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NLM Citation: Schultz KAP, Stewart DR, Kamihara J, et al. *DICER1* Tumor Predisposition. 2014 Apr 24 [Updated 2020 Apr 30]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

DICER1 Tumor Predisposition

Synonyms: *DICER1* Pleuropulmonary Blastoma Familial Tumor Predisposition Syndrome, *DICER1* Syndrome

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Created: April 24, 2014; Updated: April 30, 2020.

Summary

Clinical characteristics

DICER1 tumor predisposition (DICER1) is characterized by an increased risk for pleuropulmonary blastoma (PPB), pulmonary cysts, thyroid gland neoplasia (multinodular goiter, adenomas, and/or thyroid cancer), ovarian tumors (Sertoli-Leydig cell tumor, gynandroblastoma, and sarcoma), and cystic nephroma. Less commonly observed tumors include ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, embryonal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, central nervous system (CNS) sarcoma, other CNS tumors, and presacral malignant teratoid tumor. The majority of tumors occur in individuals younger than age 40 years. PPB typically presents in infants and children younger than age six years. Ovarian sex cord-

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stromal tumors are most often diagnosed before age 40 years. Cystic nephroma generally presents in young children but has also been reported in adolescents. Additional clinical features that may be seen include macrocephaly, ocular abnormalities, structural anomalies of the kidney and collecting system, and dental anomalies (bulbous crowns).

Diagnosis/testing

The diagnosis of DICER1 is established by identification of a heterozygous germline *DICER1* pathogenic variant that is known or suspected to cause loss of function.

Management

Treatment of manifestations: Treatment for *DICER1*-associated malignant tumors is dependent on tumor type and stage. Most often treatment involves surgical resection with or without chemotherapy. The treatment of PPB may also include radiation, primarily to treat residual disease or recurrence. Thyroid nodules that have concerning features may require biopsy and/or surgical resection. Ovarian tumors require surgery and may also require chemotherapy. Ciliary body medulloepithelioma has been treated with resection or plaque brachytherapy.

Surveillance: Chest radiograph shortly after birth is recommended for infants at risk for a germline *DICER1* pathogenic variant. In individuals with confirmed DICER1, clinical examination and imaging-based surveillance for signs and symptoms of PPB, thyroid gland neoplasia, ovarian sex cord-stromal tumors, and other *DICER1*-associated tumors is recommended. Current imaging guidelines include chest radiograph every four to six months until age eight years, and every 12 months from age eight to 12 years. Chest CT at age three to six months with repeat chest CT at age 30 months to three years should be considered. Baseline chest radiograph or chest CT should be considered in those diagnosed after age 12 years. Thyroid ultrasound is recommended beginning at age eight years with subsequent ultrasounds every three to five years. Individuals with a history of chemotherapy exposure should begin thyroid ultrasound within three to five years of treatment. Thyroid function testing is recommended for individuals with symptoms of thyroid dysfunction. Pelvic ultrasounds for surveillance for gynecologic tumors in females are recommended every six to 12 months beginning at age eight years and extending until at least age 40 years. Screening for cystic nephroma and other renal tumors includes abdominal ultrasounds every six months until age eight years and then annually until age 12 years. Visual acuity measurement and dilated ophthalmology examination for ciliary body medulloepithelioma is recommended annually from age three years until at least age ten years. Annual physical examination should include assessment of extraocular movements, assessment of red reflex, neurologic examination, and thyroid palpation. Family education is the cornerstone of surveillance.

Evaluation of relatives at risk: If a germline *DICER1* pathogenic variant has been identified in an affected family member, it is reasonable to offer molecular genetic testing to at-risk relatives of all ages to clarify their genetic status and to provide recommendations for age-appropriate surveillance and early intervention.

Pregnancy management: In rare instances large lung cysts may cause respiratory distress in newborns, and thus a third-trimester ultrasound is recommended for pregnancies in which the fetus is at risk for a *DICER1* pathogenic variant. If lung cysts are identified, consultation with specialists in high-risk obstetrics and fetal medicine is recommended.

Genetic counseling

DICER1 is inherited in an autosomal dominant manner with reduced penetrance. In individuals with PPB with a detectable germline *DICER1* pathogenic variant, approximately 80% of the germline pathogenic variants were inherited from a parent and approximately 20% were *de novo*. Each child of an individual with a *DICER1* germline pathogenic variant has a 50% chance of inheriting the variant. Given the reduced penetrance, many

individuals with a germline *DICER1* pathogenic variant remain clinically unaffected. Once a germline *DICER1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

DICER1 tumor predisposition (DICER1) **should be suspected** in individuals with the following tumors and/or clinical features:

- Pleuropulmonary blastoma (PPB)
- Single or multiple pulmonary cysts and/or pneumothorax identified in a newborn or young child
- Thyroid adenomas, multinodular goiter, and/or well-differentiated thyroid cancer, especially in individuals with a family history of additional features of DICER1. Poorly differentiated thyroid cancer has also been described.
- Ovarian tumors including sex cord-stromal tumors (e.g., Sertoli-Leydig cell tumor, gynandroblastoma, embryonal rhabdomyosarcoma, undifferentiated sarcomas)
- Cystic nephroma with or without progression to anaplastic sarcoma of kidney
- Ciliary body medulloepithelioma
- Nasal chondromesenchymal hamartoma
- Embryonal rhabdomyosarcoma of the cervix or other sites with features of adenosarcoma
- Pituitary blastoma
- Pineoblastoma
- *DICER1*-associated central nervous system (CNS) sarcoma
- Other CNS embryonal tumors / ETMR-like (embryonal tumor with multilayer rosettes)
- Presacral malignant teratoid neoplasm of infancy
- Multicystic hepatic lesions
- Pleuropulmonary blastoma-like peritoneal sarcoma (peritoneal "PPB")
- Macrocephaly

Laboratory finding on tumor tissue testing. Identification of a somatic *DICER1* pathogenic variant by molecular genetic testing of tumor tissue may suggest the presence of a germline *DICER1* pathogenic variant. Note: (1) Fresh-frozen tumor is preferable for molecular testing; formalin-fixed, paraffin-embedded samples may also be suitable. (2) Identification of a *DICER1* pathogenic variant in tumor tissue has been described in the absence of a germline *DICER1* pathogenic variant.

Note: Somatic mosaicism for a *DICER1* pathogenic variant should be suspected in individuals with features of DICER1 – for example, one of the tumors described above with or without somatic overgrowth (see Clinical Description, **GLOW syndrome**).

Establishing the Diagnosis

The diagnosis DICER1 **is established** in a proband by identification of a heterozygous germline pathogenic variant in *DICER1* that is known or suspected to cause loss of function (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of DICER1 is broad, individuals with the distinctive findings described

in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with increased tumor susceptibility are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When clinical, imaging, laboratory, and/or histopathology findings suggest the diagnosis of DICER1, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *DICER1* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A hereditary cancer multigene panel** that includes *DICER1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by increased tumor susceptibility, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *DICER1* Tumor Predisposition

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
DICER1	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 6.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2017].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. More than six families with intragenic or whole-gene *DICER1* deletions have been reported to date [Sabbaghian et al 2014, Brenneman et al 2015, de Kock et al 2018].

Testing for somatic mosaicism. Approximately 10% of individuals with a *de novo DICER1* pathogenic variant have somatic mosaicism for the variant [Brenneman et al 2015, de Kock et al 2016]. In individuals with mosaicism for a *DICER1* loss-of-function variant, clinical features appear similar to those with germline loss-of-function variants. Such individuals may have normal molecular genetic testing of *DICER1* in unaffected tissue, such as lymphocytes; thus, molecular genetic testing of tissue from more than one tissue type may be necessary to establish the presence of somatic mosaicism. When tumor DNA is tested, pathogenic variants in both *DICER1* alleles must be identified.

A small group of individuals has been identified with mosaicism for *DICER1* pathogenic variants in the RNase IIIb domain. These individuals have a higher-than-average number of disease foci (see Genotype-Phenotype Correlations) [Brenneman et al 2015, de Kock et al 2016].

Clinical Characteristics

Clinical Description

To date, more than 1,000 individuals have been identified with a germline pathogenic variant in *DICER1* including literature reports and unpublished International PPB/*DICER1* Registry and NIH Natural History Study data. The following description of the phenotypic features associated with this condition is based on these reports.

Studies to date have focused on germline *DICER1* pathogenic variants occurring in children with pleuropulmonary blastoma (PPB), in girls and women with ovarian sex cord-stromal tumors, children with cystic nephroma, and families with thyroid hyperplasia as well as other tumor types. The majority of tumors reported in individuals with a germline *DICER1* pathogenic variant occur in individuals younger than age 40 years. Less is known about the risk for malignancies or other conditions in older adults with a germline *DICER1* pathogenic variant.

