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Wilms Tumor Overview

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Summary

Disease characteristics. Wilms tumor (nephroblastoma) is an embryonal malignancy of the kidney. Current models of Wilms tumor development propose that a genetic mutation predisposes to nephrogenic rests, benign foci of embryonal kidney cells that persist abnormally into postnatal life. The vast majority of children with Wilms tumor predisposition syndromes have nephrogenic rests. Intralobar rests, which are usually solitary are associated with two syndromes associated with *WT1* mutations: WAGR (Wilms tumor-aniridia-genital anomalies-retardation) and Denys-Drash syndrome. Perilobar rests, which are often multiple, are associated with Beckwith-Wiedemann syndrome. Wilms tumor has the potential for both local and distant spread. Wilms tumor usually presents as an abdominal mass in an otherwise well-appearing child. Abdominal pain, fever, anemia, hematuria, and hypertension are seen in 25-30% of affected children. Approximately 5-10% of children with Wilms tumor have bilateral or multicentric tumors. The average age at presentation is 42-47 months for children with unilateral Wilms tumor and 30-33 months for those with bilateral Wilms tumor.

Diagnosis/testing. The workup of a child with suspected Wilms tumor begins with appropriate diagnostic imaging studies. Ultrasonography is the recommended first-line test because it provides a panoramic view of the abdomen. Computed tomography (CT) can also visualize pelvic and abdominal structures as well as lymph nodes. Magnetic resonance imaging (MRI) may facilitate the distinction between Wilms tumor and nephrogenic rests. The definitive diagnosis of Wilms tumor can be made only by surgical resection or biopsy. In 10-15% of affected individuals, Wilms tumor is considered to be heritable.

Causes. To date, only one Wilms tumor gene, *WT1*, has been identified. The syndromes in which germline *WT1* mutations occur are WAGR syndrome, caused by deletions of chromosome 11p13 that include both *PAX6* and *WT1*; Denys-Drash syndrome (XY individual with undermasculinized external genitalia that can range from ambiguous to normal appearing female, diffuse mesangial sclerosis, and Wilms tumor) caused by missense mutations in *WT1*, almost invariably in exons 8 and 9; Frasier syndrome (XY individuals with undermasculinized external genitalia that can range from ambiguous to normal appearing female, focal segmental glomerulosclerosis, gonadoblastoma) caused by point mutations in the *WT1* intron 9 donor splice site; and genitourinary (GU) anomalies without renal failure. Wilms tumor is observed in fewer than 5% of children with Beckwith-Wiedemann syndrome. Other inherited multisystem disorders are associated less frequently with Wilms tumor. In individuals with Wilms tumor. One to two percent of individuals with Wilms tumor have at least one

relative also diagnosed with Wilms tumor. Mutations in *WT1* are not implicated in most families with Wilms tumor predisposition. Linkage analysis has mapped Wilms tumor predisposition genes to 17q (locus name FWT1) and 19Q (locus name FWT2). Because some famlies do not show linkage to *WT1*, FWT1, or FWT2, the existence of one or more other familial Wilms tumor genes is likely.

Management. Treatment of Wilms tumor includes surgery, chemotherapy, and for some individuals, radiation therapy. Surgery is a cornerstone of Wilms tumor treatment and is performed at time of diagnosis or after 4-8 weeks of pre-operative chemotherapy. Because Wilms tumor can spread to the lungs, pre-operative chest radiography or chest CT scans are imperative. Nephron-sparing surgery is routinely advocated for those with bilateral Wilms tumor. Chemotherapy includes vincristine and dactinomycin for stage I and II favorable histology Wilms tumor and vincristine, dactinomycin, and doxorubicin for stage III or IV favorable histology disease. Treatment for anaplastic Wilms tumor includes vincristine, doxorubicin, cyclophosphamide or ifosfamide, etoposide, and carboplatin. After surgery children with advanced disease (stage III or IV) undergo radiation therapy. End-stage renal disease (ESRD) is treated initially with dialysis, followed by renal transplantation when possible. **Surveillance** for Wilms tumor in individuals with Beckwith-Wiedemann or isolated hemihypertrophy is recommended every three months with abdominal ultrasound examination until the child is eight years old. In individuals with WAGR syndrome, regular screening by abdominal ultrasound examination is recommended until age five to seven years. Screening sibs of an individual with familial Wilms tumor is recommended by renal ultrasound examination until the age of five to seven years. After completion of therapy for Wilms tumor, individuals with bilateral or multifocal Wilms tumors are screened by renal ultrasound examination every three months for metachronous tumors until they are seven years old. Surveillance for ESRD in individuals with DDS, WAGR syndrome, and GU anomalies includes urinalysis, blood pressure measurement, and serum chemistries (including BUN and creatinine) at least annually. Offspring of survivors of bilateral Wilms tumor are screened with renal ultrasound examinations until the age of five to seven years.

