U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Turner JT, Brzezinski J, Dome JS. Wilms Tumor Predisposition. 2003 Dec 19 [Updated 2022 Mar 24]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Wilms Tumor Predisposition

Joyce T Turner, MS,[1] Jack Brzezinski, MD, PhD,[2] and Jeffrey S Dome, MD, PhD[1]

Created: December 19, 2003; Updated: March 24, 2022.

Summary

Purpose

This *GeneReview* is intended to help clinicians determine if a genetic basis can be identified in an individual with Wilms tumor in order to provide families with natural history and recurrence risk information.

Goal 1

Briefly describe the clinical characteristics of Wilms tumor.

Goal 2

Review the mechanisms of predisposition to Wilms tumor.

Goal 3

Provide an evaluation strategy to determine if a proband with Wilms tumor has a predisposition to Wilms tumor, identify the genetic or epigenetic mechanism for Wilms tumor, and determine risks for additional medical complications.

Goal 4

Review genetic counseling issues including mode of inheritance, recurrence risk, and evaluation of relatives at risk based on the underlying genetic mechanism.

Goal 5

Review management (e.g., tumor screening) recommendations for individuals with a genetic predisposition to Wilms tumor.

Author Affiliations: 1 Children's National Hospital Washington, DC; Email: jturner@childrensnational.org; Email: jdome@childrensnational.org. 2 The Hospital for Sick Children Toronto, Ontario, Canada; Email: jack.brzezinski@sickkids.ca.

1. Clinical Characteristics of Wilms Tumor

Wilms tumor (nephroblastoma), an embryonal malignancy of the kidney, is the most common renal tumor of childhood [Fernandez et al 2021]. It usually presents as an abdominal mass in an otherwise apparently healthy child. Abdominal pain, fever, anemia, hematuria, and hypertension are seen in 25%-30% of affected children.

Approximately 5%-10% of individuals with Wilms tumor have bilateral or multicentric tumors. The prevalence of bilateral involvement is higher in individuals with a predisposition to Wilms tumor than in those without a genetic predisposition (see Mechanisms of Predisposition to Wilms Tumor), but unilateral, unifocal Wilms tumor does not preclude an underlying germline or epigenetic cause.

A definitive diagnosis of Wilms tumor can be made only on histologic assessment of the tumor. There are two main histologic subtypes: favorable and anaplastic. Tumors with anaplastic histology usually have somatic mutation of *TP53* and inferior prognosis compared to tumors with favorable histology [Ooms et al 2016, Daw et al 2020].

Nephrogenic rests, benign foci of embryonal kidney cells that persist abnormally into postnatal life, are considered to be Wilms tumor precursors. Pathogenic variants may predispose to nephrogenic rests. Additional pathogenic variants transform nephrogenic rests into a Wilms tumor [Fernandez et al 2021].

Treatment includes surgery, chemotherapy, and radiation therapy for individuals with incomplete resection or metastatic disease. Outcomes are generally outstanding with survival estimates of approximately 90%. Anaplastic histology, bilateral disease, distant metastasis, and recurrent disease are associated with less favorable outcome [Nelson et al 2021].

2. Mechanisms of Predisposition to Wilms Tumor

In 10%-15% of individuals with Wilms tumor, the cause is considered to be a germline pathogenic variant or an epigenetic alteration occurring early during embryogenesis [Mahamdallie et al 2019].

Suggestive Features of a Predisposition to Wilms Tumor

Clinical features

- Bilateral Wilms tumor
- Unilateral multicentric Wilms tumor
- Early onset Wilms tumor (age <2 years)
- Multiple nephrogenic rests (both unilateral and bilateral)
- Clinical features of Wilms tumor predisposition syndromes (See Table 1 and Table 2.)

Family history. Approximately 1%-2% of individuals with Wilms tumor have at least one relative also diagnosed with Wilms tumor. While germline pathogenic variants have been identified in some families, they are still unknown for approximately two thirds of individuals [Mahamdallie et al 2019].

Common Genes, Loci, and Syndromes Associated with Wilms Tumor Predisposition

Table 1. More Common Genes, Loci, and Syndromes Associated with Wilms Tumor Predisposition

Gene / Locus	Syndrome	% of all Wilms tumor	MOI	Estimated Wilms Tumor Risk	Other Features
REST	*REST*-related Wilms tumor (OMIM 616806)	~2%	AD	Unknown	
TRIM28	*TRIM28*-related Wilms tumor [1]	~2%	AD	Unknown	Evidence of maternal parent-of-origin effect
WT1	*WT1* disorder	1%-5%	AD	Varies by genotype: • Highest risk: truncating variants • 70%-80%: exon 8/9 missense variants • <2%: intron 9 variants • Other variants have intermediate risk. [1]	GU anomalies more common in males [2], undermasculinized genitalia, renal mesangial sclerosis, steroid resistant nephrotic syndrome, gonadoblastoma [3]
11p13	WAGR syndrome (See *PAX6*-Related Aniridia.)	0%-1%	AD	45%-60%	Aniridia, GU anomalies, ambiguous genitalia, gonadoblastoma, ID, ESRD, obesity
11p15 [4]	11p15-related Wilms tumor, incl isolated Wilms tumor [4], Beckwith-Wiedemann syndrome (BWS), and isolated hemi-hyperplasia [5] (OMIM 235000)	1%-5%	See footnote 6.	~7%-25%	In BWS: macrosomia, macroglossia, hemihyperplasia, visceromegaly, embryonal tumors (e.g., hepatoblastoma, neuroblastoma, rhabdomyosarcoma, adrenal cortical carcinoma), omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, & renal abnormalities

AD = autosomal dominant; ESRD = end-stage renal disease; GU = genitourinary; ID = intellectual disability; MOI = mode of inheritance

1. Halliday et al [2018], Diets et al [2019], Mahamdallie et al [2019], Hol et al [2021a]

2. Germline *WT1* pathogenic variants have a greater effect on sex determination and genital tract development in males; 46,XX females with a germline *WT1* pathogenic variant are less likely to exhibit genitourinary anomalies.

