleuropulmonary Blastoma

Pleuropulmonary blastoma is a rare malignant pleural and/or parenchymal lung tumor presenting in children most often under 72 months of age [11, 12, 50, 51]. Several hundred cases have been recognized, predominantly in the collection of the International PPB Registry (IPPBR) (www.ppbregistry.org) [19, 50].

Three malignant manifestations of PPB are recognized along an age and degree-of-malignancy spectrum: cystic Type I PPB in newborns and infants and cystic/solid Type II and solid Type III PPB in progressively older children. These comprise, respectively, 33%, 38%, and 29% of PPB cases [50]. In addition to these malignant PPB types, a non-malignant cystic manifestation of PPB termed Type Ir (regressed) PPB is discussed below. The radiographic appearances of PPB have been reviewed in detail [4, 52].

From birth through approximately age 2 years, cystic Type I PPB is an early malignant lesion presenting with dyspnea or as an incidental finding on a chest radiograph done for other reasons. Radiographically an innocuous-appearing air-filled multilocular lung cyst is noted, often with pneumothorax. The clinico-radiographic features mimic congenital cystic adenomatoid malformation (CCAM), which is a much more frequent disease and indeed is the pre-operative diagnosis in almost every case of Type I PPB [4]. However, PPB instead of CCAM should be suspected when a child has pneumothorax, multifocal or bilateral lung cysts, or a family history of any condition related to *DICER1* mutation (Fig. 9.1; Table 9.1) [4]. To differentiate Type I PPB from CCAM (especially from CCAM type 4 which mimics Type I PPB), expert pathological examination of a resected cyst is essential to identify the often subtle, scattered population of primitive rhabdomyomatous cells in cyst walls and septa; small nodules of immature cartilage are frequent and highly characteristic of PPB [11, 53, 54]. Delicate septations in cysts may not be appreciated in plain radiographs or computed tomography but are highly characteristic [52]. Type I PPB is cured in 90–95% of cases [33, 50].

In children from approximately ages 2 through 6 years, Type II and III PPB occur and are aggressive sarcomas with overall 5-year survival rates of approximately 70% and 50%, respectively [50]. The solid elements of Type II and III PPB

(Fig. 9.4b) express the DICER1-related mixed sarcoma patterns discussed earlier. These advanced forms present commonly as "pneumonia," with dyspnea, cough, malaise, and/or fever (occasionally with pneumothorax for Type II). Although PPB is increasingly recognized, it remains a specialized pathologic diagnosis; among cases submitted to IPPBR review pathologists, 20% are judged not to be PPB [50]. In addition, PPB is an exclusively mesenchymal tumor to be distinguished from biphasic mesenchymal and epithelial "pulmonary blastoma" which has not been reported in DICER1 syndrome [11].

It is well established that Type I PPB in a young child may progress over 1–5 years to Type II or III disease as the scant malignant population overgrows cyst walls and septa [4, 33, 53]. This phenomenon raises the possibility of early detection and possible resection of PPB cysts in variant-carrying infants in known DICER1 families [55, 56].

Type Ir PPB is a non-malignant cystic manifestation of PPB. It is thought to represent either forme fruste or regressed Type I PPB. The key difference from Type I PPB is the absence of a primitive cell population [4, 50, 53]. Type Ir PPB cysts tend to be 2–3 cm in diameter (sometimes larger) and are typically discovered in *DICER1* variant carriers at any age in radiographic studies done for other reasons (Fig. 9.4c and d) [52]. Radiographically, a Type Ir PPB is indistinguishable from a small Type I PPB. In a systematic survey of variant carriers, Type Ir PPB was discovered by computerized tomography in approximately 25–30% of carriers [19]. Because these cysts do not harbor primitive cells and because they have been discovered in adult variant carriers well beyond the ages typical for PPB cyst progression, Type Ir PPB cysts are thought not to have malignant potential. In a variant carrier, cyst progression beyond the age of approximately 8 years is considered highly unlikely, although rare exceptions exist [57, 58]. Currently in an adult variant carrier, a lung cyst can be presumptively diagnosed as Type Ir PPB without resection or pathologic examination. Type Ir PPB is also diagnosed in infants, and progression has been observed [50, 59]; such progression in young children suggests that the scattered malignant cells of Type I PPB may be missed even in detailed pathologic examination or may remain in some areas of a cyst specimen despite evidence of regression elsewhere.

Germline *DICER1* mutations are described in 65–70% of 126 reported PPB patients; somatic *DICER1* mutations, predominantly affecting RNase IIIb hotspots, are described in 94% of 64 PPB tumors [5, 21, 50, 60–63].

In one report, PPB has been noted in association with neurofibromatosis type 1 [64], and in another case report, NF1 was associated with pulmonary blastoma [65], which also contains somatic *DICER1* mutations [66]. Detailed molecular studies have not been reported, and the possible mechanistic connection between *DICER1* and *NF1*, and their associated syndromes, is unknown.

9.3.2 *Well-Differentiated Fetal Lung Adenocarcinoma (WDFLA)*

A single case of WDFLA in the context of DICER1 syndrome has been reported (see "Rare or Possible Associations").

9.4 Head and Neck

9.4.1 *Multinodular Goiter and Other Non-toxic Thyroid Diseases*

Thyroid disease occurring in childhood, adolescence, or early adulthood usually in the form of nodular hyperplasia and often progressing to frank MNG is the most frequent manifestation of a germline *DICER1* pathogenic variant (Fig. 9.5a); by age 40 years, three-quarters of at-risk females and one in six at-risk males will develop MNG or undergo thyroidectomy [18]. As early as the 1950s, there were reports of familial MNG occurring with other DICER1-related phenomena [67], but it was not until 1974 that a direct genetic link between Sertoli-Leydig cell tumor (SLCT)—a type of sex cord stromal (non-epithelial) ovarian tumor—and thyroid adenoma was postulated [68]. Although thyroid disease in general and MNG in particular are frequent in the general population [69], familial MNG is relatively unusual. One very large pedigree was linked to chromosome 14q32 in 1997 [70]. An almost completely penetrant missense mutation in *DICER1* was later identified in the family, confirming that MNG is a DICER1-related phenotype [71]. Molecular studies of DICER1-related MNG have revealed that individual nodules harbor distinct RNase IIIb hotspot mutations suggesting discrete clonal origins of nodules comprising MNG [18, 72–74].