Genetic counseling. If a proband is found to have syndromic Wilms tumor, genetic counseling for the specific syndrome is appropriate. Nonsyndromic Wilms tumor most frequently occurs in a single individual of a family. Empiric risks to the sibs of a proband who is the only affected family member are unknown but likely low. Empiric risks to the offspring of a proband who is the only affected family member are not increased. Prenatal diagnosis for pregnancies at 50% risk for inheriting a *WT1* mutation from a parent is possible when the specifc *WT1* mutation has been identified.

Definition

The classic Wilms tumor (nephroblastoma) is an embryonal malignancy of the kidney that consists of blastemal, epithelial, and stromal cells; however, not all Wilms tumors have all three cell types.

It is generally accepted that histologic classification is the most powerful prognostic factor for Wilms tumor [Green et al 1994, Pritchard et al 1995, Hill et al 2003].

- Approximately 6% of Wilms tumors contain **anaplasia**, a term that refers to nuclear enlargement and atypia with irregular mitotic figures [Beckwith & Palmer 1978]. Several large studies have demonstrated that the presence of anaplasia is associated with adverse outcome.
- Wilms tumors without anaplasia are designated as tumors of "**favorable histology**."

- Some Wilms tumors display a high degree of maturation into mature skeletal muscle elements, a variant sometimes called "**fetal rhabdomyomatous nephroblastoma (FRN)**." Such Wilms tumors typically do not respond to chemotherapy by shrinking; instead, they differentiate and occasionally grow [Anderson et al 2002]. The lack of tumor shrinkage does not necessarily portend an adverse prognosis because FRN has low metastatic potential. The incidence of FRN is higher in bilateral tumors than in unilateral tumors. FRN has been associated with *WT1* mutations [Schumacher et al 1997, Miyagawa et al 1998].

Current models of Wilms tumor development propose that a genetic mutation predisposes to **nephrogenic rests**, benign foci of embryonal kidney cells that persist abnormally into postnatal life. Nephrogenic rests are found in approximately 1% of newborn kidneys and usually regress or differentiate by early childhood [Beckwith et al 1990]. Some nephrogenic rests persist into childhood. These rests are considered to be Wilms tumor precursors [Gylys-Morin et al 1993]; nephrogenic rests that sustain additional mutations transform into a Wilms tumor [Dome & Coppes 2002]. It is thought that genetic alterations play a role in the development of Wilms tumor because Wilms tumor presents at an early age and has not been linked with major environmental risk factors. The genetic alterations may be somatic mutations that affect only the tumor cells (90-95% of Wilms tumor) or constitutional (germline) mutations that confer a genetic predisposition to Wilms tumor (5-10% of Wilms tumor). The constitutional mutations may arise *de novo* at the time of conception or be inherited; inherited germline mutations result in familial Wilms tumor.

The vast majority of children with Wilms tumor predisposition syndromes have nephrogenic rests [Beckwith 1998b]. The two types of nephrogenic rests are intralobar rests and perilobar rests [Beckwith et al 1990].