3. In the absence of genitourinary anomalies, renal mesangial sclerosis, nephrogenic rests, or bilateral tumors, the likelihood that a child with Wilms tumor has a germline *WT1* pathogenic variant is 0%-5%. A small number of families with isolated Wilms tumor have heterozygous germline *WT1* pathogenic variants.

4. Isolated Wilms tumor has been associated with constitutional alterations of chromosome 11p15 most commonly hypermethylation at IC1 and paternal uniparental disomy of 11p15. Loss of methylation at IC2 and genomic abnormalities of 11p15 may be associated with Wilms tumor but reports are rare and the evidence is still emerging.

5. Molecular alterations at 11p15 including loss of methylation at IC2, gain of methylation at IC1, and 11p15 paternal uniparental disomy have been reported in individuals who have apparently isolated hemihyperplasia (see Beckwith-Wiedemann Syndrome, Allelic Disorders).

6. 85% of individuals with BWS have no family history of BWS; approximately 15% have a family history consistent with parent-of-origin autosomal dominant transmission.

***TRIM28*-related Wilms tumor.** Among 890 individuals with Wilms tumor, a germline *TRIM28* pathogenic variant was identified in 21 affected individuals [Mahamdallie et al 2019]. Age of onset ranged from five months to nine years (median age 13 months). Among individuals with a germline *TRIM28* variant who develop Wilms tumor, tumors develop before age seven years in 83% and before age eight years in 93% [Diets et al 2019, Mahamdallie et al 2019, Hol et al 2021a]. *TRIM28*-related Wilms tumors can be either unilateral or bilateral, predominantly have epithelial-type histology, and are frequently accompanied by nephrogenic rests. Immunohistochemistry studies show negative staining for TRIM28. With few exceptions, the reported germline variants are truncating or splice site variants located throughout the protein coding regions with evidence suggestive of a maternal parent-of-origin effect. The prognosis is favorable with a low rate of metastasis or relapse. Germline *TRIM28* pathogenic variants do not appear to be associated with any phenotype other than Wilms tumor [Halliday et al 2018, Diets et al 2019, Mahamdallie et al 2019, Hol et al 2021a].

***REST*-related Wilms tumor.** Age of Wilms tumor onset ranges from six months to six years (median age 3.25 years). Those reported have predominantly had unilateral tumors with triphasic, blastemal, and/or epithelial histology [Mahamdallie et al 2015, Mahamdallie et al 2019]. Individuals with a germline *REST* pathogenic variant have been reported to have additional clinical features, although no additional clinical features or other malignancies have been consistently reported [Mahamdallie et al 2015].

Table 2. Less Common Genes and Syndromes Associated with Wilms Tumor Predisposition

Gene	Syndrome	MOI	Estimated Wilms Tumor Risk [1]	Other Clinical Features
AMER1 (*WTX*)	Osteopathia striata with cranial sclerosis	XL	~5%	Sclerosis of cranium & long bones, macrocephaly, characteristic facial features, ±DD/ID
ASXL1	Bohring-Opitz syndrome	AD	~7%	Growth deficiency, characteristic facial features, distinct posture, seizures. cardiac anomalies, DD/ID
BLM	Bloom syndrome	AR	~6%	Growth deficiency, immune deficiency, sun sensitivity, diabetes, multiple cancers
BRCA2	*BRCA2*-related Fanconi anemia	AR	~20%-60%	Growth deficiency, congenital anomalies, dysmorphic features, early-onset leukemia, medulloblastoma. pigmentary abnormalities
BUB1B	Mosaic variegated aneuploidy syndrome (OMIM 257300)	AR	>85%	Growth deficiency, microcephaly, CNS anomalies, dysmorphic features, genitourinary anomalies, DD/ID, nephroblastoma, rhabdomyosarcoma, leukemia.
CDC73	*CDC73*-related disorders	AD	~3%	Hyperparathyroidism, parathyroid adenoma & cancer, osseous fibroma(s) of the jaw
CHEK2	*CHEK2* cancer susceptibility (OMIM 609265)	AD	~3%	Breast cancer, ↑ risk of some additional cancers (prostate, GI, sarcomas, renal)
CTR9	Familial WT [2]	AD	>60%	Paternally inherited

Table 2. continued from previous page.