Table 2. Select Features of *DICER1* Tumor Predisposition

Feature	% of Persons w/*DICER1* Germline Pathogenic Variant w/Feature	Comment
Macrocephaly	~42%	

Table 2. continued from previous page.

Feature	% of Persons w/*DICER1* Germline Pathogenic Variant w/Feature	Comment
Pleuropulmonary blastoma	Lung cysts / type Ir PPB in 25%-40%; PPB types I, II, & III in <10%	65% of children w/PPB had a *DICER1* germline pathogenic variant.
Multinodular goiter	32% of women; 13% of men	By age 20 yrs
	75% of women; 17% of men	By age 40 yrs
Ovarian sex cord-stromal tumors	<10%	~50% of persons w/SLCT & gynandroblastoma had a *DICER1* germline pathogenic variant. [1]
Cystic nephroma	≤10%	
Ciliary body medulloepithelioma	~3%	
Differentiated thyroid carcinoma	Rare	16- to 24-fold ↑ risk
Nasal chondromesenchymal hamartoma	Rare	~1% of persons ascertained by family history (non-probands)
Other tumors	Rare	Embryonal rhabdomyosarcoma, pituitary blastoma, pineoblastoma, CNS sarcomas, presacral malignant teratoid tumor, & other CNS embryonal tumors/ETMR-like
Multicystic hepatic lesions	Very rare [2]	

CNS = central nervous system; ETMR = embryonal tumor with multilayer rosettes; PPB = pleuropulmonary blastoma; SLCT = Sertoli-Leydig cell tumor; type Ir PPB = regressed or nonprogressed PPB

1. Schultz et al [2017]

2. Two instances of multicystic hepatic lesions reported [Apellaniz-Ruiz et al 2019]

Pleuropulmonary blastoma (PPB) occurs primarily in very young children. Clinically significant PPB typically presents in infants and in children younger than age seven years; however, rare occurrences have been reported in older children and one adult [Hill et al 1999].

PPB occurs in four main types:

- Type I PPB is a purely cystic lesion containing a layer of malignant cells. If left in situ, the malignant component of type I PPB may proliferate further, leading to type II PPB. Typically, type I PPB becomes evident in infants and young children (median age at diagnosis: 8 months) with difficulty breathing due to a large space-occupying cyst in the lung or pneumothorax secondary to a rupture of the air-filled cyst. Occasionally lung cysts are identified in asymptomatic children when radiographic studies are performed for nonrespiratory symptoms or surveillance. Five-year survival for type I PPB is 89% [Messinger et al 2015].
- Type II PPB is a mixed cystic and solid tumor that presents at a median age of 35 months. A child with type II PPB typically presents with weight loss, fever, shortness of breath, and opacity or pneumothorax on chest radiograph. Five-year survival for type II PPB is 71% [Messinger et al 2015].
- Type III PPB is a purely solid, aggressive sarcoma which may present with respiratory distress and mediastinal shift. Type III PPB presents at a median age of 41 months. Children with type III PPB typically present with weight loss, fever, shortness of breath, and opacity on chest radiograph. Five-year survival for type III PPB is 53% [Messinger et al 2015].
- Type Ir (regressed or nonprogressed) PPB presents in individuals of any age and lacks a malignant component. Five-year survival for type Ir PPB is 100% [Messinger et al 2015].

The natural history of PPB suggests that many tumors have a precancerous / early cancerous stage in the form of lung cysts. Although not all PPB lung cysts transform into high-grade sarcoma, no radiographic characteristics can yet identify which cysts will progress to sarcoma. Progression from cyst to sarcoma can occur quickly. When progression occurs, the mesenchymal cells of a type I PPB expand and overgrow the cyst septa and replace the cyst with a cystic and solid (type II) or purely solid (type III) sarcoma. Type I PPB has no metastatic potential, but individuals with type II or III PPB can present with or develop metastasis to the brain, bone, local thoracic lymph nodes, and liver.

Children with PPB type II or III may have tumor recurrence locally in the thorax and/or distant metastatic disease. The brain, followed by bone, is the most common site of distant metastasis in PPB. The outcome for these individuals is poor, although some have survived long-term [Priest et al 2007, Nakano et al 2019a].

Multinodular goiter (MNG) and thyroid cancer. Germline *DICER1* pathogenic variants are associated with an increased risk of developing thyroid nodules and/or MNG. By age 20 years, 32% of women and 13% of men with a *DICER1* pathogenic variant will be diagnosed with MNG and/or have undergone a thyroidectomy [Khan et al 2017b].

However, data also suggest a risk for *DICER1*-associated differentiated thyroid cancer (DTC) including papillary and follicular thyroid cancer [Hill et al 2009, Rio Frio et al 2011, Slade et al 2011, Rutter et al 2016]. *DICER1*-associated DTC is often encapsulated and is typically not associated with lymphovascular invasion, extrathyroidal extension, or regional lymph node metastasis [Rutter et al 2016, van der Tuin et al 2019].

A history of PPB is associated with an increased risk of *DICER1*-associated DTC with a shorter latency, within five years of PPB therapy [de Kock et al 2014b]. The etiology for this increased risk may be secondary to *DICER1*-associated DTC confounded by exposure to the chemotherapy and/or repeated radiologic imaging. Outcome of thyroid tumors in *DICER1*-associated DTC is favorable with a high likelihood of achieving remission.

Poorly differentiated thyroid cancer has rarely been reported [Chernock et al 2020].

Ovarian sex cord-stromal tumors. Age of onset varies widely from early childhood to late adulthood, although most individuals are diagnosed within the reproductive years (95% before age 40 years). Most ovarian sex cord-stromal tumors present at an early stage. Types of ovarian sex cord-stromal tumors include the following:

- **Sertoli-Leydig cell tumor (SLCT)** may present with typical signs of an ovarian tumor including abdominal distention, abdominal pain, or mass. Menstrual cycle irregularity, amenorrhea, and precocious puberty may be noted. Signs of virilization such as hirsutism, voice changes, or acne may also be seen and warrant measurement of testosterone levels. While the tumor can occur at any age, it occurs most often in adolescents and young adults.

  Ovarian sex cord-stromal tumors are staged using the International Federation of Gynecology and Obstetrics (FIGO) staging system. Well-differentiated, stage Ia tumors generally behave in a benign fashion. Poorly differentiated or higher-stage tumors are associated with a poorer prognosis. Most *DICER1*-associated SLCTs have moderately differentiated features although well differentiated and poorly differentiated forms have been described.

- **Gynandroblastoma.** Girls and young women with this tumor may present with or without signs of excess hormonal production. Gynandroblastoma is associated with a favorable prognosis if found as stage Ia. Individuals with higher risk histologic features (e.g., poorly differentiated, sarcomatous elements) or higher-stage disease may require adjuvant therapy.

Cystic nephroma (CN) is the most common renal manifestation in individuals with DICER1. CN is considered a benign neoplasm that presents as a cystic parenchymal renal tumor (most commonly as a painless, enlarging

abdominal or flank mass). CN is most common in children younger than age four years, although *DICER1*-associated CN has also occurred in adolescents. Hematuria, hypertension, and urinary tract infection are uncommon presentations. CN may grow rapidly and cause concern for mass effect on normal-functioning kidneys, a particular concern in bilateral tumors.

A small number of children with *DICER1*-associated CN have later developed high-grade renal sarcomas resembling PPB [Doros et al 2014]. This sarcomatous transformation in the kidney is similar to the transformation observed in the lung from type I to III PPB. These tumors are known as anaplastic sarcomas of the kidney [Wu et al 2018].

Ciliary body medulloepithelioma (CBME) is a primitive neuroepithelial neoplasm arising from the nonpigmented ciliary epithelium. CBMEs are typically identified in young children with an average age at diagnosis of six years. Individuals may be asymptomatic when the tumor is small; however, decreased visual acuity, leukocoria, or new strabismus is often noted. On examination, a visible retrolental ciliary body mass or cataract with subluxation and possible secondary glaucoma may be identified.

Although CBMEs are considered malignant neoplasms based on their histology, distant metastasis and mortality are rare. Mortality from CBME usually results from intracranial spread rather than systemic metastases. In a study of 103 individuals with a germline *DICER1* pathogenic variant, three individuals with CBME were identified; two of the children presented with vision loss of unknown duration, with a normal dilated eye exam noted within one year prior to CBME diagnosis [Huryn et al 2019].