- **Intralobar rests** are usually solitary and randomly distributed throughout the kidney, although they tend to be situated centrally within the renal lobe. Intralobar rests are associated with two syndromes associated with *WT1* mutations: WAGR (Wilms tumor-aniridia-genital anomalies-retardation) and Denys-Drash syndrome.
- **Perilobar rests** tend to be located at the periphery of the kidney and are often multiple. Perilobar rests are associated with Beckwith-Wiedemann syndrome (BWS).

The term **nephroblastomatosis** is used to describe the presence of multiple nephrogenic rests. Nephroblastomatosis may be manifest as a diffuse overgrowth of rests, producing a rim that enlarges the kidney, or as multiple distinct rests [Perlman et al 2006]. It is sometimes challenging to distinguish nephrogenic rests from Wilms tumors, even with biopsies. Although nephrogenic rests are considered benign, chemotherapy has been advocated if the rests are growing or if a child becomes symptomatic. Some evidence indicates that chemotherapy may decrease the risk of subsequent Wilms tumor development in children with nephrogenic rests [Coppes et al 1999].

Wilms tumor has the potential for both local and distant spread. Local spread typically occurs into the renal hilar structures and may penetrate the renal capsule. The tumors have a propensity to invade the renal vein and to form thrombi in the inferior vena cava, sometimes progressing into the heart. Local and distant lymph node involvement can also occur. The most common sites of distant metastases are the lungs and liver, with rare instances of spread to bone and brain.

The National Wilms Tumor Study Group (NWTSG) designated five tumor stages with higher stages associated with greater risks of recurrence. These staging criteria were recently modified by the Children's Oncology Group (COG), which now conducts Wilms tumor clinical trials in North America [Metzger & Dome 2005] (Table 1).

Table 1. Children's Oncology Group Clinicopathologic Staging of Wilms Tumor

Stage	Description
I	• Tumor limited to kidney and completely excised • No penetration of the renal capsule or involvement of renal sinus vessels
II	• Tumor extending beyond the kidney but completely excised • No residual tumor apparent at or beyond the margins of excision • Tumor thrombus in vessels outside the kidney is stage II if the thrombus is removed en bloc with the tumor.[1]
III	• Gross or microscopic residual tumor remaining postoperatively, including: - Inoperable tumor - Positive surgical margins - Diffuse tumor spillage or biopsy - Regional lymph node metastases, or - Transected tumor thrombus
IV	• Hematogenous metastases (lung, liver, bone, brain) or lymph node metastases outside the abdominal or pelvic cavities
V	• Bilateral renal tumors at diagnosis

1. Note: Although tumor biopsy or local spillage confined to the flank were considered stage II by the NWTSG in the past, such events will be considered stage III on upcoming COG studies.

Clinical Manifestations

Wilms tumor usually presents as an abdominal mass in an otherwise well-appearing child. Abdominal pain, fever, anemia, hematuria, and hypertension are seen in 25-30% of affected children [Green 1985].

Approximately 5-10% of individuals with Wilms tumor have bilateral or multicentric tumors. Although the prevalence of bilateral involvement is higher in individuals with genetic predisposition syndromes as compared to individuals without predisposition syndromes, 85% of individuals with WAGR (see Aniridia) or BWS have unilateral tumors [Huff 1998, Porteus et al 2000].

The average age at presentation is 42-47 months for children with unilateral Wilms tumor and 30-33 months for those with bilateral Wilms tumor [Breslow et al 1993]. Wilms tumor occasionally occurs in adults. Several studies have shown that adults with Wilms tumor have worse outcomes compared to children, but under treatment is a likely contributory factor [Terenziani et al 2004]. When treated with regimens similar to those used for children, most adults with Wilms tumor can be cured [Kalapurakal et al 2004, Reinhard et al 2004].

Girls have a slightly increased risk of Wilms tumor, with a male-to-female ratio of 0.92 to 1.00.

Establishing the Diagnosis

Imaging. The workup of a child with suspected Wilms tumor begins with appropriate diagnostic imaging studies to define the extent of disease and to help plan the surgical intervention.