Gene	Syndrome	MOI	Estimated Wilms Tumor Risk [1]	Other Clinical Features
DICER1	*DICER1* tumor predisposition	AD	<1% [3]	Pleuropulmonary blastoma, pulmonary cysts, thyroid gland neoplasia, ovarian tumors, & cystic nephroma, ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, pineoblastoma, pituitary blastoma
	GLOW syndrome (See *DICER1* Tumor Predisposition.)	Somatic mosaic / AD [4]	Unknown; possibly >50%	GLOW; also macrocephaly, characteristic facial features, autism
DIS3L2	Perlman syndrome (OMIM 267000)	AR	65%	Fetal ascites, neonatal demise, macrosomia, characteristic facial features, visceromegaly, DD/ID
FBXW7	*FBXW7*-related Wilms tumor [5]	AD	Unknown	Adult-onset osteosarcoma (in 1 person); extrarenal rhabdoid (1 person); HL, FSGS, ovarian cystadenoma, & breast cancer (1 person) [6]
GPC3 *GPC4*	Simpson-Golabi-Behmel syndrome type 1	XL	4%-9%	Macrosomia, macroglossia. DD/ID, multiple congenital anomalies, hepatoblastoma, neuroblastoma, gonadoblastoma, hepatocellular carcinoma, medulloblastoma.
KDM3B	*KDM3B*-related Wilms tumor [5]	AD	<1%	In 1 person each: hepatoblastoma, AML, HL
MLH1 *MSH2* *MSH6* *PMS2* [7]	Constitutional mismatch repair deficiency (CMMRD) (See Lynch Syndrome.)	AR	<1%	Multiple tumor types; predominantly brain tumors & GI tumors
NYNRIN	*NYNRIN*-related Wilms tumor [5]	AR	Unknown	Unknown
NSD1	Sotos syndrome	AD	<3%	Overgrowth, macrocephaly, DD/ID, leukemia, lymphoma, neuroblastoma, teratoma, & other cancer types.
PALB2	*PALB2*-related Fanconi anemia	AR	~40%	Growth deficiency, multiple congenital anomalies, pigmentary abnormalities, medulloblastoma.
PIK3CA	*PIK3CA*-related overgrowth spectrum	Usually somatic mosaic	1%-2%	Disproportional overgrowth, brain malformations, DD/ID, lipomas, fibroadipose hyperplasia, vascular malformations
TP53	Li-Fraumeni syndrome	AD	<1%	Multiple cancers: breast, adrenal cortical carcinoma, osteosarcoma, medulloblastoma, choroid plexus carcinoma, rhabdomyosarcoma, hypodiploid ALL.
TRIM37	Mulibrey nanism syndrome (OMIM 253250)	AR	6%	IUGR, characteristic facial features, heart disease, skeletal anomalies

Table 2. continued from previous page.

Gene	Syndrome	MOI	Estimated Wilms Tumor Risk [1]	Other Clinical Features
TRIP13	Mosaic variegated aneuploidy syndrome (OMIM 617598)	AR	~10%	Growth deficiency, microcephaly, dysmorphic features, DD/ID

AD = autosomal dominant; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; AR = autosomal recessive; DD = developmental delay; FSGS = Focal segmental glomerular sclerosis; GI = gastrointestinal; GLOW = *g*lobal developmental delay, *l*ung cysts, *o*vergrowth, *W*ilms tumor; HL = Hodgkin's lymphoma; ID = intellectual disability; IUGR = intrauterine growth restriction; MOI = mode of inheritance; WT = Wilms tumor; XL = X-linked

1. Maciaszek et al [2020], Hol et al [2021b]

2. Hanks et al [2014]

3. One large family with multiple individuals with *DICER1* tumor predisposition syndrome due to c.2407G>A (p.Gly803Arg) had four individuals with Wilms tumor [Palculict et al 2016].

4. Somatic mosaic pathogenic variants affecting the RNase IIIb domain have been identified in several individuals with GLOW syndrome [Klein & Martinez-Agosto 2020]. Four individuals have been reported with a germline *DICER1* pathogenic variant and additional clinical features overlapping with GLOW syndrome (e.g., skeletal findings, facial dysmorphism, developmental delay); one of the reported individuals also had a germline *ARID1B* pathogenic variant [Venger et al 2021].

5. Mahamdallie et al [2019]

6. Roversi et al [2015]

7. Wilms tumor has been reported in individuals with *MLH1*- and *MSH6*-related CMMRD [Citak et al 2021, Durno et al 2021]; It is unknown if biallelic *MSH2* or *PMS2* pathogenic variants increase the risk of Wilms tumor.

Other Syndromes That May Be Associated with Wilms Tumor

Trisomy 13 and trisomy 18 (both characterized by multiple congenital anomalies and intellectual disability) are associated with an estimated <1% risk of Wilms tumor.

A non-recurrent deletion at chromosome 9q22.3 encompassing a 352-kb critical region including *PTCH1* is characterized by the clinical findings of nevoid basal cell carcinoma syndrome as well as developmental delay and/or intellectual disability, metopic craniosynostosis, obstructive hydrocephalus, pre- and postnatal macrosomia, and seizures. Affected individuals are also at increased risk for Wilms tumor [Cayrol et al 2019].

One individual with Wilms tumor and a germline pathogenic variant of *XPO5* has been reported [Gadd et al 2017].

3. Evaluation Strategy to Identify the Genetic Cause of Wilms Tumor in a Proband

Establishing a specific genetic cause of Wilms tumor:

- Can aid in discussions regarding risks for additional medical complications;
- Can aid in discussion regarding appropriate cancer surveillance;
- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, family history, and molecular genetic testing.

Medical history for radiographic/histologic features. Bilateral or multifocal Wilms tumor and/or the presence of bilateral/ipsilateral nephrogenic rests is suggestive of a genetic predisposition. However, unilateral/unifocal Wilms tumor is frequently reported in individuals with *TRIM28*-, *FBXW7*-, *NYNRIN*-, *KDM3B*-related Wilms tumor, Beckwith-Wiedemann syndrome (BWS), and isolated hemihyperplasia.