Nasal chondromesenchymal hamartoma (NCMH) typically presents in children with chronic sinusitis, congestion, or other sinonasal symptoms. NCMH is considered a benign neoplasm. Surgical removal is generally curative; however, local recurrences can occur (see Management). A study of 102 individuals with a germline *DICER1* pathogenic variant, not ascertained for a tumor (non-probands), found that approximately 1% had NCMH [Stewart et al 2019].

Embryonal rhabdomyosarcoma (ERMS) of the cervix in individuals with a *DICER1* germline pathogenic variant most commonly occurs in pubertal and postpubertal adolescent girls and young women. ERMS may present with vaginal bleeding or passage of tissue.

Pituitary blastoma is a rare tumor described in children age two years and younger who may present with Cushing syndrome, ophthalmoplegia, and diabetes insipidus; ACTH levels are elevated in the majority of individuals [de Kock et al 2014a]. Treatment has included resection with or without adjuvant therapy, which can be curative, although in one series, five of thirteen individuals died after resection [de Kock et al 2014a].

Pineoblastoma is a type of primitive neuroectodermal tumor of the pineal gland that typically occurs in children. To date, fewer than ten instances have been associated with a *DICER1* germline pathogenic variant [de Kock et al 2020]. Pineoblastomas are generally large and associated with obstructive hydrocephalus at diagnosis [Tate et al 2011]. Treatment includes surgical resection with craniospinal irradiation and chemotherapy [Mynarek et al 2017]. Pineoblastoma has been described to have a short clinical course and poor prognosis.

Central nervous system (CNS) sarcoma is a more recently identified *DICER1*-associated tumor type. *DICER1*-associated CNS sarcoma has histologic features similar to CNS metastases from PPB including spindle cell, rhabdomyosarcomatous, and chondroid patterns. When this histologic pattern is seen in a primary intracranial neoplasm, especially in a child, further workup is indicated (including chest and abdominal imaging) to confirm that the CNS sarcoma is primary and not due to metastatic PPB or other metastatic *DICER1*-associated sarcomas [de Kock et al 2018, Koelsche et al 2018, Das et al 2019, Kamihara et al 2020].

Other CNS embryonal tumors/ETMR-like (embryonal tumor with multilayer rosettes) occurring in the posterior fossa and thalamus and sparing the pineal gland have been described in two individuals with a germline *DICER1* pathogenic variant [Uro-Coste et al 2019, de Kock et al 2020].

Presacral malignant teratoid tumor is a *DICER1*-associated neoplasm recognized in infancy whose mixed primitive pathology can be mistaken for sacrococcygeal teratoma, [Nakano et al 2019b]. Rhabdomyosarcoma in the absence of yolk sac tumor is the clue to this tumor type.

Wilms tumor may rarely be associated with a germline *DICER1* pathogenic variant.

Multicystic hepatic lesions have been reported as mesenchymal hamartoma of the liver in individuals with *DICER1* [Apellaniz-Ruiz et al 2019]. This lesion resembles solitary (non-parasitic) bile-ducts cysts [Vargas & Perez-Atayde 2019]. These hepatic lesions appear analogous to cystic nephroma and PPB type I and may have the potential to progress to a primitive sarcoma.

Pleuropulmonary blastoma-like peritoneal sarcoma may present as one or several masses or diffuse pelvic and peritoneal thickening. Histopathology may show diffuse, but discontinuous foci of a cambium layer-like proliferation of a primitive sarcoma with and without rhabdomyosarcomatous features and scattered chondroid nodules. The histopathology is similar to cervical embryonal rhabdomyosarcoma with overlapping features of adenosarcoma [Bean et al 2019].

Other clinical features [Choi et al 2019, Huryn et al 2019, Khan et al 2018]

- **Macrocephaly** has been reported in 42% of individuals with DICER1. Macrocephaly, defined as a head circumference greater than the 97th percentile in published reference populations, may be observed in early childhood (age <5 years); data are lacking on the frequency of a congenital presentation of this phenotype. There are no published data on brain imaging findings in *DICER1*-associated macrocephaly [Khan et al 2017a].
- **Structural abnormalities of the collecting system or kidney.** In a family-based cohort study, eight (9%) of 89 individuals with a pathogenic germline variant in *DICER1* harbored ultrasound-detected structural abnormalities of varying severity within the collecting system or kidney, nephrolithiasis, or nephrocalcinosis; none of the family controls (0/61) had similar findings on ultrasound [Khan et al 2018].
- **Retinal abnormalities**. In a family-based cohort study, a significant difference in the rate (11/103; 11%) of retinal abnormalities in individuals with a pathogenic germline variant in *DICER1* was observed versus family controls (1/69; 1.5%). Retinal abnormalities included pigmentary abnormalities, epiretinal membranes, drusen, and retinitis pigmentosa [Huryn et al 2019].
- **Dental anomalies** (e.g., bulbous crowns)

Somatic mosaicism for a *DICER1* pathogenic variant has been described in individuals with:

- Thyroid nodules, including benign follicular adenomas and nodules of indeterminate cytology;
- Differentiated thyroid cancer, often low-invasive, encapsulated, follicular variant of papillary thyroid cancer or minimally invasive follicular thyroid cancer, to solid-variant and poorly differentiated follicular thyroid carcinoma associated with spindle cell sarcoma with rhabdomyosarcoma differentiation [Ravella et al 2018, Wasserman et al 2018, Yang et al 2018];
- Wilms tumor.

GLOW syndrome (*g*lobal developmental delay, *l*ung cysts, *o*vergrowth, *W*ilms tumor). Two children with somatic mosaicism for a *DICER1* pathogenic variant in the RNase IIIb domain were described with developmental delay, very large, multiple lung cysts, overgrowth, macrocephaly, and bilateral Wilms tumor [Klein et al 2014]. The phenotype was hypothesized to arise from activation of the PI3K/AKT/mTOR pathway [Klein & Martinez-Agosto 2020]. Five children with mosaic RNase IIIb domain pathogenic variants harbored significantly more disease foci than children with *DICER1* germline loss-of-function variants [Brenneman et al 2015] and had a significantly earlier mean age of diagnosis. A detailed study of four children with somatic mosaicism for a *DICER1* pathogenic variant in RNase IIIb domain showed it to be an important cause of more severe *DICER1*-associated phenotypes, including higher tumor burden [de Kock et al 2016].

Genotype-Phenotype Correlations

A higher number of disease foci and overgrowth have been observed in individuals with mosaicism for *DICER1* pathogenic variant in the RNase IIIb domain. No other genotype-phenotype correlations have been identified.

Penetrance

The penetrance of heterozygous germline *DICER1* pathogenic variants is reduced and age dependent. In a longitudinal natural history study of 145 individuals with a germline *DICER1* pathogenic variant and 135 family controls, the cumulative incidence of MNG or thyroidectomy by age 40 years was 75% in women and 17% in men versus 8% and 0% in control women and men [Khan et al 2017b].

Risk for cancers associated with DICER1 varies according to age and sex. In a study of 102 female and male non-proband individuals with a germline *DICER1* pathogenic variant, by age ten years 5.3% (95% CI, 0.6% to 9.7%) had developed a neoplasm (females, 4.0%; males, 6.6%). By age 50 years 19.3% (95% CI, 8.4% to 29.0%) had developed a neoplasm (females, 26.5%; males, 10.2%). After age ten years, female risk was greater than male risk [Stewart et al 2019].

Nomenclature

Pleuropulmonary blastoma (PPB) has been referred to as "rhabdomyosarcoma arising in congenital cyst."

Pulmonary blastomas, biphasic epithelial and mesenchymal malignancies of the lung occurring in a broader age group, are not generally related to pleuropulmonary blastoma.

Nodular hyperplasia of the thyroid is commonly called goiter.

Ciliary body (or ocular) medulloepithelioma has also been called diktyoma or a teratoneuroma.

Prevalence

In an analysis of 53,105 non-cancer exomes from the Exome Aggregation Consortium, the prevalence of a germline loss-of-function and/or previously published *DICER1* pathogenic variant was between 1:2,529 and 1:10,600 [Kim et al 2017]. A similar analysis in the Cancer Genome Atlas calculated the prevalence of *DICER1* pathogenic variants to be 1:4,600 [Kim et al 2019].

Genetically Related (Allelic) Disorders

No phenotypes other than those described in this *GeneReview* have been associated with germline *DICER1* pathogenic variants [Klein et al 2014, de Kock et al 2016].

DICER1 pathogenic variants that occur solely in somatic tissue are not considered allelic disorders; they are discussed briefly in Molecular Genetics, Cancers and Benign Tumors with Somatic *DICER1* Pathogenic Variants.