Individuals with DICER1 syndrome have an approximately 16-fold increased risk of differentiated thyroid carcinoma (DTC) compared to Surveillance, Epidemiology and End Results (SEER) rates [18] hypothesized to be due to increased prevalence of premalignant thyroid lesions in heterozygotes [18, 73]. However, the overall contribution of *DICER1* mutations both to familial MNG and to familial DTC appears to be very small [23, 70, 71, 75]. Analysis of *DICER1* is probably not justified in such families unless there are other phenotypes suggesting *DICER1* mutation. An exception could be made in the case of childhood- or adolescent-onset familial MNG/DTC or when involving a male under approximately 18 years of age with MNG/DTC [18]. DICER1-related MNG is predominantly diagnosed between ages 10 and 30 years [18, 71, 76]; DICER1-related DTC also occurs at similar ages but is much less frequent than MNG [18, 19]. Several DTCs have occurred in children intensively treated for PPB and other tumors raising the possibility of a causal link between *DICER1* mutation and intensive multimodal therapy [23, 77, 78]. However, DTC also occurs in *DICER1* heterozygotes in

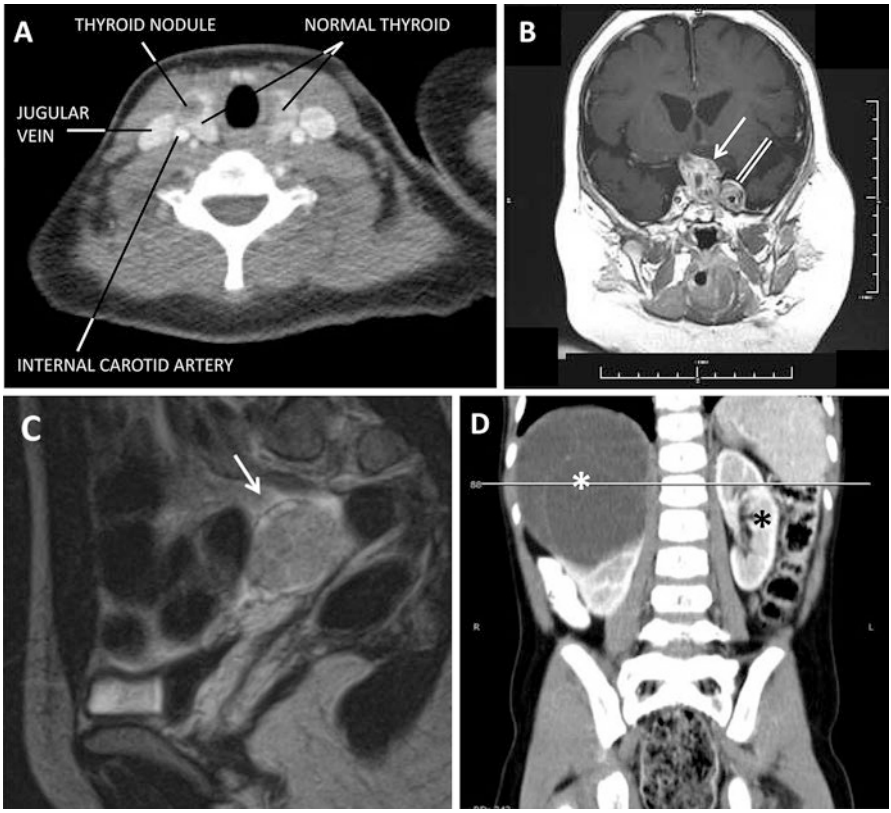

Fig. 9.5 Radiology images. (**a**) Axial cervical region contrast-enhanced CT image of multinodular goiter. (**b**) Coronal gadolinium-enhanced magnetic resonance image of pituitary blastoma (white arrow) with left cavernous sinus involvement (double white line). (**c**) Sagittal pelvic region CT image showing ovarian Sertoli-Leydig cell tumor (arrow). (**d**) Coronal contrast-enhanced abdominal CT image showing multilocular fluid-filled mass pathologically proven to be cystic nephroma in the upper pole of right kidney (white asterisk) above residual normal right lower pole; normal left kidney indicated by black asterisk. (Images courtesy of the patient [A], Marek Niedziela, M.D. Ph.D. [C], and Yves Heloury, M.D. FRACS [D])

the absence of prior treatments [72, 79]. Given their low propensity for metastasis, it is postulated that DICER1-related DTC may form a low-risk subgroup [74, 80]. On the other hand, a recent study identified young-onset clinically aggressive poorly differentiated thyroid carcinoma to be a rare manifestation of DICER1 syndrome [81].

A case of medullary thyroid carcinoma in a patient with a germline *RET* alteration has been reported to harbor two somatic *DICER1* mutations [82]. Eight cases of malignant teratoid tumors of the thyroid have been reported to bear one or more somatic *DICER1* mutations [83–85]. Neither of these tumors has yet been reported in association with germline *DICER1* pathogenic variants.

9.4.2 Cranial and Intracranial Tumors

Because the central nervous system (CNS) is the site of multiple DICER1 syndrome phenotypes including PPB metastases and several primary intracranial tumors, careful diagnosis is essential.

9.4.2.1 Metastasis of Pleuropulmonary Blastoma to the Central Nervous System

Metastasis of PPB to the cerebral hemispheres complicates the course of approximately 7% of Type II PPB cases and 15% of Type III PPB cases and is the most frequent intracranial pathology in DICER1 syndrome [50, 86]. The metastases tend to occur in the first 36 months after chest diagnosis, often without chest recurrence, and may be multiple, fulminant, and recurrent [86]. Cerebral PPB metastasis is also rarely present at the time of chest diagnosis [50]. Cure is possible in perhaps 20% of cases [86, 87]. The pathologic features of the metastases tend to be less complex than the original PPB with predominant rhabdomyoblastic or spindle cell elements consistent with a DICER1 sarcoma as discussed earlier. In fact, the differential diagnosis of PPB metastasis to the brain includes primary cerebral sarcoma—DICER1 mutant [14, 86]. In confusing cases, molecular studies of both chest and cerebral tumors might differentiate metastasis from primary sarcoma in that a metastasis will involve the same *DICER1* hotspot mutation as the chest primary, whereas a primary sarcoma might, though not necessarily, harbor a different hotspot mutation. Leptomeningeal and spinal PPB metastases are extremely rare [86].

Pleuropulmonary blastoma can also affect the cerebrum following a chest resection with tumor embolism causing both hemorrhagic and occlusive vascular events and both early and late tumor growth at the embolic site [86]. Glioblastoma multiforme has occurred in one child 4 years following radiation for PPB CNS metastasis [Sciot, personal communication].