Histologic features can suggest a specific genetic cause including fetal rhabdomyomatous nephroblastoma or stromal (*WT1*), epithelial-type histology (*TRIM28, FBXW7*), and anaplastic Wilms tumor (most often associated

with somatic *TP53* variants, although anaplastic Wilms tumor can be associated with germline *TP53* variants). A contiguous deletion at 4q12 including *REST* was identified in one infant with diffuse hyperplastic perilobar nephroblastomatosis [Hyder et al 2021].

Physical examination. Physical features suggestive of a *WT1*-related Wilms tumor include aniridia, genitourinary anomalies including ambiguous genitalia, renal insufficiency or failure, and intellectual disability. Features suggestive of BWS include macrosomia, ear creases/pits, macroglossia, omphalocele, visceromegaly, other embryonal tumors (e.g., hepatoblastoma, neuroblastoma, and rhabdomyosarcoma), hemihyperplasia, adrenocortical cytomegaly, and renal abnormalities. Distinct physical features may also be observed in other syndromes that predispose to Wilms tumor (see Tables 1 and 2).

Family history. A family history including clinical features described in Tables 1 and 2 and all childhood- and adult-onset malignancies among first-, second-, and third-degree relatives (including age of onset and tumor type) should be taken. A family history of another individual with Wilms tumor, the presence of more than one primary tumor in a family member, and/or multiple individuals with tumors/cancer is suggestive of a cancer predisposition syndrome.

Molecular genetic testing should be considered in individuals with Wilms tumor who have physical, radiographic, and/or histologic features suggestive of a genetic predisposition. Testing should also be considered in individuals with early-onset (age <2 years) Wilms tumor and in individuals with a family history of Wilms tumor and/or other tumors.

Molecular genetic testing approaches can include a combination of a **multigene panel**, **DNA methylation studies**, **single-gene testing**, and **chromosomal microarray (CMA)**. The choice of test should be based on the absence or presence of additional clinical features and/or family history.

Individuals with Wilms Tumor and Additional Clinical Features and/or Family History of Other Cancers

Genitourinary anomalies or renal failure. Sequence analysis of *WT1* is performed first followed by gene-targeted deletion/duplication analysis of *WT1* if a pathogenic variant is not identified. Note: (1) Ophthalmology examination should be done to assess for aniridia. (2) A karyotype should be considered in phenotypic females with a *WT1* pathogenic variant to evaluate for complete sex reversal.

Physical features of BWS. DNA methylation analysis of IC1 and IC2 should be performed first (see Beckwith-Wiedemann Syndrome for additional recommended testing). Analysis of affected tissue (e.g., skin biopsy of area affected with hemihyperplasia) may be necessary to identify those with somatic mosaicism for paternal uniparental disomy for 11p15. Note: *CDKN1C* pathogenic variants have not been associated with an increased risk of Wilms tumor.

Aniridia. CMA should be performed first in individuals with suspected WAGR (*W*ilms tumor, *a*niridia, *g*enital anomalies, *r*etardation). CMA can detect 11p13 deletions encompassing *WT1* and *PAX6,* provide detailed information regarding size of the deletion, and identify deletions and duplications in the remainder of the genome. CMA-SNP array will allow detection of uniparental disomy at 11p15.5 in individuals with long stretches of homozygosity.

Overgrowth. An overgrowth multigene panel that includes *DIS3L2, GPC3*, *GPC4*, *NSD1*, and DNA methylation analysis of IC1 and IC2 for BWS should be considered first in infants with pre- and postnatal overgrowth. In those with asymmetric overgrowth, molecular analysis of *PIK3CA* using affected tissue should be considered.

Stromal or epithelial-predominant Wilms tumor (defined as >66% of the tumor specimen composed of that specific cell type). Sequence analysis of *WT1* is recommended either in a targeted fashion or as part of a

multigene panel for stromal-predominant tumors. Sequence analysis of *TRIM28* is recommended for epithelial-predominant tumors.

Family history of other specific cancers. Single-gene analysis or a multigene panel can be considered in those with a family history of specific cancers (see also Table 2):

- *DICER1*. Thyroid cancer, cystic nephroma, ovarian Sertoli Leydig cell tumor, botryoid rhabdomyosarcoma, pleuropulmonary blastoma, pineoblastoma, pituitary blastoma, ciliary body medulloepithelioma, and/or a nasal chondromesenchymal hamartoma
- *BRCA2, PALB2, CHEK2,* and *TP53*. Breast, ovarian, prostate, and pancreatic cancer, and pediatric brain tumors and sarcomas
- *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Colorectal and uterine cancer

Individuals with Isolated Bilateral and/or Multifocal, Early-Onset (age <2 years), and/or Familial Wilms Tumor

A multigene panel that includes *WT1*, *TRIM28*, and *REST* may be considered first or a multigene panel that also includes additional Wilms tumor predisposition genes (see Tables 1 and 2) may be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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. (5) Multigene panels may not include DNA methylation analysis used to detect 11p15.5 alterations.

DNA methylation studies of IC1 and IC2 at 11p15.5 should be considered either concurrently or subsequent to a multigene panel as Wilms tumor can be the presenting feature of BWS and other features may be subtle or absent. Although Wilms tumors are infrequent in individuals with BWS resulting from loss of methylation at IC2, instances have been reported [Brzezinski et al 2017, Duffy et al 2021].

Individuals with Unilateral Wilms Tumor without Features Suggestive of Genetic Predisposition

The risk for genetic predisposition is low in those with unilateral unifocal Wilms tumor and no apparent risk factors, although germline variants have been identified in some individuals. Parents and/or affected individuals should be counseled regarding the small chance of the presence of an underlying genetic predisposition for Wilms tumor and given the option of further evaluation. Note: Some centers recommend molecular testing for all individuals with Wilms tumor.