Differential Diagnosis

Pleuropulmonary Blastoma (PPB)

Congenital pulmonary airway malformation (CPAM) or congenital cystic adenomatoid malformation (CCAM). Type I PPB cannot be distinguished radiographically from benign congenital cystic lung malformations; however, pneumothoraces and the presence of multifocal or bilateral cysts are more common in PPB than in other conditions. The difficulties in distinguishing PPB from CPAM have led some pediatric surgeons to advocate excision of all CCAMs [Priest et al 2009, Oliveira et al 2011].

Pulmonary sequestrations and peripheral bronchogenic cysts are more complex lesions that are commonly diagnosed prenatally. Although their radiographic and histologic features should facilitate differentiation from PPB [Shanti & Klein 2008], there is one report of a pulmonary sequestration in an individual with DICER1 [Foulkes et al 2011].

Lung cysts and pneumothoraces. Multiple inherited (see Table 3) and noninherited disorders can present with lung cysts and/or pneumothorax. However, many of these can be distinguished from PPB on the basis of medical history and physical examination.

Solid lung tumors of childhood. Other thoracic tumors are rare in children younger than age seven years, the age at which PPB most commonly occurs.

- Most non-PPB tumors presenting in the newborn period are solid lung tumors; they include fetal lung interstitial tumor [Dishop et al 2010], congenital peribronchial myofibroblastic tumor, and solid type 3 CPAM. There are no known genetic associations with these three conditions. To date, solid PPB has only rarely been observed in newborns.
- Synovial sarcoma is the main differential diagnosis for PPB in adolescents and young adults. Synovial sarcomas can be pleural-based and cystic [Cummings et al 2010]. PPBs are typically more heterogeneous than synovial sarcomas, but the spindle cell components of PPB and synovial sarcoma can be remarkably similar. Immunohistochemistry demonstrating epithelial markers or identification of a fusion protein involving the *SS18* (*SYT*) is helpful for making a diagnosis of synovial sarcoma.
- Rhabdomyosarcoma and Ewing sarcoma tend to originate in the chest wall or soft tissue of the diaphragm rather than the lung parenchyma. Rarely, malignant peripheral nerve sheath tumors may have sarcomatous elements which resemble PPB.
- Pulmonary blastoma is a biphasic tumor with malignant epithelial elements and mesenchyme with a median age range at presentation of 43 years [Van Loo et al 2011].
- Inflammatory myofibroblastic tumor (IMT) originates in the lung (typically in children age >3-4 years) as a well-circumscribed, lobar-based mass. These tumors comprise myofibroblasts that can be demonstrated by immunostain for smooth muscle actin; 40%-50% of IMTs have translocations involving *ALK* (encoding ALK tyrosine kinase receptor) and show immunostaining for the ALK protein.

Other Tumors

Multinodular goiter (MNG)

- Nonsyndromic MNG is associated with iodine deficiency, female sex, and advancing age. Elevated thyroid stimulating hormone from iodine deficiency, goitrogens, and inborn errors of thyroid hormone biosynthesis are also associated with an increased risk of developing MNG.
- The method of detection correlates with disease prevalence: a higher percent of disease is found by ultrasound examination or autopsy compared to physical examination. In general, in iodine-sufficient countries the prevalence of MNG is estimated at 4% of the population [Pinchera et al 1996]. Familial MNG is suggested by early-onset MNG without iodine deficiency and most frequently described with an autosomal dominant pattern of inheritance [Paschke 2011].
- MNG is common in adults, even outside of iodine-deficient regions [Colamaio et al 2012]. Familial MNG and MNG associated with other non-thyroid tumors should prompt consideration of familial nonmedullary thyroid carcinoma and familial multinodular goiter (see Phenotypic Series: Goiter, multinodular). See Table 3 for additional hereditary disorders associated with MNG.

Ovarian sex cord-stromal tumors

- Ovarian germ cell tumors are seen more commonly in young children and adolescent girls whereas epithelial ovarian tumors are seen more often in older women.

- Ovarian small cell carcinoma of the hypercalcemic type may histologically mimic an ovarian sex cord-stromal tumor. Preoperative measurement of calcium levels may be helpful in distinguishing this unique tumor.
- Sertoli-Leydig cell tumor and (rarely) juvenile granulosa cell tumor may also secrete alpha-fetoprotein (AFP), thus leading to consideration of immature teratoma or yolk sac tumor. Typically, the elevation in AFP is <500 ng/mL with sex cord-stromal tumors, and pathologic examination generally confirms the correct diagnosis.

Renal cysts and cystic tumors

- Cystic renal tumors or lesions include congenital mesoblastic nephroma (solid and cystic), cystic partially differentiated nephroblastoma, cystic Wilms tumor, renal cell carcinoma, clear cell sarcoma, and multicystic dysplastic kidney.
- Mixed epithelial and stromal tumor (MEST) of the kidney, which includes adult cystic nephroma (CN), occurs in women older than age 50 years. Unlike pediatric CN, MEST is not associated with germline *DICER1* pathogenic variants [Vanecek et al 2017].
- Although also seen in individuals with *DICER1*, isolated renal cysts are common in the general population, and the prevalence rises with age. Simple renal cysts (Bosniak category I) and cystic renal dysplasia are most commonly seen in children. Birt-Hogg-Dubé syndrome [Toro et al 2007] is also associated with renal cysts, oncocytoma, and chromophobe renal cell carcinoma. None of these latter lesions are known to be associated with *DICER1* germline pathogenic variants.
- Multiple renal cysts may also be seen in von Hippel-Lindau syndrome, autosomal recessive polycystic kidney disease, and autosomal dominant polycystic kidney disease (see Table 3).

Ciliary body medulloepithelioma

- In children, the clinical differential diagnosis of a mass in the ciliary body includes an anteriorly located retinoblastoma, ciliary body cyst, leiomyoma, and juvenile xanthogranuloma of the ciliary body. Anteriorly located retinoblastoma occurs in older children and is frequently calcified [Vajaranant et al 2005].
- In adults, the clinical differential diagnosis of a mass in the ciliary body includes adenoma or adenocarcinoma of the ciliary epithelium (pigmented or nonpigmented), mesoectodermal leiomyoma, neurilemmoma, metastatic carcinoma, ciliochoroidal melanoma, intraocular toxocariasis, and granuloma [Tadepalli et al 2019].

Nasal chondromesenchymal hamartoma (NCMH)

- The cartilaginous nodules surrounded by a compact, hypercellular zone of immature stromal cells of NCMH can be confused with embryonal rhabdomyosarcoma. However, the stromal cells of NCMH lack a myogenic phenotype.
- Other patterns in NCMH may mimic aneurysmal bone cyst or fibrous dysplasia.

Embryonal rhabdomyosarcoma (ERMS) of the cervix or other genitourinary sites

- Because cervical ERMS is a pedunculated polyp presenting at the cervical os, a benign cervical polyp composed in part of endocervical glands and a squamous mucosa is a common clinical impression.
- Other non-neoplastic polypoid lesions of the cervix are granulation tissue polyp, decidua, and squamous papilloma.
- Mesodermal stromal polyp is composed of enlarged stellate and spindle cells in a pale staining myxoid stroma without any glandular structures. These stromal cells lack the features of rhabdomyoblasts.
- Müllerian papilloma is a purely epithelial lesion with a complex papillary pattern which may cause bleeding in children.

- Müllerian adenosarcoma is a malignant polypoid lesion of the cervix with a pattern of benign endocervical glands and a spindle cell sarcomatous stroma without rhabdomyoblastic differentiation. There is overlap with cervical embryonal rhabdomyosarcoma.

Pituitary blastoma

- Clinically, a pituitary mass in a young child should prompt consideration of craniopharyngioma, adenoma, pituitary hyperplasia, germinoma, Langerhans cell histiocytosis, and much rarer entities including pituitary carcinoma, hamartoma, or teratoma.
- Non-neoplastic inflammatory and granulomatous entities may also affect this region.

Pineoblastoma

- Pineoblastomas must be distinguished from better-differentiated pineal parenchymal tumors like pineocytoma and pineal parenchymal tumor of intermediate differentiation. Pineal cysts may also occur. The pineal gland is also a common location for germ cell tumors.
- Other embryonal tumors such as medulloblastoma should be considered if the tumor is not localized to the pineal region but rather extends into the infratentorial region.