9.4.2.2 Pituitary Blastoma

Pituitary blastoma is an extremely rare, primitive tumor of the anterior pituitary described in one child in 2008 with five confirmatory cases in 2012 [88, 89]. The disease is reported only in children under 24 months of age, and the hallmark symptom is Cushing syndrome, which is otherwise extremely rare in this age group (Fig. 9.5b). Predisposing *DICER1* alterations and/or classic hotspot changes were reported in 2014 in 12 of 12 fully studied cases [22, 90]. Among 17 pituitary blastoma cases now reported, 16 have DICER1 involvement (15 with molecular evidence; 1 with strong clinical evidence of DICER1 syndrome; molecular studies were not possible in 1 case without clinical evidence of DICER1 syndrome) [22, 90–93]. There is a brief report of an 18th case of pituitary blastoma in a 19-year-old

woman [94], which has since been determined to harbor two *DICER1* alterations (Foulkes et al, unpublished data). Thus, pituitary blastoma is virtually pathognomonic for DICER1 syndrome. Despite the blastoma label, which refers in part to the tumor recapitulating pituitary embryology, the biologic behavior of pituitary blastoma is uncertain; about 50% of children with the disease succumb, with several deaths from early medical/surgical and later treatment-related complications. Metastasis has not been reported, and surgery leads to long-term survival in some children without additional oncologic therapies [22]. Hormonal replacement therapies are necessary.

9.4.2.3 Pineoblastoma

Pineoblastoma is a rare, aggressive embryonal tumor that arises in pineal gland. It usually occurs in childhood. It was first linked to *DICER1* in 2012 [95]; the association was confirmed 2 years later [96]. Recently, three publications extended these observations [97–99], showing that DICER1 and other miRNA biogenesis proteins are implicated in at least a quarter of all pineoblastomas. Methylation analysis of 70 pineoblastomas revealed 5 molecular sub-groups, and *DICER1* mutant pineoblastomas were exclusively placed in groups 1 and 2, which also included tumors with mutations in another miRNA processor, *DGCR8*, but excludes tumors with RB or MYC pathway alterations. Groups 1 and 2 were also quite distinct from the other three groups in terms of copy number profiles [97]. In this study, of the 23 cases that had germline *DICER1* testing, 5 (22%) had pathogenic variants. In a second study of 43 pineoblastomas, 12 (25%) were evaluated for germline *DICER1* pathogenic variants, and 3 cases were positive [98], and in the third, including 53 pineoblastomas, no cases had germline evaluation [99]. Overall, it appears that about one-fifth of pineoblastomas will occur as part of DICER1 syndrome and a third will have a germline pathogenic variant in *DICER1*, a somatic mutation in *DICER1*, or both. Notably, the second hit in DICER1-related pineoblastoma is much more likely to be a LOH event than in other *DICER1* mutant tumors—in a recent overview, 33/49 (67%) of *DICER1*-mutated pineoblastomas had LOH, compared with 26/619 (4%) in all other tumor types combined ($P < 0.0001$) [31]. This very high prevalence of complete loss of full-length DICER1 in pineoblastomas, together with mutually exclusive, frequent biallelic loss-of-function variants in other miRNA biogenesis genes in these tumors, suggests that the cell of origin of pineoblastoma is uniquely tolerant of miRNA perturbations [31]. Younger individuals with pineoblastoma are more likely to be associated with DICER1 syndrome than older individuals with pineoblastoma; pineoblastoma in a very young child may also result from other genetic causes such as *RB-1* alterations [97–99].

9.4.2.4 Primary CNS Sarcoma, DICER1-Mutant

Primary sarcomatous cerebral tumors are rare in children but are now increasingly recognized as a discrete phenotype in DICER1 syndrome. Like DICER1 anaplastic sarcoma of the kidney, these tumors have been described as PPB-like and are clearly DICER1-related sarcomas [3, 9, 14, 16, 96, 100–104]. Approximately 6 cases in DICER1-predisposed persons have been reported. The tumors revealed typical germline predisposing and/or somatic RNase IIIb *DICER1* alterations or occurred in children with other DICER1 phenotypes or phenotypic relatives [3, 9, 16, 31, 101, 104]; a total of 35 cases involving one or more germline and/or somatic *DICER1* alterations are documented [3, 9, 14, 16, 96, 100–104]. Among 13 cases where germline and tumor DNA have been studied, only 5 revealed germline involvement [31]. These data suggest that, in addition to DICER1 syndrome examples, exclusively somatic *DICER1* alterations contribute to many primary DICER1-related CNS sarcomas. Typical for most DICER1 syndrome tumors, primary CNS sarcoma—*DICER1* mutant tumors occur in the first two decades of life, with emphasis in the first 10 years. They predominantly affect the cerebral hemispheres; one has been reported in the brainstem, although it was not possible to distinguish it molecularly from possible metastasis of the patient's earlier DICER1-related sarcoma of the uterine cervix [96].

9.4.2.5 ETMR-Like Infantile Tumors

Eleven aggressive and unusual tumors resulting from *DICER1* alterations pathologically very similar to embryonal tumor with multilayered rosettes (ETMR) have been reported [43, 44, 100]. ETMR tumors encompass a set of aggressive early childhood CNS tumors that include entities previously described as ependymoblastoma and medulloepithelioma. They occur predominantly in children under 3 years of age [105]; 70% are supratentorial and 30% infratentorial [105]. Ninety percent of ETMR tumors reveal *C19MC* amplification, which is associated with dysregulated miRNA profiles [44]. About 10% of ETMRs do not demonstrate *C19MC* amplification ("*C19MC*-negative ETMR"), frequently have biallelic *DICER1* alterations ("ETMR *DICER1*-altered"), and tend to be infratentorial [105]. Thus, the *DICER1*-altered ETMR are likely to be infratentorial. ETMR tumors are highly likely to express LIN28A immunopositivity, regardless of their molecular signature [105]. Of the recently reported *DICER1*-altered ETMR, 11 of 11 had 2 *DICER1* alterations including an RNase IIIb variant; in 10 of the 11, the non-RNase IIIb variant was proven to be in the germline [43, 44, 100]. Three cases are reported in detail and occurred in infants less than 12 months of age; two were in the cerebellum [43, 100]; the third was large with an uncertain origin, but it was intraventricular and infiltrated the thalamus and superficially the cerebellar vermis [43, 100]. The three tumors were LIN28A positive; the pathology suggested ETMR, although in one child no true rosettes were identified [43]. None had *C19MC* amplification. The eight additional *DICER1*-altered ETMR tumors were reported with limited clinical

information; the site of the tumors was predominantly infratentorial [44]. An intracranial medulloepithelioma has been reported in one DICER1 syndrome kindred although molecular studies were not done [106].

In addition to *DICER1*-altered and *C19MC*-related ETMR tumors, two ETMR tumors have been reported with amplification of the *miR-17-92* miRNA cluster (*MIR17HG*) [44].