4. 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.

If an individual has a specific disorder associated with Wilms tumor (e.g., WAGR syndrome or *BUB1B*-related mosaic variegated aneuploidy syndrome [see Tables 1 and 2]), genetic counseling for that condition is indicated.

Recent studies have shown that some bilateral Wilms tumors arise from somatic genetic or epigenetic alterations that occur early during nephrogenesis before lateralization, affecting both kidneys but not the entire germline. Predisposition caused by somatic genetic or epigenetic alterations is not heritable if the underlying pathogenic variant is isolated to the kidney tissue and not present in germ cells [Coorens et al 2019, Foulkes & Polak 2020]. However, mosaicism restricted to kidney tissue cannot be definitely proven, and therefore ultrasound surveillance should be considered for the offspring of individuals with bilateral or multifocal Wilms tumor, as the risk to offspring of an individual with germline mosaicism would be up to 50% (see Surveillance for Relatives at Risk for Wilms Tumor Predisposition).

If a causative genetic alteration has not been identified in an affected family member, and the proband has:

- Features suggestive of a predisposition to Wilms tumor (e.g., bilateral or multifocal Wilms tumor and/or a family history of Wilms tumor) the empiric risk to offspring is estimated to be higher than the population risk and ultrasound surveillance is recommended for their offspring. The benefit of surveillance of sibs of the proband is unclear; the chance of detecting Wilms tumor in a sib of a proband with bilateral Wilms tumor in the absence of known familial disease is less than 1%. (See Surveillance for Relatives at Risk for Wilms Tumor Predisposition.)
- Unilateral, unifocal Wilms tumor without features suggestive of genetic predisposition (i.e., no physical, radiologic, histologic, or family history features suggestive of a genetic predisposition following a detailed, targeted evaluation), the risk to sibs of the proband and offspring of the proband is less than 1%. No Wilms tumor was observed in the 179 offspring of 96 long-term survivors who had been diagnosed with unilateral, nonfamilial Wilms tumor [Li et al 1988].

Related Genetic Counseling Issues

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

Genetic cancer risk assessment and counseling. For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

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 of having a Wilms tumor-related genetic alteration.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). In cases where somatic mosaicism is a consideration, skin biopsies can be taken at the time of nephrectomy to establish fibroblast culture for the purposes of DNA banking.

Prenatal Testing and Preimplantation Genetic Testing

Once a Wilms tumor-related genetic alteration has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

- **International WAGR Syndrome Association**
  Email: Reachingout@wagr.org
  http://www.wagr.org/

5. Management

Surveillance of Children with a Germline Pathogenic Variant or with Wilms Tumor-Associated Syndromes

General considerations. The goal of surveillance in individuals with a genetic predisposition to Wilms tumor is to detect tumors while they are low-stage and require less treatment and/or treatment is likely to be more successful compared to that of advanced-stage tumors. Consider the risks of surveillance including economic cost and the possibility of false positive results that can lead to unnecessary interventions and psychosocial distress. Experts recommend surveillance in individuals with a greater-than-1% [Kalish et al 2017] to 5% [Scott et al 2006, Brioude et al 2018] risk of Wilms tumor. However, recommendations vary by region and providers should consider regional practices in their decision making. Wilms tumors can double in size every week [Beckwith 1998], therefore, abdominal ultrasound examination should be performed every three months.

Most guidelines recommend continuing surveillance until the age at which 90%-95% of Wilms tumors will have occurred. One method to determine how long to continue Wilms tumor surveillance in an individual with a specific syndrome is to calculate the residual risk of Wilms tumor using the overall and age-related risk of Wilms tumor. For example, in WAGR syndrome, the overall Wilms tumor risk is ~50%, 90% of tumors occur by age four years, and 98% of tumors occur by age seven years, the residual Wilms tumor risk for an individual age four years is 5% (0.5 x 0.1) and for an individual by age seven years is 1% (0.5 x 0.02). Therefore, surveillance would continue until age five to eight years depending on the risk tolerance of the provider, affected individual, and family.

For *WT1* and BWS spectrum disorders, refer to other *GeneReviews* chapters for tumor surveillance recommendations. Individuals with Wilms tumor predisposition syndromes for which there are published surveillance guidelines (e.g., Li-Fraumeni syndrome, *DICER1* syndrome, constitutional mismatch repair deficiency [Durno et al 2021]) should undergo surveillance as recommended for their syndrome. For cancer predisposition for which the at-risk age for Wilms tumor has not been established, surveillance with abdominal ultrasound examination is recommended every three months until age eight years.

Individuals with bilateral and/or multifocal Wilms tumor without an identified molecular cause. After completion of therapy for Wilms tumor, individuals should be screened for metachronous tumors by renal ultrasound examination every three months until age eight years. Recent evidence suggests that individuals with bilateral Wilms tumor have either a germline pathogenic variant predisposing to Wilms tumor or a somatic pathogenic variant that arose early in embryogenesis before lateralization [Coorens et al 2019, Foulkes & Polak 2020]. Either a germline variant or an early somatic variant increases the risk of a metachronous Wilms tumor.

Surveillance for Relatives at Risk for Wilms Tumor Predisposition

In families with more than one individual with Wilms tumor and families with one individual with **bilateral and/or multifocal Wilms tumor,** it is appropriate to evaluate relatives at risk to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Evaluations may include molecular genetic testing if the causative genetic alteration has been identified in an affected family member. Surveillance with ultrasound may be pursued if the Wilms tumor risk associated with the causative variant is sufficiently high.