Table 3. Other Genes of Interest in the Differential Diagnosis of *DICER1* Tumor Predisposition

Key Clinical Feature(s) Overlapping w/DICER1	Gene(s)	Differential Disorder	MOI	Comment on Differential Disorder
Pneumothorax, pulmonary cysts, multinodular goiter, renal tumors	*FLCN*	Birt-Hogg-Dubé syndrome	AD	• Pneumothoraces typically in adulthood • Lung cysts usually bilateral & multifocal • Unclear whether MNG reported in assoc w/BHD is truly syndrome related • Renal tumors typically bilateral & multifocal; median age of diagnosis 48 yrs • Characteristic skin lesions (fibrofolliculomas, trichodiscomas, & acrochordons) appear in 3rd & 4th decades of life.
Lung cysts &/or pneumothorax	*CFTR*	Cystic fibrosis	AR	• Obstructive lung disease w/bronchiectasis • ↑ immunoreactive trypsinogen & sweat chloride • GI/nutritional abnormalities • Congenital absence of vas deferens
	COL3A1	Vascular Ehlers-Danlos syndrome	AD [1]	• Spontaneous &/or recurrent pneumothoraces • Vascular rupture/dissection • GI perforation or organ rupture
	FBN1	Marfan syndrome	AD	• Recurrent pneumothorax associated w/ lung bullae • Connective tissue findings • Ectopia lentis • Aortic root enlargement
	SERPINA1	Alpha-1 antitrypsin deficiency	AR	• Chronic obstructive pulmonary disease (emphysema &/or chronic bronchitis), primarily in adults • Incidence of liver disease increases w/age
	TSC1 *TSC2*	Tuberous sclerosis complex	AD	• Lymphangioleiomyomatosis • Renal angiomyolipoma & cysts

Table 3. continued from previous page.

Key Clinical Feature(s) Overlapping w/DICER1	Gene(s)	Differential Disorder	MOI	Comment on Differential Disorder
Multinodular goiter, tumors	*FOXE1* *HABP2* *NKX2-1* *SRGAP1*	Familial nonmedullary thyroid carcinoma (OMIM PS188550)	AD	Assoc w/multifocal & bilateral papillary thyroid carcinoma & multinodular goiter [2]
	PTEN	*PTEN* hamartoma tumor syndrome	AD	PHTS assoc w/thyroid, breast, endometrial tumors & distinct mucocutaneous lesions
	GNAS	Fibrous dysplasia / McCune-Albright syndrome	See footnote 3.	• Thyroid lesions w/or w/o non-autoimmune hyperthyroidism • Café au lait macules, fibrous dysplasia, & other endocrinopathies
	DUOX2 *IYD* *SLC5A5* *TG* *TPO* *TSHR*	Thyroid dyshormonogenesis (OMIM 274400, 274500, 274700, 274800, 603372, 607200)	AR	Familial MNG
	APC	*APC*-associated polyposis conditions	AD	• Cribriform-morular variant papillary thyroid cancer • Adenomatous colonic polyps, polyps of gastric fundus & duodenum, osteomas, dental anomalies, congenital hypertrophy
	PRKAR1A	Carney complex	AD	• Familial MNG, mostly nonfunctioning thyroid follicular adenomas • Skin pigmentary abnormalities, myxomas, endocrine tumors or overactivity, & schwannomas
	TFAP2A	Werner syndrome	AD	• MNG • No growth spurt during teen years; loss/graying of hair, hoarseness, scleroderma-like skin changes, bilateral cataracts, diabetes mellitus, hypogonadism, skin ulcers, & osteoporosis
Ovarian tumors	*SMARCA4* *SMARCB1*	Rhabdoid tumor predisposition syndrome	AD	• Small cell carcinoma of the ovary, hypercalcemic type (malignant rhabdoid tumor of the ovary) • Rhabdoid tumor in kidney • Cancer in early childhood (age <5 yrs)

Table 3. continued from previous page.

Key Clinical Feature(s) Overlapping w/DICER1	Gene(s)	Differential Disorder	MOI	Comment on Differential Disorder
Renal cysts & cystic tumors	*DNAJB11* *GANAB* *PKD1* *PKD2*	Autosomal dominant polycystic kidney disease	AD	• Multiple renal cysts • Liver cysts & ↑ risk of intracranial aneurysms
	PKHD1	Autosomal recessive polycystic kidney disease	AR	• Multiple renal cysts • Biliary ductal ectasia & congenital hepatic fibrosis
	VHL	Von Hippel-Lindau syndrome	AD	• Multiple renal cysts & clear cell renal carcinoma • Hemangioblastomas, pheochromocytoma, pancreatic cysts, neuroendocrine tumors, endolymphatic sac tumors, epididymal & broad ligament cysts
	WT1 [4]	Wilms tumor	AD	Cystic renal tumors
Pineal gland tumors	*RB1*	Pineoblastoma	AD	Intraocular retinoblastoma

AD = autosomal dominant; AR = autosomal recessive; BHD = Birt-Hogg-Dubé syndrome; GI = gastrointestinal; MNG = multinodular goiter; MOI = mode of inheritance

1. Vascular Ehlers-Danlos syndrome is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported.

2. Shin et al [2001], Oue et al [2008], Rome et al [2008]

3. Fibrous dysplasia / McCune-Albright syndrome (FD/MAS) is not inherited. No parent of a child with FD/MAS has been demonstrated to have any significant, distinctive manifestations of the disorder. The risk to sibs is expected to be the same as in the general population. There are no verified instances of vertical transmission of FD/MAS.

4. The most commonly reported germline genetic and epigenetic variants in individuals with Wilms tumor involve *WT1* and the 11p15.5 locus. A growing number of variants in other genes have been reported.

Management

Evaluations Following Initial Diagnosis

For an individual diagnosed with a *DICER1* tumor predisposition (DICER1), the two considerations for evaluations following initial diagnosis are:

- The extent of disease spread (staging) for malignant or potentially malignant *DICER1*-associated tumors;
- The presence of other synchronous DICER1 conditions (see Surveillance).

Extent of Disease Spread (Staging)

Pleuropulmonary blastoma types I and Ir. Initial imaging and follow-up imaging should include chest CT. No metastatic potential is associated with this type; thus, the only additional evaluation is for synchronous *DICER1*-associated tumors and clinical features (see Surveillance).

Pleuropulmonary blastoma types II and III

- CT of the chest to evaluate extent of disease and completeness of resection
- Brain MRI to evaluate for metastatic disease. This should be performed at diagnosis and throughout treatment and follow up.
- Radionuclide bone scan and/or PET scan to evaluate for metastatic disease and as a baseline relative to follow-up imaging

- Echocardiography as needed to define intracardiac extension of tumor, tumor thrombi, or pericardial effusion
- Rarely, spine MRI for paraspinal or intraspinal extension
- In the event of systemic embolization and any suggestion of vascular involvement (facial plethora, vena cava syndrome, cardiac murmur), investigation with vascular ultrasound examination
- CT of the abdomen/pelvis to assess for liver or other intraabdominal metastases

  Note: Bone marrow involvement is extremely rare.

Ovarian sex cord-stromal tumors

- When an ovarian sex cord-stromal tumor is suspected based on clinical features or individual or family history of DICER1, preoperative assessment of testosterone levels, AFP, inhibin A and B, and estradiol may be helpful in establishing one or more of these as a tumor marker.
- Intraoperative staging should be performed according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria and should include peritoneal cytology and assessment for preoperative or intraoperative rupture. Care should be taken to avoid rupturing the tumor if possible.
- Spread of ovarian sex cord-stromal tumors to the chest without extensive abdominopelvic disease is unlikely; however, baseline evaluation with chest CT is reasonable given the concern for synchronous conditions.

Ciliary body medulloepithelioma. Staging includes brain MRI to evaluate for direct intracranial extension and metastatic disease.

Botryoid-type embryonal rhabdomyosarcoma of the cervix or other sites or ovarian sarcoma. Staging includes MRI or CT to evaluate extent of primary tumor and for presence of metastatic disease in lymph nodes, liver, and lungs.

Central nervous system (CNS) malignancies: pituitary blastoma, pineoblastoma, CNS sarcomas, and other intracranial tumors. Staging includes brain and spine MRI, and cerebrospinal fluid cytology examination.

Treatment of Manifestations

Pleuropulmonary Blastoma (PPB)

Type I PPB is treated with complete surgical removal with or without adjuvant chemotherapy. The five-year overall survival for individuals with ytype I PPB is 89%; the only PPB-related deaths in type I PPB have occurred following progression to type II or III PPB. Individuals with type Ir PPB are treated with resection alone (or observation in certain clinical circumstances including adulthood). PPB-related survival is 100% for individuals with type Ir PPB [Messinger et al 2015].