9.4.3 Ciliary Body Medulloepithelioma

Ciliary body medulloepithelioma (CBME) is a very rare embryonal ocular tumor occurring both sporadically and in association with DICER1 syndrome [107, 108]. CBME is histologically similar to medulloepithelioma within the ETMR tumors discussed above, and CBME is LIN28A positive [105]. However, CBME does not reveal *C19MC* amplification [105, 109]. As discussed below, *DICER1* alterations play a role in some CBME. Presenting with leukocoria and/or decreased visual acuity, CBME occurs in the latter half of the first decade of life in both DICER1-associated and presumed sporadic cases and usually leads to enucleation, but monitoring without surgery and in some cases with intraocular chemotherapy have been reported [110, 111]. CBME is classified histologically as teratoid or non-teratoid, either of which may be benign or malignant; cases associated with DICER1 syndrome are typically benign and a mixture of histologic types; one malignant CBME has been reported [9]. Bilateral disease has not been observed, although one individual with a mosaic predisposing *DICER1* alteration had multiple phenotypes as well as CBME in one globe; the other eye was "prephthisical secondary to anterior segment dysgenesis and had no light perception since early childhood" [7, 8, 112]. CBME cases are rare, and their incidence among carriers of pathogenic *DICER1* variants is difficult to ascertain. However, among approximately 300 PPB cases, 4 CBME were reported [110]; among 207 variant carriers studied systematically, 4 CBME were observed [19]; and among 103 variant carriers in a systematic survey who underwent comprehensive ophthalmologic examinations, 1 carrier had a history of CBME, and 2 carriers developed CBME 4.5 and 5 years, respectively, following normal comprehensive ophthalmologic examination [113]. These data involve ascertainment bias, and we estimate that 1% or less of variant carriers may develop CBME. A somatic RNase IIIb mutation has been reported in CBME and was not associated with a predisposing genetic abnormality [114]. A further six CBMEs harbored somatic RNase IIIb hotspot mutations; the germline status of these patients was not ascertained [9, 109, 115].

Congenital phthisis bulbi and related ocular dysplasia may also very rarely be related to *DICER1* mutation [8, 112, 116].

9.4.3.1 Nasal Chondromesenchymal Hamartoma

Nasal chondromesenchymal hamartoma (NCMH) is a very rare, benign tumor of the sinus and nasal cavities. Like some other tumors in DICER1 syndrome such as PPB and DICER1 anaplastic sarcoma of the kidney (discussed below), NCMH itself was first codified as a discrete pathologic entity in recent years [117]. Clinically, NCMH presents with nasal congestion and/or tissue at the nares. Histologically, NCMH is a complex mixture of cystic and solid cartilaginous and mesenchymal elements, typical of many DICER1 syndrome proliferations but without features of malignancy [117]. NCMH is an expansile proliferation in the nasal cavity and/or paranasal sinuses, may be bilateral, frequently effaces nearby delicate boney structures, and is managed with surgery even when there are recurrences [118, 119]. The co-occurrence of NCMH with PPB was noted in 2010 [118], and germline, mosaic, and somatic *DICER1* mutations have been demonstrated [119]. In the general population, NCMH occurs primarily in infants, whereas in DICER1 syndrome, NCMH is observed from the ages of approximately 6 to 21 years [117–119]. Its rarity is evidenced by 8 cases noted among 207 carriers of *DICER1* variants in DICER1 syndrome families [19]. Seven of the eight NCMH cases occurred in variant carriers who also had lung cysts and/or PPB. Other sinonasal proliferations than NCMH have also been observed in a small number of DICER1 syndrome patients and may result from coincidence [119].

9.5 Gastrointestinal Tract

9.5.1 Cystic Mesenchymal Hamartoma Liver

Apellaniz-Ruiz et al. reported on two children who developed hepatic cysts at very early ages (diagnosed at 26 months and 9 months, respectively) [45]. In the first child, hepatic resection of the partly cystic, partly solid lesion was followed by enlargement, and a repeat resection (hepatic lobectomy) was required 4 months later. The second child was found on magnetic resonance imaging at age 9 months to have a solid 14 mm liver tumor with clustered tiny cysts. The tumor gradually increased to 66 mm by age 39 months and had become predominantly cystic. At 75 months, a needle biopsy was undertaken. No resection was performed, and the cysts regressed over time. Subsequently the children developed other lesions typical for DICER1 syndrome, and both were found to possess germline pathogenic variants in *DICER1*. Only the first child's liver cyst gave a clear result—an RNase IIIb hotspot mutation was present. The authors decided, on the basis of the known lesions that occur in DICER1 syndrome, as well as the clinical presentation, course of the disease (including regression), pathological findings, and results of imaging studies, that the most plausible diagnosis was a cystic form of mesenchymal hamartoma of the liver (MHL) [120, 121]. This was strengthened by the known

association between *C19MC* and MHL and the pathological similarity between *DICER1*-related ETMR and *C19MC*-related ETMR (see above). However, two expert pathologists [122], on reviewing the published images, thought the correct diagnosis was solitary (nonparasitic) bile duct cysts of the liver [123]. Further studies will be required to resolve this controversy, but it seems that cystic hepatic tumors are a rare manifestation of DICER1 syndrome.

9.5.2 Hamartomatous Intestinal Polyps

Juvenile hamartomatous intestinal polyps have occurred in children in DICER1 syndrome kindred or in children with other DICER1 syndrome phenotypes; in some cases, constitutional *DICER1* mutations have been shown [124]. The most frequent site of the polyps is the ileum, where they may cause intussusception, but polyps from the esophagus to the rectum have been observed [4, 124]. Patients are typically under 5 years of age. The triad of intestinal polyps, lung cysts, and renal cysts in infants is strongly suggestive of DICER1 syndrome, perhaps especially so for *DICER1* RNase IIIb mosaicism [4, 7, 8, 32–35]. One published case of juvenile intestinal polyp had a proven predisposing *DICER1* alteration (a mosaic RNase IIIb variant) and a loss-of-function second mutation in a polyp [7]. In two cases, germline *DICER1* pathogenic variants were present, but polyp analysis revealed no somatic mutation or LOH [8, 45].

9.6 Gynecological Tract

9.6.1 Ovarian Sex Cord-Stromal Tumors and Other Ovarian Tumors

Ovarian sex cord-stromal tumors (OSCST), which include granulosa cell tumor and SLCT, are uncommon non-epithelial ovarian cancers definitively described by Young [125, 126]. As mentioned above, the association of ovarian SLCT (then known as arrhenoblastoma) and MNG was noted in 1974 [68]; germline pathogenic variants in *DICER1* were identified to be the genetic link (OMIM #138800) [71]. Both Schultz et al. and Slade et al. identified SLCT and other OSCST in PPB patients and their relatives in whom germline *DICER1* pathogenic variants were demonstrated [5, 127]. The pairing of SLCT with MNG or other hallmark DICER1 syndrome tumors in a proband or relatives is strongly suggestive of DICER1 syndrome [5, 71].