- **Ultrasonography** is the recommended first-line test for children suspected of having Wilms tumor because it provides a panoramic view of the abdomen, including the patency of the inferior vena cava.

- **Computed tomography (CT)** can also visualize the pelvic and abdominal structures, as well as lymph nodes.
- **Magnetic resonance imaging (MRI)** is not a routine component of the evaluation of Wilms tumor, although MRI may facilitate the distinction between Wilms tumor and nephrogenic rests.

Surgical resection or biopsy. Although imaging studies may suggest a diagnosis of Wilms tumor, the definitive diagnosis can be made only upon histologic assessment of the tumor.

- The COG recommends performing nephrectomy/tumor resection and regional lymph node sampling before chemotherapy to obtain the most accurate staging information. If the tumor is deemed unresectable, a biopsy is recommended to confirm the diagnosis [Green 2004, Metzger & Dome 2005].
- The International Society of Pediatric Oncology (SIOP) recommends administering pre-operative chemotherapy to all individuals (with or without a biopsy, depending on the individual's age) to shrink the tumor with the aim of facilitating surgery [de Kraker & Jones 2005].

Differential Diagnosis

The differential diagnosis of Wilms tumor includes other primary renal malignancies of childhood such as clear cell sarcoma and malignant rhabdoid tumor. These two tumors, once considered variants of Wilms tumor, are now recognized to be distinct entities. Other renal neoplasms that occur in children include congenital mesoblastic nephroma, renal sarcoma, and renal cell carcinoma.

Benign renal processes that may be confused with Wilms tumor include nephrogenic rests, autosomal recessive polycystic kidney disease (ARPKD) and occasionally autosomal dominant polycystic kidney disease (ADPKD), hydronephrosis, renal carbuncles, and hemorrhage.

Neuroblastoma, an embryonal malignancy of the adrenal gland, may be confused with Wilms tumor because these two tumors affect the same age group and commonly arise in the same general region of the abdomen.

Prevalence

Wilms tumor affects approximately one of every 8,000-10,000 children in North America [Breslow et al 1993]. It is the most common pediatric kidney cancer and comprises 6.3% of malignancies in children younger than 15 years of age [Miller et al 1995].

Causes

Heritable Causes

In individuals with Wilms tumor, 10-15% are considered to have a heritable cause. These may or may not be associated with known syndromes. A heritable cause of Wilms tumor may be suggested by clinical features of genetic predisposition syndromes such as hypospadias or undescended testes (6%); hemihypertrophy and other features of Beckwith-Wiedemann syndrome (BWS) (4%); or aniridia (1%) [Breslow et al 1993]. In the absence of syndromic features, a heritable cause may also be implied by the existence of other family members with a history of Wilms tumor.

Syndromic Causes—*WT1*-related. To date, only one Wilms tumor gene, *WT1,* has been identified (Table 2). *WT1* encodes a zinc finger transcription factor that is critical to normal

development of the kidneys and gonads [Pelletier et al 1991,Kreidberg et al 1993]. Numerous studies have identified putative transcriptional targets of the WT1 protein, many of which are involved in cell growth, differentiation, and apoptosis. The biologically relevant precise targets that are involved in Wilms tumorigenesis remain to be determined.

Table 2. Molecular Genetics of Syndromic Wilms Tumor

Gene Symbol	Locus	Protein	Test Availability
WT1	11p13	Wilms tumor protein	Clinical Testing

The following are syndromes in which germline *WT1* mutations occur:

- **WAGR syndrome** (**W**ilms tumor, **a**niridia, **g**enital anomalies, **r**etardation) is caused by deletions of chromosome 11p13 that include both *PAX6* and *WT1*. Aniridia arises from deletion of the *PAX6* gene, which lies adjacent to the *WT1* gene. The risk of Wilms tumor in simplex cases (i.e., a single occurrence of aniridia ina family) (so-called "sporadic" aniridia) is 40-50% if the individual has a 11p13 deletion that encompasses *WT1*. If a *WT1* deletion is not detected by FISH in a simplex case of aniridia, the risk of Wilms tumor is low [Gronskov et al 2001, Muto et al 2002].