Types II and III PPB are treated with aggressive surgical resection and intensive chemotherapy; five-year overall survival is 71% and 53% for types II and III PPB respectively. Extent of disease may preclude initial surgical resection for some children with type II or III PPB. In these instances, biopsy followed by neoadjuvant chemotherapy followed by resection followed by subsequent chemotherapy has been performed.

Resection of PPB should be performed with care so as not to disrupt the tumor or induce tumor spill, similar to the care taken with removal of Wilms tumor. Since solid components of PPB are very friable, piecemeal removal and spill are often inevitable.

If it is evident at the time of surgery that the tumor has spread to the chest wall, pericardium, and/or diaphragm, removal of all grossly visible tumor is recommended. Sites of unresectable residual disease may be titanium

clipped for radiographic localization and possible radiotherapy. Involvement of the diaphragm may require excision of a portion of the diaphragm and use of a Gore-Tex patch.

Delayed resection after chemotherapy is performed for tumors deemed unresectable at the time of diagnosis. Individuals receiving neoadjuvant chemotherapy may have marked tumor reduction; however, this response may be transient and tumor can recur rapidly. Chemotherapy alone is insufficient to eradicate solid PPB.

If gross-total resection is not achieved with the first or second surgery, additional surgery may be required for local control.

Pleural effusions. Drainage of pleural effusions should be approached with caution. Solid tumors often invade the chest wall, obliterating the pleural space. Proper placement of needle and catheter can be difficult without radiographic guidance.

Surgery for metastases. Brain parenchyma is the most common distant metastatic site for PPB. Resection is strongly suggested for intracranial mass lesion(s). Several individuals in whom cerebral PPB metastases have been resected have survived [Priest et al 2007, Nakano et al 2019a].

Radiation therapy is used primarily to treat PPB recurrence or metastasis, or in the setting of local control of residual, unresectable tumor [Priest et al 1997, Kamenova et al 2006, Indolfi et al 2007, Williams et al 2012]. Radiation may also be used as local control for other manifestations of PPB such as brain metastases.

Treatment for recurrence requires an individualized approach. Additional information regarding treatment and results from a uniformly treated cohort of individuals with PPB is available from the International PPB/*DICER1* Registry (www.PPBregistry.org; dicer1@childrensmn.org).

Multinodular goiter (MNG) and thyroid cancer

- **Observation with or without biopsy.** The approach to preoperative investigation is the same for individuals with a sporadic nodule with or without a *DICER1* pathogenic variant. See guidelines (available for purchase) from the American Thyroid Association and from the American Association of Clinical Endocrinologists / American College of Endocrinolgy / Associazione Medici Endocrinologi collaborative [Gharib et al 2016] (full text).
- **Ultrasound examination** is used to confirm the presence and characteristics of the nodule(s) and to determine the need for fine needle aspiration biopsy (FNA) [Francis et al 2015, American College of Radiology]. FNA of smaller nodules should be considered in individuals with a history of previous radiation exposure and/or concerning sonographic features including (but not limited to) solid composition, hypoechoic echotexture, taller-than-wide shape on transverse imaging, spiculated/lobulated or invasive margins, hyperechoic foci consistent with microcalcifications, and abnormal lymph nodes. FNA results that show benign-appearing follicular cells (including Hürthle cells and/or lymphocytes) indicate (in most cases) nodular hyperplasia, follicular adenoma, or lymphocytic thyroiditis. Continued follow-up care is appropriate in the presence of a stable nodule(s).
- **Surgery** is appropriate for symptomatic nodules, nodules with significant growth on serial US examination, or nodules with abnormal cytology based on the Bethesda System for Reporting Thyroid Cytology [Pusztaszeri et al 2016]. If the results of the FNA are positive for papillary thyroid carcinoma, total thyroidectomy is the treatment of choice for individuals who are surgical candidates.
- **Radioactive iodine** is the most effective medical treatment for individuals found to have distant (lung) metastasis or persistent disease not amenable to repeat surgery.

Ovarian Sex Cord–Stromal Tumors

Ovarian sex cord-stromal tumors (including Sertoli-Leydig cell tumor [SLCT] and gynandroblastoma) are rare and few studies have focused on clinical variables, treatment, and prognosis. Treatment regimens are based on

those used for ovarian germ cell tumors and data are limited [Schneider et al 2002, Schultz et al 2012, Schultz et al 2017].

If imaging or laboratory studies suggest the presence of an ovarian tumor, consultation with specialists in gynecologic oncology is suggested. Surgical resection with staging procedures is usually the initial treatment. Fertility-sparing surgery is recommended for most girls and young women.

Most individuals undergo unilateral salpingo-oophorectomy with sampling of peritoneal fluid and cytologic examination of peritoneal washings. Lymph nodes should be assessed radiographically, carefully examined intraoperatively, and removed if they are clinically concerning. Level of differentiation and stage influence outcome and are critical to determining whether adjuvant therapy is necessary. Effort must be made to avoid rupture of the tumor as this would result in an increased stage for some individuals. If rupture occurs, the timing of rupture (preoperative vs intraoperative rupture) must be carefully documented as it may influence the need for adjuvant therapy in some tumor types.

The decision to use adjuvant treatment such as chemotherapy following surgery for SLCT is based on histology and stage:

- **Sertoli-Leydig cell tumor.** For SLCT stage greater than Ia (including Ic with perioperative or preoperative rupture) or poorly differentiated SLCT, adjuvant chemotherapy is often needed. Depending on the stage, pathology, and desire or need for fertility preservation, consideration should also be given to additional surgery.

  When chemotherapy is used, a platinum-based regimen such as cisplatin, etoposide, and bleomycin (PEB) or cisplatin, etoposide, and ifosfamide (PEI) is often used. Additional regimens more often used in adults may include taxanes or anthracyclines. A Phase II randomized trial is currently open through Gynecology Oncology Group comparing PEB to carboplatin and paclitaxel for individuals with previously untreated sex cord-stromal tumors requiring chemotherapy.

  Follow-up monitoring for ovarian sex cord-stromal tumors should include attention to tumor markers and imaging. Imaging with either MRI or ultrasound may be preferred over CT as neither involves ionizing radiation; however, the use of MRI in very young children is limited by the need for sedation. Available modalities lack sensitivity for small tumors and peritoneal disease. If MRI is used, the radiologist should be notified of the clinical concern for ovarian tumor so that appropriate imaging protocols are used.

- **Gynandroblastoma.** Similar to above, treatment for gynandroblastoma is based on stage at diagnosis and level of differentiation of the SLCT component.

Other Tumors

Cystic nephroma

- **Surgery.** Treatment consists of surgical resection via partial or full nephrectomy. Surgical removal of every cyst may not be possible for individuals with extensive bilateral cysts.
- **Chemotherapy.** Although the use of chemotherapy has been considered in rare cases with extensive bilateral disease and continued rapid growth, its efficacy has not been studied.

Ciliary body medulloepithelioma (CBME). The five management options include:

- **Observation.** In one individual age nine years with CBME and PPB, the CBME was monitored in six-month intervals over a two-year period by high-resolution imaging and ocular examination. The histology of the CBME was unknown [Priest et al 2011].

- **Local resection.** Small, well-circumscribed (<3 clock hours) tumors may be treated by local resection with preservation of useful vision. However, many of these tumors will progress. In one series of 41 individuals with CBME, eight were initially treated with local resection and 50% had tumor recurrence [Kaliki et al 2013].
- **Plaque brachytherapy** can be considered in small tumors. In one series of six individuals treated with brachytherapy, tumor control was achieved in five individuals with globe salvage in four eyes. Two individuals underwent enucleations; one due to local recurrence and one secondary to radiation effects leading to phthisis bulbi [Ang et al 2019]. In another series of 41 individuals with CBME, plaque brachytherapy was successfully used as the primary treatment in three individuals with no recurrence over a median follow-up period of one year [Kaliki et al 2013].
- **Enucleation.** CBME with advanced features at the time of diagnosis (large tumor with friable appearance, a neoplastic cyclitic membrane, and neovascular glaucoma) should prompt enucleation. Long-term survival is common after this definitive therapy. Four of the five individuals reported with CBME and PPB underwent enucleation with follow up ranging from seven months to 44 years [Priest et al 2011, Laird et al 2013].
- **Orbital exenteration.** Although rarely indicated, exenteration (with consideration of adjunct chemotherapy and radiation) is required for a CBME that extends beyond the globe. Although long-term survival has been observed following exenteration, it is generally associated with a poor prognosis [Tadepalli et al 2019].