In 2011, Heravi-Mousavi et al. identified somatic *DICER1* RNase IIIb hotspot mutations in 60% of 43 unselected SLCT and initiated the search for such hotspot mutations in other phenotypes [25]. Subsequent studies have determined that

biallelic *DICER1* alterations characterize a large majority of SLCTs, particularly the moderately or poorly differentiated variants, including those with retiform areas and heterologous elements [27, 128–134]. Heterologous elements, including areas resembling rhabdomyosarcoma, may be a particular feature of some DICER1-related SLCT, but fully sarcomatous ovarian tumors are also seen in DICER1 syndrome, discussed below. At least 30% of reported moderately and poorly differentiated SLCTs arose in persons with germline *DICER1* mutations; it is likely that upward of 50% are syndromic [6, 27, 128–134]. It is speculated that the well-differentiated variant of SLCT is a fundamentally different tumor type from the moderate and poorly differentiated variants and is not DICER1 related [128]. Although most often unilateral, SLCT may occur bilaterally; bilateral SLCT is highly likely to be DICER1 related and, through genetic testing, has been found to represent independent primary tumors rather than metastatic neoplasms, which may have important implications for clinical management [135, 136].

SLCT associated with *DICER1* pathogenic variants can occur from early childhood to the fifth decade of life with most occurring from approximately age 10–25 years. Abdominal mass, abnormal menstruation, and hormonal perturbation such as androgenization are typical presenting signs. A sagittal section magnetic resonance image of DICER1-related left ovarian SLCT is shown in Fig. 9.5c.

Rarely, OSCST other than SLCT are DICER1 related, including juvenile granulosa cell tumor and pure Sertoli cell tumors [127]. Gynandroblastoma is an OSCST displaying both male and female sex cord differentiation; a subset of gynandroblastoma containing components of moderately or poorly differentiated SLCT and juvenile granulosa cell tumor exhibit *DICER1* hotspot mutations [137]. DICER1-related gynandroblastoma may represent morphological variants of SLCT [137].

Primary sarcoma of the ovary is another rare example of a DICER1-related sarcoma. Six cases have been reported: 5 were associated with germline *DICER1* pathogenic variants and bore somatic hotspot mutations [14, 127, 138–141] and one occurring in a 60-year-old harbored biallelic somatic *DICER1* mutations [13]. Other ovarian tumors, in particular the commonly seen epithelial ovarian tumors, are rarely if ever implicated in *DICER1* syndrome [25, 27, 142].

9.6.2 Embryonal Rhabdomyosarcoma of Uterine Cervix and Corpus

DICER1-related sarcoma of the uterine cervix is highly indicative of DICER1 syndrome. Known for years as cervical sarcoma botryoides or cervical embryonal rhabdomyosarcoma (ERMS), its association with SLCT has long been noted [126, 143–146]. It was definitively linked to *DICER1* alterations in 2011, and many cases have been reported [24, 26, 124, 147–149]. This disease presents in the second and third decades of life, most commonly among teenagers. Vaginal bleeding, passage of a vaginal polypoid mass, or a mass (often large) at the introitus are presenting

signs. The self-consciousness regarding sexual matters in teenage years probably accounts for delayed diagnosis in some cases. Recently it has been noted that cervical polyps judged benign, such as inflammatory polyps, can precede DICER1-related cervical sarcoma [150]; especially in any young woman with personal or family evidence of other syndrome phenotypes, molecular studies might reveal the *DICER1* involvement in polyps even when not frankly sarcomatous. In such instances, subtle benign-looking cervical polyps may in fact be sarcomas [151].

Two cases of DICER1 sarcomas of the uterine corpus have been reported in individuals with germline *DICER1* variants, and both tumors harbored an RNase IIIb hotspot mutation [152, 153]. Confusion as to the exact origin of some of these tumors is possible. In general, the cervical tumors are anatomically distinguishable from those arising from the uterine body; however, occasionally a tumor is considered to originate high in the vagina yet in fact may have a cervical origin.

9.6.3 Other Gynecologic Structures

A newly described entity which can involve various gynecologic structures is a "PPB-like" DICER1 sarcoma arising in the abdominal cavity from visceral or parietal peritoneum [13, 17]. Four such tumors appeared to arise from fallopian tube serosa. Biallelic *DICER1* mutations were identified in these tumors [13, 17]. The "PPB-like" moniker was used by one author because two of the tumors mimicked cystic Type I PPB [17]. A separate ERMS of the broad ligament bearing biallelic somatic *DICER1* alterations was fatal in a 23-year-old [154].

9.7 Kidney, Urinary Tract, and Testes

9.7.1 Cystic Nephroma, Anaplastic Renal Sarcoma, Wilms Tumor, and Bladder ERMS

Cystic nephroma (CN) and anaplastic sarcoma of the kidney are strongly associated with *DICER1* variants; Wilms tumor is very rarely encountered. CN is considered benign and is among the more frequent manifestations of DICER1 syndrome (Fig. 9.1, Table 9.1), occurring in between 5 and 10% of variant carriers [19, 35, 155, 156]. Except that CN cysts are fluid-filled, CN is grossly reminiscent of Type I PPB with exuberant clusters of thin-walled multilocular cysts (Fig. 9.5d). Microscopically CN also differs from Type I PPB in that there are no primitive cells. Using both molecular signatures and detailed pathologic examination, CN in young children can now be differentiated from a similar-appearing tumor in adult women (age > 50 years) with which it has been comingled in the past [157, 158]. Like PPB, CN may be bilateral and occurs in early childhood as most pathological diagnoses

are made by age 48 months [35, 156, 159]; radiographic detection may occur later [19, 160]. CN may develop after a normal ultrasound, and one unusual case revealed CN developing at age 12 years in a child followed closely with frequent abdominal imaging because of an earlier ovarian tumor [138]. Although classified pathologically as non-neoplastic, CN can progressively efface renal parenchyma leading rarely to bilateral nephrectomy and renal replacement [34]. Segmental or complete nephrectomy is frequent. Stable multicystic lesions or small areas of "recurrence" following partial nephrectomy have been untreated without complication, and because CN may be detected incidentally beyond early childhood, resecting CN may not be essential although more data must be collected [7]. Childhood CN is strongly associated with *DICER1* mutations: among 20 unselected cases, 15 had germline *DICER1* mutations, and 18 had somatic RNase IIIb hotspot mutations [156]. Bilateral CN and familial CN are highly suggestive of *DICER1* involvement [35, 155].

Cystic partially differentiated nephroblastoma (CPDN) is a cystic neoplasm with similarities to CN and to cystic Wilms tumor [158]. The few cases of CPDN studied have not revealed *DICER1* variants, and it has not been reported in DICER1 syndrome [156].