If the causative genetic alteration has not been identified in an affected family member:

- Offspring of the affected individual should be screened with abdominal ultrasound examination every three months until age eight years. Note: The risk for Wilms tumor in the children of survivors of bilateral Wilms tumor is unknown. Some bilateral Wilms tumors arise from somatic or epigenetic alterations that occur early during embryogenesis before lateralization and affect both kidneys, but are not present in the germline. Such variants are not heritable [Coorens et al 2019, Foulkes & Polak 2020].
- The benefit of surveillance of sibs of the affected individual is unclear. A National Wilms Tumor Study on familial Wilms tumor showed that 15 of 456 individuals (3.3%) with bilateral Wilms tumor had a family member with Wilms tumor and six of those individuals clustered within three families [Breslow et al 1996]. Because most affected family members are not sibs, the chance of detecting Wilms tumor in the sib of an individual with bilateral Wilms tumor in the absence of known familial disease is less than 1%. The decision for tumor screening should take regional practices and family preferences into account.

Chapter Notes

Author History

Jack Brzezinski, MD, PhD (2022-present)
Jeffrey S Dome, MD, PhD (2003-present)
Vicki Huff, PhD; University of Texas MD Anderson Cancer Center (2003-2022)
Joyce T Turner, MS (2022-present)

Revision History

- 24 March 2022 (sw) Comprehensive update posted live
- 20 October 2016 (sw) Comprehensive update posted live
- 19 September 2013 (me) Comprehensive update posted live
- 14 June 2011 (me) Comprehensive update posted live
- 10 April 2006 (me) Comprehensive update posted live
- 24 May 2004 (cd) Revision: Genetic Counseling
- 19 December 2003 (me) Overview posted live
- 14 July 2003 (jsd) Original submission

References

Literature Cited

Beckwith JB. Children at increased risk for WilmsTumor: monitoring issues. J Pediatr. 1998;132:377–9. PubMed PMID: 9544882.

Breslow NE, Olson J, Moksness J, Beckwith JB, Grundy P. Familial Wilms' tumor: a descriptive study. Med Pediatr Oncol. 1996;27:398–403. PubMed PMID: 8827065.

Brioude F, Kalish JM, Mussa A, Foster AC, Bliek J, Ferrero GB, Boonen SE, Cole T, Baker R, Bertoletti M, Cocchi G, Coze C, De Pellegrin M, Hussain K, Ibrahim A, Kilby MD, Krajewska-Walasek M, Kratz CP, Ladusans EJ, Lapunzina P, Le Bouc Y, Maas SM, Macdonald F, Ounap K, Peruzzi L, Rossignol S, Russo S, Shipster C, Skorka A, Tatton-Brown K, Tenorio J, Tortora C, Gronskov K, Netchine I, Hennekam RC, Prawitt D, Tumer Z, Eggermann T, Mackay DJG, Riccio A, Maher ER. Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. Nat Rev Endocrinol. 2018;14:229–49. PubMed PMID: 29377879.

Brzezinski J, Shuman C, Choufani S, Ray P, Stavropoulos DJ, Basran R, Steele L, Parkinson N, Grant R, Thorner P, Lorenzo A, Weksberg R. Wilms tumour in Beckwith-Wiedemann Syndrome and loss of methylation at imprinting centre 2: revisiting tumour surveillance guidelines. Eur J Hum Genet. 2017;25:1031–9. PubMed PMID: 28699632.

Cayrol J, Nightingale M, Challis J, Campbell M, Sullivan M, Heloury Y. Wilms tumor associated with the 9q22.3 microdeletion syndrome: 2 new case reports and a review of the literature. J Pediatr Hematol Oncol. 2019;41:e517–e520. PubMed PMID: 30371535.

Citak EC, Sagcan F, Gundugan BD, Bozdogan ST, Yilmaz EB, Avci E, Balci Y, Karabulut YY. Metachronous Wilms tumor, glioblastoma, and T-cell leukemia in an child with constitutional mismatch repair deficiency syndrome due to novel mutation in MSH6 (c.2590G>T). J Pediatr Hematol Oncol. 2021;43:e198–e202. PubMed PMID: 31815888.

Coorens THH, Treger TD, Al-Saadi R, Moore L, Tran MGB, Mitchell TJ, Tugnait S, Thevanesan C, Young MD, Oliver TRW, Oostveen M, Collord G, Tarpey PS, Cagan A, Hooks Y, Brougham M, Reynolds BC, Barone G, Anderson J, Jorgensen M, Burke GAA, Visser J, Nicholson JC, Smeulders N, Mushtaq I, Stewart GD, Campbell PJ, Wedge DC, Martincorena I, Rampling D, Hook L, Warren AY, Coleman N, Chowdhury T, Sebire N, Drost J, Saeb-Parsy K, Stratton MR, Straathof K, Pritchard-Jones K, Behjati S. Embryonal precursors of Wilms tumor. Science. 2019;366:1247–51. PubMed PMID: 31806814.

Daw NC, Chi YY, Kalapurakal JA, Kim Y, Hoffer FA, Geller JI, Perlman EJ, Ehrlich PF, Mullen EA, Warwick AB, Grundy PE, Paulino AC, Gratias E, Ward D, Anderson JR, Khanna G, Tornwall B, Fernandez CV, Dome JS. Activity of Vincristine and Irinotecan in Diffuse Anaplastic Wilms Tumor and Therapy Outcomes of Stage II to IV Disease: Results of the Children's Oncology Group AREN0321 Study. J Clin Oncol. 2020;38:1558–68. PubMed PMID: 32134700.