Nasal chondromesenchymal hamartoma (NCMH). NCMH is usually managed by complete surgical resection. When access to the tumor is adequate, one approach is endonasal endoscopy with resection. If complete resection is difficult, these tumors can be effectively debulked in most cases; however, complete extirpation is preferred.

Embryonal rhabdomyosarcoma (ERMS) of the cervix may not require hysterectomy since these tumors are usually confined to the cervix and typically do not have deep stromal invasion. Local resection followed by chemotherapy appropriate for ERMS is one management approach. On completion of chemotherapy, biopsies are performed to determine if residual viable tumor is present. The decision for additional treatment is based on the results of the post-chemotherapy biopsies and follow-up imaging studies.

Pituitary blastoma. Surgical resection is the mainstay of management. Among the cases described in the literature, adjuvant, usually multiagent chemotherapy with or without radiation therapy has also been described [Scheithauer et al 2012]. Normalization of endocrine laboratory values, especially ACTH, is expected postoperatively and is a useful marker of disease activity.

Pineoblastoma. Immediate management issues may include interventions for obstructive hydrocephalus. Open resection, rather than biopsy, is the treatment of choice and an aggressive surgical approach is associated with prolonged survival. Following maximal surgical resection, standard adjuvant therapy includes fractionated radiotherapy (to brain and spine) and chemotherapy [Tate et al 2011]. This combination has been reported to lead to progression-free survival of 60%-70% in nonmetastatic pineoblastoma, while survival remains poor for young children who do not receive radiotherapy [Mynarek et al 2017].

***DICER1*-associated CNS sarcoma.** Treatment aimed at gross total resection is central to management; the use of adjuvant radiation and multi-agent chemotherapy have also been described.

Surveillance

Surveillance guidelines for individuals with a germline *DICER1* pathogenic variant have been established [Schultz et al 2018]. Provider and individual/family education is the cornerstone of surveillance. Individuals and

caregivers should be advised of signs and symptoms of concern. Note that if signs of tumor are detected, additional evaluation will be needed. This table is not intended to address post-tumor surveillance.

Table 4. Recommended Surveillance for Individuals with *DICER1* Tumor Predisposition

System/Concern	Evaluation	Frequency
Pleuropulmonary blastoma	Clinical eval as indicated for any signs/symptoms (e.g., tachypnea, cough, fever, pain, pneumothorax)	Prompt eval for any signs/symptoms of concern
	Chest CT & chest x-ray	• Chest x-ray at birth, every 4-6 mos until age 8 yrs, then annually until age 12 • Consider chest CT at age 3-6 mos. If initial CT normal: consider repeat CT at age 2.5-3 yrs. • If diagnosed after age 12 yrs, consider baseline chest x-ray or chest CT.
Multinodular goiter / thyroid gland neoplasia	Thyroid physical exam for thyroid gland asymmetry &/or nodules	• At diagnosis (any age) • Annually
	Thyroid US	• Consider US by age 8 yrs. [1] If normal, consider repeat US every 3-5 yrs. • Earlier for thyroid gland asymmetry &/or nodules • Post-chemotherapy: By age 10 yrs or w/in 3-5 yrs of treatment
	Thyroid function testing	If clinical signs/symptoms of hypo- or hyperthyroidism
Ovarian sex cord-stromal tumors (& other tumors of the female genital tract incl cervical tumors)	• Clinical eval as indicated for any signs/symptoms (e.g., hirsutism, virilization, abdominal distension, pain, mass, vaginal bleeding) • Pelvic & abdominal US	Females: pelvic US every 6-12 mos beginning by age 8 yrs until at least age 40 [2]
Cystic nephroma (& other renal tumors)	• Clinical eval as indicated for any signs/symptoms (e.g., abdominal or flank mass, pain, hematuria) • Abdominal US	• Abdominal US every 6 mos until age 8 yrs, then annually until age 12 • If diagnosed after age 12 yrs, consider baseline abdominal US
Ciliary body medulloepithelioma	• Visual acuity measurement • Dilated ophthalmic exam	• At diagnosis (any age) • Annually from age 3 yrs until at least age 10
Nasal chondro-mesenchymal hamartoma	Clinical eval to screen for respiratory & feeding difficulties, rhinorrhea, epistaxis, visual disturbances, & otitis media	• Annually • Referral to ENT for any signs/symptoms

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Pituitary blastoma	Immediate clinical eval for signs/symptoms of (e.g.) cortisol excess (e.g., Cushing syndrome), ophthalmoplegia, strabismus, & diabetes insipidus	Annually w/education re importance of prompt workup incl imaging for any concerning symptoms
Pineoblastoma	Immediate clinical eval for signs/symptoms of obstructive hydrocephalus incl headache, full fontanel, vomiting, lethargy, or other neurologic features (e.g., upward gaze paralysis, nystagmus)	
***DICER1*-associated CNS sarcoma**	Immediate clinical eval for signs/symptoms incl headache, vomiting, gait changes, or other neurologic changes	

CNS = central nervous system; ENT = ear, nose, and throat physician; US = ultrasound
1. Thyroid carcinoma seen in individuals with DICER1 is generally well differentiated. The importance of early detection of differentiated thyroid carcinoma has not been established, as it has been for tumor predispositions with increased risk for medullary thyroid carcinoma. Some providers and families may favor physical exams in childhood with transition to ultrasound by age 18 yrs. Poorly differentiated thyroid carcinoma has rarely been seen in individuals with a *DICER1* pathogenic germline variant [Chernock et al 2020].
2. Consideration should be given to starting pelvic ultrasound early, at times of abdominal ultrasound in childhood. Optimal end of surveillance range is not known; however, 95% of SLCTs were diagnosed before age 40. Please note in children and young adolescents, transabdominal pelvic ultrasound is most appropriate. Transition to transvaginal ultrasound should be considered in older adolescents and adults when appropriate for the individual.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an affected individual by molecular genetic testing for the *DICER1* pathogenic variant in the family in order to provide recommendations for age-appropriate surveillance and early intervention.

- Testing of at-risk newborns (before age 4 months) for the family-specific pathogenic variant is recommended. Pulmonary screening by CT scan can then be initiated for those with a known *DICER1* pathogenic variant [Schultz et al 2018].
- If not already performed, molecular genetic testing should be prioritized for children younger than age seven years (because they are at greatest risk for PPB tumors that may need intervention) and young girls/women (because of the risk of ovarian tumors during late childhood/early adolescence and young adult years).

Note: If at-risk first-degree relatives are not able to or choose not to undergo molecular genetic testing for a known familial *DICER1* pathogenic variant, surveillance should be based on the recommendations detailed in Surveillance unless/until genetic testing confirms that they did not inherit the familial variant.

Relatives of a proband with a suspected *DICER1* pathogenic variant. If confirmatory *DICER1* molecular genetic testing of an affected family member is not possible, at-risk relatives can undergo molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis. If a *DICER1* pathogenic variant is identified, the family member is considered to have tumor susceptibility. If a *DICER1* pathogenic variant is not identified, the family member's a priori tumor susceptibility risk remains unchanged.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Based on data from the International PPB/*DICER1* Registry (www.PPBregistry.org), prenatal ultrasound examination has detected lung cysts as early as 31-35 weeks' gestational age. Based on this finding, a third-trimester ultrasound is recommended.

Because large lung cysts can in rare cases cause respiratory distress in newborns, it is recommended that prenatal identification of lung cysts prompt consultation with specialists in high-risk obstetrics and fetal medicine to monitor the pregnancy and manage delivery.

Therapies Under Investigation

Multiple research efforts are underway to refine surveillance guidelines and improve outcomes for children and adults with *DICER1*-associated cancers. For more information, please visit www.PPBregistry.org.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

DICER1 tumor predisposition (DICER1) is inherited in an autosomal dominant manner with reduced penetrance.

Risk to Family Members

Parents of a proband

- Approximately 80% of individuals diagnosed with *DICER1*-associated pleuropulmonary blastoma (PPB) inherited the *DICER1* germline pathogenic variant from a parent who may or may not have PPB or other *DICER1*-associated findings.
- Approximately 20% of individuals with a *DICER1*-associated PPB have *DICER1* as the result of a *de novo* germline pathogenic variant [Hill et al 2010].
- Molecular genetic testing is recommended for the parents of a proband to clarify the genetic status of the parents and to determine if the proband inherited a pathogenic variant from a heterozygous parent, or if the *DICER1* pathogenic variant occurred *de novo* in the proband.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or, theoretically, germline mosaicism in a parent.

  Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.