In 2007, anaplastic renal sarcoma was described as a distinct new pathologic entity among 20 individuals ranging in age from 10 months to 41 years, median age 5 years [49]. The authors noted that the tumors had the appearance of PPB and seven cases had distinct cystic components; as described earlier, this disease is a characteristic DICER1 sarcoma (Table 9.1). Between 2014 and 2018, several reports described additional cases of anaplastic renal sarcoma and an association with somatic and/or classic biallelic *DICER1* alterations and/or clinical evidence of DICER1 syndrome. These cases have led to the label "DICER1 anaplastic sarcoma of kidney" (D1ASK). In addition, some D1ASK are associated with prior or concurrent diagnoses of CN [136, 156, 161]. In one complex case, a cystic renal tumor appeared to be CPDN except that it manifested scattered anaplastic nuclei and atypical mitoses not consistent with CPDN; after germline and somatic *DICER1* mutations were identified, the tumor was finally considered to be an incipient D1ASK, i.e., CN in transition to D1ASK [161]. The association of prior CN with later D1ASK may mimic transition of Type I PPB into Type II or III PPB, although CN→D1ASK appears much less frequent than pulmonary progression [156]. That D1ASK may follow CN raises the question of whether all remnants of CN should be surgically extirpated; because the phenomenon is so infrequent, firm recommendations about resecting a clinically asymptomatic CN cannot yet be made.

Wilms tumor has been reported in several families with DICER1 syndrome and in individuals with *DICER1* alterations making *DICER1* a rare cause of this tumor [5, 7, 20, 28, 37, 96, 124, 153, 162–165]. However, large surveys of the genetics of Wilms tumor reveal that it is only rarely associated with predisposing *DICER1* alterations, at most in 1% of cases [166–170]. Expert pathology review is important because D1ASK can be misinterpreted as Wilms tumor [136]. Of narrow importance are the observations of three Wilms tumors associated with the *DICER1* RNase IIIa mutation c.4031C>T, p.Ser1344Leu; two mutations were somatic in

tumor [28, 166] and one was in the germline [37]. There were additional pathologies in all three children which led to genetic testing. Also, a study of 48 families with multiple Wilms tumors found 2 families with distinct *DICER1* alterations [122]. Except for the above rare examples, a sporadic case of Wilms tumor should not raise suspicion for *DICER1* involvement unless other DICER1 phenotypes appear in the patient or their family.

Despite the lack of a frequent connection between predisposing *DICER1* alterations and Wilms tumor, exclusively somatic mutations in the broad family of miRNA processing genes (*DROSHA*, *DGCR8*, *DICER1*, *XPO5*, and *TARBP2*) indeed play a role in up to one-third of Wilms tumors [1, 166–170].

9.7.2 Bladder DICER1 Sarcoma (and Other Childhood Rhabdomyosarcomas)

DICER1 sarcoma in the urinary bladder has been reported in several children in DICER1 syndrome kindred or children who harbor germline *DICER1* alterations [4, 24, 106, 136, 171]. In one case, biallelic mutations have been demonstrated [136]. The children have been diagnosed from the first though the 14th years of life; both males and females are affected.

Bladder ERMS is among the sites of classic early childhood ERMS, which include also the vulva and vagina, the paratesticular tissues, the prostate, and the orbit/nasopharynx/parameningeal site. Among these sites, only for bladder ERMS have multiple examples been associated with DICER1 syndrome. A vaginal ERMS is reported at age 5 years [160]. An unusual low-grade myxoid sarcoma in the paratestis is reported in a child with a germline *DICER1* variant who also had CN (Table 9.1); both tumors harbored an RNase IIIb hotspot mutation [172]. The same publication reports no *DICER1* alterations in 13 paratesticular ERMS [172]. To our knowledge, surveys for *DICER1* alterations of ERMS in the other typical childhood sites have not been reported.

9.7.3 Testicular Tumors

Germline pathogenic variants in *DICER1* do not appear to predispose to testicular germ cell tumors [142, 173]. The equivalent testicular tumors to ovarian Sertoli-Leydig cell tumor would be Sertoli cell tumors and Leydig cell tumors. There is an unpublished report of a young boy with a germline *DICER1* pathogenic variant who developed a PPB and Sertoli cell tumor of the testis that contains an RNase IIIb hotspot mutation, but clearly, they are extremely rare occurrences.

9.8 Other Abdominal Tumors

9.8.1 Presacral Malignant Teratoid Tumor

Two very young infants have been recently reported with unusual DICER1-related tumors labeled presacral malignant teratoid tumors (Fig. 9.1, Table 9.1) [160]. A 1-week-old child had an intraspinal-canal extradural tumor from vertebral body L2 to the sacrum. A 4-month-old child had a large presacral pelvic mass. Pathologically the first tumor was multipatterned with a mixture of medulloepithelioma-like and mesenchymal ERMS elements. The second tumor was composed of primitive neuroepithelium and ERMS elements. Both tumors had immature cartilage, and neither had broader germ layer components to be considered malignant teratomas. Both tumors harbored a germline loss-of-function *DICER1* pathogenic variant coupled with a typical somatic RNase IIIb hotspot mutation. The first child succumbed to recurrent disease after a few months. The second child survived and later developed vaginal ERMS, D1ASK in a CN, papillary thyroid microcarcinoma, CN in the contralateral kidney, and NCMH.

9.8.2 PPB-Like Peritoneal Sarcoma

Discussed briefly above with gynecologic tumors are two recent reports describing several children and one adult with "PPB-like" DICER1 sarcomas arising in the abdominal cavity from visceral or parietal peritoneum; two of the cases appear to be included in each report [13, 17]. The patients ranged from 3 to 14 years of age (median age 13 years) with one additional primary ovarian sarcoma in a 60-year-old woman; all but one of the cases were in females. With the exception of the ovarian sarcoma [13], the tumors arose upon the serosal surfaces of fallopian tubes ($n = 4$), colon ($n = 1$), and pelvic sidewall ($n = 2$). Two of the tumors comprised clusters of cysts resembling Type I and Ir PPB, respectively, leading Schultz et al. to identify their cases as "PPB-like peritoneal sarcomas" mimicking the cystic to solid continuum of PPB [17]. Apart from the cystic tumors, the tumors were complex DICER1 sarcomas. In six of the seven cases, tumor DNA revealed biallelic loss-of-function and RNase IIIb *DICER1* alterations. Four of five tested children had germline *DICER1* alterations. Six of the seven children survived 10–155 months (median 65 months) from peritoneal sarcoma diagnosis.