Diets IJ, Hoyer J, Ekici AB, Popp B, Hoogerbrugge N, van Reijmersdal SV, Bhaskaran R, Hadjihannas M, Vasileiou G, Thiel CT, Seven D, Uebe S, Ilencikova D, Waanders E, Mavinkurve-Groothuis AMC, Roeleveld N, de Krijger RR, Wegert J, Graf N, Vokuhl C, Agaimy A, Gessler M, Reis A, Kuiper RP, Jongmans MCJ, Metzler M. TRIM28 haploinsufficiency predisposes to Wilms tumor. Int J Cancer. 2019;145:941–51. PubMed PMID: 30694527.

Duffy KA, Getz KD, Hathaway ER, Byrne ME, MacFarland SP, Kalish JM. Characteristics associated with tumor development in individuals diagnosed with Beckwith-Wiedemann spectrum: novel tumor-(epi)genotype-phenotype associations in the BWS population. Genes (Basel). 2021;12:1839. PubMed PMID: 34828445.

Durno C, Ercan AB, Bianchi V, Edwards M, Aronson M, Galati M, Atenafu EG, Abebe-Campino G, Al-Battashi A, Alharbi M, Azad VF, Baris HN, Basel D, Bedgood R, Bendel A, Ben-Shachar S, Blumenthal DT, Blundell M, Bornhorst M, Bronsema A, Cairney E, Rhode S, Caspi S, Chamdin A, Chiaravalli S, Constantini S, Crooks B, Das A, Dvir R, Farah R, Foulkes WD, Frenkel Z, Gallinger B, Gardner S, Gass D, Ghalibafian M, Gilpin C, Goldberg Y, Goudie C, Hamid SA, Hampel H, Hansford JR, Harlos C, Hijiya N, Hsu S, Kamihara J, Kebudi R, Knipstein J, Koschmann C, Kratz C, Larouche V, Lassaletta A, Lindhorst S, Ling SC, Link MP, Loret De Mola R, Luiten R, Lurye M, Maciaszek JL. MagimairajanIssai V, Maher OM, Massimino M, McGee RB, Mushtaq N, Mason G, Newmark M, Nicholas G, Nichols KE, Nicolaides T, Opocher E, Osborn M, Oshrine B, Pearlman R, Pettee D, Rapp J, Rashid M, Reddy A, Reichman L, Remke M, Robbins G, Roy S, Sabel M, Samuel D, Scheers I, Schneider KW, Sen S, Stearns D, Sumerauer D, Swallow C, Taylor L, Thomas

G, Toledano H, Tomboc P, Van Damme A, Winer I, Yalon M, Yen LY, Zapotocky M, Zelcer S, Ziegler DS, Zimmermann S, Hawkins C, Malkin D, Bouffet E, Villani A, Tabori U. Survival Benefit for Individuals With Constitutional Mismatch Repair Deficiency Undergoing Surveillance. J Clin Oncol. 2021;39:2779–90. PubMed PMID: 33945292.

Fernandez C, Geller J, Ehrlich P, van den Heuvel-Eibrink M, Graf N, Mullen E, Hill D, Kalapurakal J, Dome J. Renal tumors. In: Blaney S, Helman LJ, Adamson PC, eds. *Pizzo and Poplack's Pediatric Oncology*, 8 ed. Wolters Kluwer; 2021:673-92.

Foulkes WD, Polak P. Bilateral tumors - inherited or acquired? N Engl J Med. 2020;383:280–2. PubMed PMID: 32668120.

Gadd S, Huff V, Walz AL, Ooms AHAG, Armstrong AE, Gerhard DS, Smith MA, Auvil JMG, Meerzaman D, Chen QR, Hsu CH, Yan C, Nguyen C, Hu Y, Hermida LC, Davidsen T, Gesuwan P, Ma Y, Zong Z, Mungall AJ, Moore RA, Marra MA, Dome JS, Mullighan CG, Ma J, Wheeler DA, Hampton OA, Ross N, Gastier-Foster JM, Arold ST, Perlman EJ. A Children's Oncology Group and TARGET initiative exploring the genetic landscape of Wilms tumor. Nat Genet. 2017;49:1487–94. PubMed PMID: 28825729.

Halliday BJ, Fukuzawa R, Markie DM, Grundy RG, Ludgate JL, Black MA, Skeen JE, Weeks RJ, Catchpoole DR, Roberts AGK, Reeve AE, Morison IM. Germline mutations and somatic inactivation of TRIM28 in Wilms tumour. PLoS Genet. 2018;14:e1007399. PubMed PMID: 29912901.

Hanks S, Perdeaux ER, Seal S, Ruark E, Mahamdallie SS, Murray A, Ramsay E, del Vecchio Duarte S, Zachariou A, de Souza B, Warren-Perry M, Elliott A, Davidson A, Price H, Stiller C, Pritchard-Jones K, Rahman N. Germline mutations in the PAF1 complex gene CTR9 predispose to Wilms tumour. Nat Commun. 2014;5:4398. PubMed PMID: 25099282.

Hol JA, Diets IJ, de Krijger RR, van den Heuvel-Eibrink MM, Jongmans MC, Kuiper RP. TRIM28 variants and Wilms' tumour predisposition. J Pathol. 2021a;254:494–504. PubMed PMID: 33565090.