- The family history of some individuals with a single or multiple *DICER1*-associated tumors may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, or lack of information about the family. Therefore, an apparently negative clinical family history cannot confirm absence of familial pathogenic variation. Note: Although multiple PPBs within a family with DICER1 are rare, approximately 35% of index cases with *DICER1*-associated PPB have a close relative with one or more lung cysts or another *DICER1*-associated tumor and/or clinical feature.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has a germline *DICER1* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant and associated tumor predisposition is 50%.
- If the germline pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *DICER1* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for *DICER1*-associated tumors and clinical features because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a germline *DICER1* pathogenic variant has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has a germline *DICER1* pathogenic variant, his or her family members may be at risk for PPB and/or associated tumors and clinical features.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once a germline *DICER1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Note: Although prenatal molecular genetic testing can be used to identify the presence of a germline *DICER1* pathogenic variant, prenatal testing cannot be used to predict whether a *DICER1*-associated tumor(s) will develop (see Penetrance).

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  DICER1 syndrome
- **American Cancer Society**
  Phone: 800-227-2345
  cancer.org
- **American Childhood Cancer Organization**
  Phone: 855-858-2226
  www.acco.org
- **CancerCare**
  Phone: 800-813-4673
  Email: info@cancercare.org
  cancercare.org
- **National Cancer Institute (NCI)**
  Phone: 800-4-CANCER
  Email: NCIinfo@nih.gov
  Children with Cancer: A Guide for Parents
- **National Coalition for Cancer Survivorship (NCCS)**
  Phone: 877-NCCS-YES
  Email: info@canceradvocacy.org
  canceradvocacy.org
- **International Ovarian and Testicular Stromal Tumor Registry**
  Cancer and Blood Disorders
  Children's Hospitals and Clinics of Minnesota
  910 East 26th Street
  Suite LL08
  Minneapolis MN 55404
  Phone: 612-813-7121
  Fax: 612-813-7108
  Email: krisann.schultz@childrensMN.org; otst@childrensmn.org
  www.otstregistry.org
- **International Pleuropulmonary Blastoma (PPB) / DICER1 Registry**
  Cancer and Blood Disorders
  Children's Hospitals and Clinics of Minnesota
  910 East 26th Street
  Suite LL08
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Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. DICER1 Tumor Predisposition: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DICER1	14q32.13	Endoribonuclease Dicer	DICER1 database	DICER1	DICER1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for DICER1 Tumor Predisposition (View All in OMIM)

138800	GOITER, MULTINODULAR 1, WITH OR WITHOUT SERTOLI-LEYDIG CELL TUMORS; MNG1
180295	RHABDOMYOSARCOMA, EMBRYONAL, 2; RMSE2
601200	PLEUROPULMONARY BLASTOMA; PPB
606241	DICER 1, RIBONUCLEASE III; DICER1

Molecular Pathogenesis

DICER1 encodes an RNase III that functions in the microRNA (miRNA) and siRNA biogenesis pathways, cleaving precursor double-stranded RNAs into their active forms. Loss-of-function germline pathogenic variants in *DICER1* coupled with somatic missense pathogenic variants in particular amino acids (see below) lead to defective production of mature miRNAs from the 5' (5p) end of the miRNA hairpin [Pugh et al 2014]. Most individuals who are heterozygous for a germline *DICER1* loss-of-function pathogenic variant are healthy, presumably because *DICER1* enzyme expression from the wild type allele can be upregulated.

Mechanism of disease causation. *DICER1* tumor predisposition (DICER1) occurs through a loss-of-function mechanism that requires a somatic "second hit" for disease manifestation (see below).

***DICER1*-specific laboratory technical considerations.** Somatic mosaicism has been reported in this disorder; therefore, either primary or follow-up sequencing assays should be designed to detect expected levels of mosaicism.

Cancers and Benign Tumors with Somatic *DICER1* Pathogenic Variants

Somatic *DICER1* pathogenic variants have been described [Slade et al 2011, de Boer et al 2012, Heravi-Moussavi et al 2012, de Kock et al 2013a, Wu et al 2013, Doros et al 2014, Pugh et al 2014] in many tumor types.

Somatic missense pathogenic variants appear to preferentially affect amino acids in the RNase IIIb domain (codons 1705, 1709, 1809, 1810, or 1813) and are characterized as "missense hot spots." These somatic pathogenic variants lead to defective production of mature miRNAs from the 5' (5p) end of the miRNA hairpin but preserve the cleavage of the 3' (3p) end of the hairpin [Gurtan et al 2012, Anglesio et al 2013, Pugh et al 2014].

Examples of somatic *DICER1* variants identified in other tumors:

- Nearly all Sertoli-Leydig cell tumors and gynandroblastoma (based on tumor testing) [Schultz et al 2017], half of which are associated with a germline or mosaic *DICER1* pathogenic variant

- Three out of 15 (20%) PPBs with tumor-specific loss-of-function and missense pathogenic variants in *DICER1* with normal germline [Pugh et al 2014]
- Eighteen out of 20 (90%) CNs with loss-of-function pathogenic variants in 70% (14/20); however, germline DNA was not examined [Doros et al 2014].
- Two out of 52 (4%) ERMS tumors with loss-of-function pathogenic variants; however, germline DNA was not examined [Doros et al 2012].
- Two pineoblastomas from children with a germline *DICER1* pathogenic variant did *not* have a tumor-specific somatic missense pathogenic variant, suggesting an alternate tumorigenesis pathway [Sabbaghian et al 2012].
- Ninety-five percent of primary intracranial sarcomas in children [Koelsche et al 2018]
- Multiple cases of nasal chondromesenchymal hamartoma. A systematic review of the literature identified 48 cases of NCMH [Mason et al 2015].
- Thyroid nodules with indeterminate cytology and a spectrum of disease that spans the range from benign follicular adenomas to differentiated thyroid cancer and rarely poorly differentiated thyroid cancer [Ravella et al 2018, Wasserman et al 2018, Yang et al 2018, Chernock et al 2020]

Chapter Notes

Author Notes

Websites with additional information about *DICER1* tumor predisposition:

- www.PPBregistry.org
- ppb.cancer.gov
- www.OTSTregistry.org

About the authors' research. The authors of this study represent a multidisciplinary collaborative group that seeks to understand the clinical, pathologic, and genetic basis of *DICER1*-related cancers and associated conditions. The International PPB/*DICER1* Registry's mission is to improve outcomes for children and adults with *DICER1*-related cancers by defining optimal therapy, validating testing and surveillance guidelines, and development of novel diagnostics and therapeutics. The PPB/*DICER1* Registry has recently established the first cohort of uniformly treated individuals with PPB and shares available information with individuals, families, and treating physicians. Together with the Registry, Dr Hill identified heterozygous germline mutation of *DICER1* as the genetic basis of PPB. Preliminary data from PPB mouse models and study of human tumors suggests that *DICER1* protein is diminished in lung epithelium overlying the mesenchymal tumor, suggesting that loss of miRNAs in developing lung epithelium may affect regulation of secreted growth factors driving mesenchymal proliferation and setting the stage for cancerous transformation. Further work of the Hill group and others has identified recurrent, somatic missense *DICER1* pathogenic variants in tumor cells, confirming that *DICER1* functions as a two-hit tumor suppressor and loss of *DICER1* protein leads to loss of miRNAs important in controlling proliferation and differentiation in development. A better understanding of this syndrome is essential to the development of clinical criteria for identifying affected families and for guiding their medical care. The International PPB/*DICER1* Registry is closely affiliated with the International Ovarian and Testicular Stromal Tumor (OTST) Registry, which is devoted to understanding these rare tumors including Sertoli-Leydig cell tumor and gynandroblastoma.

Dr Stewart's group at the National Cancer Institute is focused on the determination of *DICER1* pathogenic variant prevalence, penetrance, and phenotype to enable evidence-based early detection of PPB (and other *DICER1*-associated neoplasms) through identification of individuals with *DICER1* pathogenic variants. His work focuses primarily on the recognition of pathogenic germline *DICER1* variants and their associated phenotype, risk, and outcomes.

Acknowledgments

The authors thank Dr John R Priest and Gretchen M Williams for their contributions to data collection used in this review.

This work was supported in part by National Cancer Institute (NCI), NIH/NCI R01CA143167 (PI Hill), the Intramural Research Program of the NIH, Hyundai Hope on Wheels, Pine Tree Apple Tennis Classic, MF Schutt Foundation and Children's Minnesota Foundation, and St Baldrick's Foundation.

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Revision History

- 30 April 2020 (sw) Comprehensive update posted live
- 24 April 2014 (me) Review posted live
- 23 July 2012 (dh/ym) Original submission

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