9.9 Rare or Possible Associations

DICER1 syndrome features the characteristic tumors and dysplasias discussed above, but in addition, children with DICER1 phenotypes or their kindred may develop other pediatric tumors. Although some such tumors may be coincidental, in

view of the pleiotropy of the syndrome, some can result from DICER1 dysfunction, particularly if similar tumors have been observed in syndromic settings. For example, sarcomas with pathological features other than the typical DICER1-related sarcoma [48] have been reported in persons with germline *DICER1* mutations (synovial sarcoma in in a cousin of a PPB patient [3], pleomorphic sarcoma with leiomyosarcomatous features in a woman aged 26 years [124], and paraspinal rhabdomyosarcoma at age 20 years [71] (see also the low-grade myxoid paratesticular sarcoma discussed below [172])).

Pulmonary sequestration was discovered in a child with a germline *DICER1* mutation and CN [174]; the sequestration specimen was found not to have a typical RNase IIIb mutation (de Kock and Foulkes, unpublished data). Two other children with pulmonary sequestration were found to harbor PPBs within resected sequestration specimens (Types I and II, respectively) [175, 176]. In each case, the sequestrations had non-pulmonary artery feeding vessels and had pleural membranes distinct from nearby lobes. In neither of these children were molecular studies performed. Transposition of the great arteries was noted in a *DICER1*-affected kindred [124], but a larger study of transposition of the great arteries suggested that there is no association with germline *DICER1* variants [177]. Three cases of Ewing sarcoma-type tumors have been observed: one arising in the cervix [124] and two on the chest wall ([154] and de Kock and Foulkes, unpublished). In the former case, the patient carried a germline *DICER1* pathogenic variant, but the cervical tumor was not evaluated; in the latter two cases, the germline revealed a loss-of-function *DICER1* pathogenic variant, but there was no "second hit" in *DICER1* in the tumors ([154] and de Kock and Foulkes, unpublished). A child reported to have CCAM (later considered to be Type I PPB) also had an intracranial vein of Galen cyst; no molecular studies were done [178].

Various other classical childhood tumors may arise incidentally in *DICER1* variant carriers. For example, neuroblastoma has been noted, but no study has identified a somatic *DICER1* mutation to indicate canonical *DICER1* causality [5, 179–181]. An atypical choroid plexus papilloma in a child with PPB Type I was carefully determined not to be related to *DICER1* mutation [38, 182]. In contrast, the recent report of one male with an unusual low-grade myxoid paratesticular sarcoma is probably a true, albeit very rare, association, in view of the presence of a germline *DICER1* pathogenic variant, his history of CN, and the presence of different somatic RNase IIIb missense hotspot mutations in the sarcoma and the CN [172]. Similarly, the sole report of a well-differentiated fetal lung adenocarcinoma arising in a child with DICER1 syndrome is supported by the presence of a characteristic "second hit" in the tumor [183]. There is a single unpublished report of a child with a germline *DICER1* pathogenic variant, PPB, and a testicular Sertoli cell tumor, wherein the testicular tumor has a typical RNase IIIb hotspot mutation, making it likely that this is a true association. Other very rare but real associations are likely to continue to emerge.

Adult-onset tumors have been reported in DICER1 syndrome, but these could be incidental. For example, Cotton and Ray reported on the case of a pituitary microadenoma (prolactinoma) occurring in a 50-year-old woman with DICER1

syndrome, but no molecular work was performed on the pituitary tumor [184]. The patient may have had the prolactinoma for over 20 years, but early-onset pituitary adenomas are not known to be related to DICER1 syndrome [185]. A pathologically diagnosed prolactinoma occurred in a 25-year-old woman who also had SLCT and was in a DICER1 kindred; the tumor was not studied [JRP personal observation]. In another DICER1 kindred with a proven *DICER1* germline variant, at age 43 years, the brother of a man (with childhood lung cysts and an eye tumor) had a radiographically diagnosed pituitary microadenoma which was treated chemically [JRP personal observation]. Prolactinomas are not rare, but with pituitary blastoma such a characteristic DICER1 tumor, these observations of prolactinoma deserve attention.

9.10 Non-neoplastic Phenotypes in DICER1 Syndrome

Four surveys have systematically studied various anatomical sites of *DICER1* variant carriers and identified certain non-neoplastic manifestations of DICER1 syndrome. The studies focused on auxology, kidneys and urinary tract, eyes, and dentition.

In the auxology study, various body measurements were compared between 76 known *DICER1* variant carriers and 53 *DICER1* wild-type family members [186]. Both male and female variant carriers had significantly larger occipito-frontal head circumference (OFC) than population norms and family controls ($p < 0.001$); 42% of all carriers (33% of males and 50% of females) were "macrocephalic" defined as OFC greater than the 97th percentile of published norms; however, the difference between carriers and controls was only significant among adults. In general, the OFCs of variant carriers ranged from the 50th to above the 97th percentiles of published norms, whereas OFCs of family controls ranged between the 3rd and 97th percentiles. Variant carriers were significantly taller than family controls ($p = 0.048$), but the proportions of both variant carriers and family members above the 97th percentile for height were similar and not different from population controls. Large OFC did not correlate with height. There were no differences between carriers and family controls in upper body length (symphysis pubis to top of head) versus lower body length (symphysis pubis to floor) nor in arm span.

In the study of kidney and urinary collecting system structures, 89 *DICER1* variant carriers were compared to 61 *DICER1* wild-type family controls using renal ultrasound and blood and urine biochemical tests [159]. A renal cyst was detected in 1 of 33 children who did not have a prior history of CN (8 of 41 carrier children had had a prior CN diagnosis). In adults, ultrasound-detected renal cysts were similar in carriers and controls (in ~20% of each group). Eight of 89 variant carriers had ultrasound-detected kidney and collecting system anomalies, which included nephrocalcinosis, nephrolithiasis, and structural abnormalities of varying severity. The structural anomalies involved partially duplicated collecting system ($n = 2$), collecting system dilatation following a uretero-pelvic junction repair ($n = 1$) and

incomplete rotation of the kidney ($n = 1$). There were no notable biochemical differences between study subjects based on plasma, serum, or urine chemistries.

In the ophthalmologic study, 103 *DICER1* variant carriers were compared to 69 *DICER1* wild-type family controls using a wide array of detailed ophthalmologic examinations (which did not include imaging modalities) [113]. Among variant carriers, 97% had visual acuity of 20/40 or greater; 23 variant carriers (22%) had various ocular abnormalities of retinal pigment, increased cup-to-disc ratio, or optic nerves compared to 4 such findings in controls ($p = 0.005$). One carrier had the unexpected finding of retinitis pigmentosa with a novel variant of unknown significance in *PRPF31*. Three of the 103 variant carriers had developed CBME by the time the study was reported: one prior to enrollment in the study and two 7-year-old carriers developed CBME 4.5 and 5 years, respectively, following normal findings in the extensive evaluations of the study. Each of these two children had developed symptomatology (vision loss and strabismus, respectively) which led to ophthalmologic examination and discovery of CBME.