Hol JA, Jewell R, Chowdhury T, Duncan C, Nakata K, Oue T, Gauthier-Villars M, Littooij AS, Kaneko Y, Graf N, Bourdeaut F, van den Heuvel-Eibrink MM, Pritchard-Jones K, Maher ER, Kratz CP, Jongmans MCJ. Wilms tumour surveillance in at-risk children: Literature review and recommendations from the SIOP-Europe Host Genome Working Group and SIOP Renal Tumour Study Group. Eur J Cancer. 2021b;153:51–63. PubMed PMID: 34134020.

Hyder Z, Fairclough A, Groom M, Getty J, Alexander E, van Veen EM, Makin G, Sethuraman C, Tang V, Evans DG, Maher ER, Woodward ER. Constitutional de novo deletion CNV encompassing REST predisposes to diffuse hyperplastic perilobar nephroblastomatosis (HPLN). J Med Genet. 2021;58:581–5. PubMed PMID: 32917767.

Kalish JM, Doros L, Helman LJ, Hennekam RC, Kuiper RP, Maas SM, Maher ER, Nichols KE, Plon SE, Porter CC, Rednam S, Schultz KAP, States LJ, Tomlinson GE, Zelley K, Druley TE. Surveillance recommendations for children with overgrowth syndromes and predisposition to Wilms tumors and hepatoblastoma. Clin Cancer Res. 2017;23:e115–e122. PubMed PMID: 28674120.

Klein SD, Martinez-Agosto JA. Hotspot mutations in DICER1 causing GLOW syndrome-associated macrocephaly via modulation of specific microRNA populations result in the activation of PI3K/ATK/mTOR signaling. Microrna. 2020;9:70–80. PubMed PMID: 31232238.

Li FP, Williams WR, Gimbrere K, Flamant F, Green DM, Meadows AT. Heritable fraction of unilateral Wilms tumor. Pediatrics. 1988;81:147–9. PubMed PMID: 2827098.

Maciaszek JL, Oak N, Nichols KE. Recent advances in Wilms' tumor predisposition. Hum Mol Genet. 2020;29:R138–R149. PubMed PMID: 32412586.

Mahamdallie S, Yost S, Poyastro-Pearson E, Holt E, Zachariou A, Seal S, Elliott A, Clarke M, Warren-Perry M, Hanks S, Anderson J, Bomken S, Cole T, Farah R, Furtwaengler R, Glaser A, Grundy R, Hayden J, Lowis S, Millot F, Nicholson J, Ronghe M, Skeen J, Williams D, Yeomanson D, Ruark E, Rahman N. Identification of

new Wilms tumour predisposition genes: an exome sequencing study. Lancet Child Adolesc Health. 2019;3:322–31. PubMed PMID: 30885698.

Mahamdallie SS, Hanks S, Karlin KL, Zachariou A, Perdeaux ER, Ruark E, Shaw CA, Renwick A, Ramsay E, Yost S, Elliott A, Birch J, Capra M, Gray J, Hale J, Kingston J, Levitt G, McLean T, Sheridan E, Renwick A, Seal S, Stiller C, Sebire N, Westbrook TF, Rahman N. Mutations in the transcriptional repressor REST predispose to Wilms tumor. Nat Genet. 2015;47:1471–4. PubMed PMID: 26551668.

Nelson MV, van den Heuvel-Eibrink MM, Graf N, Dome JS. New approaches to risk stratification for Wilms tumor. Curr Opin Pediatr. 2021;33:40–8. PubMed PMID: 33394739.

Ooms AH, Gadd S, Gerhard DS, Smith MA, Guidry Auvil JM, Meerzaman D, Chen QR, Hsu CH, Yan C, Nguyen C, Hu Y, Ma Y, Zong Z, Mungall AJ, Moore RA, Marra MA, Huff V, Dome JS, Chi YY, Tian J, Geller JI, Mullighan CG, Ma J, Wheeler DA, Hampton OA, Walz AL, van den Heuvel-Eibrink MM, de Krijger RR, Ross N, Gastier-Foster JM, Perlman EJ. Significance of TP53 Mutation in Wilms tumors with diffuse anaplasia: a report from the Children's Oncology Group. Clin Cancer Res. 2016;22:5582–91. PubMed PMID: 27702824.

Palculict TB, Ruteshouser EC, Fan Y, Wang W, Strong L, Huff V. Identification of germline DICER1 mutations and loss of heterozygosity in familial Wilms tumour. J Med Genet. 2016;53:385–8. PubMed PMID: 26566882.

Roversi G, Picinelli C, Bestetti I, Crippa M, Perotti D, Ciceri S, Saccheri F, Collini P, Poliani PL, Catania S, Peissel B, Pagni F, Russo S, Peterlongo P, Manoukian S, Finelli P. Constitutional de novo deletion of the FBXW7 gene in a patient with focal segmental glomerulosclerosis and multiple primitive tumors. Sci Rep. 2015;5:15454. PubMed PMID: 26482194.

Scott RH, Walker L, Olsen OE. Levitt g, Kenney I, Maher E, Owens CM, Pritchard-Jones K, Craft A, Rahman N. Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. Arch Dis Child. 2006;91:995–9. PubMed PMID: 16857697.

Venger K, Elbracht M, Carlens J, Deutz P, Zeppernick F, Lassay L, Kratz C, Zenker M, Kim J, Stewart DR, Wieland I, Schultz KAP, Schwerk N, Kurth I, Kontny U. Unusual phenotypes in patients with a pathogenic germline variant in DICER1. Fam Cancer. 2021. Epub ahead of print. PubMed PMID: 34331184.

License