In the study of the dental phenotype of DICER1 syndrome, 57 *DICER1* variant carriers were compared to 55 *DICER1* wild-type family controls [187]. Each was evaluated with dental examination, dental radiographs, and oral photograph. Compared to family controls, carriers were significantly more likely to exhibit periodontitis and bulbous crowns. A bulbous crown is a relative ballooning of the crown of the tooth and relative belt-like constriction at the junction between the crown and root, whereas a normal tooth has a less full crown and a gradual tapered profile as the crown blends to the root. In the molars of variant carriers, the examiners also noted taurodontism in which the upper body of the tooth (and its internal pulp cavity) is relatively enlarged compared to the roots, with the result that the roots are correspondingly shorter than normal. In logistic regression analysis, only bulbous crowns and periodontitis were confirmed as significant observations in carriers versus family controls.

9.11 Notes on Tumor Surveillance in DICER1 Syndrome

Although the DICER1 phenotype will likely evolve, recognition and genetic confirmation of the syndrome are now practical. Commercial and research *DICER1* assays are available from several sources. When routine studies fail to identify a pathogenic *DICER1* variant, highly suggestive cases may be solved by more intensive analysis including evaluating for large or small deletions or mosaicism [188]. A diagnosis of even one of the highly characteristic DICER1 phenotypes deserves suspicion (Fig. 9.1, Table 9.1). Two or more of the less distinctive conditions in a patient or family also deserve inquiry. Because of low penetrance and pleiotropy, detailed family histories may reveal unexpected associations [106], and focused pathologic reevaluations may reveal associated diagnoses.

For affected kindred and their caregivers, questions of carrier identification, genetic counseling, disease screening, and early diagnosis will arise. In general,

the authors recommend genetic counseling, testing for carrier status, and continuing family education. That many carriers are unaffected and diseases often not life-threatening may reassure families (Table 9.1). Once variant carriers are identified, screening for DICER1 phenotypes must be addressed; many factors influence the reasonableness of screening. Is the goal of screening early detection and will early detection likely affect outcome? Will screening provide reassurance to families or cause excess anxiety? Penetrance is generally quite low, and several conditions are exceedingly rare. Phenotypes like MNG and ovarian stromal tumors present along a protracted age spectrum from approximately 5 years or earlier to 40 years and beyond. In contrast, PPB, CN, pituitary blastoma, the ETMR-like cerebral tumors, CBME, and NCMH occur in narrower age ranges (Table 9.1). Family education should include the differences among phenotypes and also include some warnings like respiratory distress or "pneumonia" as possible signs of PPB and menstrual changes or hirsutism as signs of a cervical or ovarian tumor, respectively. Screening modalities can include questioning for symptoms or signs, physical examinations, and imaging which may range from less invasive ultrasound to computed tomography or magnetic resonance, which in infants may require anesthesia. The frequency of screening must address the conflict between high frequency, which might actually result in early detection, or low frequency with reduced chances that a disease will be detected before it becomes symptomatic.

Screening for ovarian stromal cell tumors exemplifies the problem: the age range for diagnosis extends from age ~2 years to age 40–50 years or more. Death from SLCT and other ovarian phenotypes appears to be uncommon. Do these circumstances support years of screenings such as abdominal or vaginal ultrasound? And at what intervals? In contrast, PPB occurs in a much tighter age range from birth to age 72 months. Whether serial chest radiographs or computed tomography with its higher likelihood of detection is justified will likely be local decisions with family input. And again, how often? The authors suggest that careful education as well as reasonable efforts at reassurance can help DICER1 families, with recognition that each family will have its own determinants for reassurance, which are likely to evolve over time.

There have been some expert recommendations about screening, but they vary widely. At one institution, frequent evaluations including annual whole-body magnetic resonance imaging are suggested [189]. A broad consortium of physicians has published screening guidelines that address each phenotype and organ system [56]. The most focused screening schema involves the detection of cystic PPB in proven *DICER1* variant carriers in the first 2 years of life and is based on the observation that extirpation of cystic Type I PPB may prevent evolution of such a lesion to aggressive Types II or III PPB [55].

9.12 Late-Breaking Update, April 2021

9.12.1 DICER1 Sarcomas

In a similar fashion to this opening section, McCluggage and Foulkes [192] have put forward the notion that many of the diagnostically discrete entities that are discussed in Sects. 9.2, 9.6.2, 9.6.3, 9.7.1, 9.7.2, 9.8.1, and 9.8.2 share common features and have called for efforts to unify the nomenclature. In support of this, Kommoss et al. [193] have recently reported that DICER1-related genitourinary ERMS share distinct methylation profiles that distinguish them from non-DICER1-related ERMS. This paper is also relevant to Sect. 9.6.2.

9.12.2 Chest

Some PPBs, especially later-stage tumors, harbor somatic *TP53* mutations. When present, the PPBs appear to have a worse outcome. This may be important in management [194].

9.12.3 Cranial and Intracranial Tumors

Two important papers on pituitary blastoma have described the clinicopathological and molecular features, respectively—the former showing that nearly half of the children have died, and that resection extent was associated without outcome [195]; the latter showed that PRAME, an antigen expressed in normal testes, is significantly over-expressed in pituitary blastoma [196].

9.12.4 Gastrointestinal Tract

A recent case report described a primary biphasic hepatic sarcoma with an RNase IIIb somatic mutation in a child with DICER1 syndrome [197]. The authors of the report consider this entity to be the sarcomatous equivalent of the lesion described by Apellaniz-Ruiz et al., reported in Sect 9.5.1.

9.12.5 Kidney, Urinary Tract, and Testes

Mentioned in Sect. 9.9, the first report of a Testicular Stromal Cell tumor with both germline and somatic hotspot alterations has emerged. Clearly the testes are much more rarely affected than the ovaries, but it is likely that additional reports, possibly also of Leydig cell tumors, will be identified in future [198].

9.12.6 Rare or Possible Associations

The child described in [37] has subsequently been determined to have had a well-differentiated fetal lung adenocarcinoma (with a second *DICER1* "hit"), supporting the finding first reported in [183]. The question of whether Ewing's sarcoma is part of DICER1 syndrome was posed in this section, as no Ewing's tumor occurring in person with DICER1 syndrome had been found to have a hotspot second hit. The story has become more complicated as there is a recent case report of a 16-year-old female who was diagnosed with a high-grade undifferentiated cancer consisting of blastemal-like small blue cells [199]. The *EWSR1* gene rearrangement was found in ~16% of nuclei, but no fusion partner was found. A somatic hotspot mutation in *DICER1* was identified, however. Thus, it remains uncertain whether classical Ewing's tumor is part of DICER1 syndrome.

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