  As shown in Table 3, affected individuals have an earlier age of Wilms tumor diagnosis and more frequent occurrence of bilateral disease than individuals without WAGR. Interestingly they also have a high incidence of intralobar nephrogenic rests and their tumors invariably exhibit a favorable histology. Individuals with WAGR generally respond well to treatment for WT [Breslow et al 2003] and have short-term survival comparable to non-WAGR persons. However, individuals with WAGR often develop end-stage renal disease (ESRD) around adolescence, resulting in declining survival. In studies employing the NWTS patient population, 34-40% of individuals with WAGR who survived WT subsequently developed ESRD, and a 48% (±17%) survival rate at 27 years from diagnosis of WT was estimated for this group [Breslow et al 2000,Breslow et al 2003,Breslow et al 2005].

- **Denys-Drash syndrome (DDS)** (undermasculinized external genitalia in an individual with a 46,XX karyotype that can range from ambiguous to normal-appearing female, diffuse mesangial sclerosis leading to early-onset renal failure, and Wilms tumor) is caused by *WT1* mutations. The risk for Wilms tumor in individuals with DDS is estimated to be greater than 90%. As shown in Table 4, the genotype/phenotype relationship is strong such that most individuals with DDS have germline missense mutations in exons 8 and 9 [Huff 1996,Royer-Pokora et al 2004]. The observation of other types of *WT1* mutations in a small number of affected individuals is likely due, at least in part, to the diagnosis of "DDS" in the absence of renal failure [Royer-Pokora et al 2004] along with variable expressivity of these missense mutations. In contrast to the renal failure associated with WAGR syndrome, the renal failure associated with DDS tends to be early-onset. The NWTSG recently reported that the cumulative incidence of renal failure in those with DDS 20 years after Wilms tumor diagnosis was 74% [Breslow et al 2005]. However, not all individuals in this series had *WT1* molecular genetic testing, so it is possible that some designated as having DDS did not have the typical exon 8 and 9 mutations.

- **Frasier syndrome** (undermasculinized external genitalia in an individual with a 46,XY karyotype that can range from ambiguous to normal-appearing female, focal segmental glomerulosclerosis, gonadoblastoma) is caused by point mutations in the *WT1* intron 9 donor splice site [Barbaux et al 1997]. Although Frasier syndrome is not typically associated with Wilms tumor, several cases have been reported.

- **Genitourinary (GU) anomalies without renal failure.** Some individuals with germline *WT1* point mutations have GU anomalies and Wilms tumor, but do not have early renal failure. As shown in Table 4, these findings are predominantly associated with *WT1* gene deletions and nonsense and frameshift mutations.

Table 3. Findings in WAGR and Non-WAGR Wilms Tumor

	WAGR	Non-WAGR [1]
Mutation type	Contiguous gene deletion	Mutation status not determined
Population frequency	0.75%	99.25%
Birth weight	2.94 kg	3.45 kg
Median age at diagnosis	22 months	39 months
Bilateral	17%	6%
Metastatic disease	2%	13%
Favorable histology	100%	92%
ILNR	77%	22%
4-yr survival	95±3%	92±0.3%
27-yr survival	48±17% [2]	486±1%
Observed ESRD [2]		
Unilateral WT	11/37 (29.7%)	44/5489 (0.8%)
Bilateral WT	5/10 (50%)	55/440 (12.5%)

Breslow et al 2003
WAGR = Wilms tumor, aniridia, genital anomalies, retardation
WT = Wilms tumor
ILNR = Intralobar nephrogenic rests
ESRD = End-stage renal disease
1. Includes individuals with DDS
2. Mean follow-up 12.6 years following WT diagnosis

Table 4. Genotype/Phenotype Correlations

	Gene Deletion [1] (n=21)	Missense: Exon 8 or 9 (n=25)	Missense: Other Exons (n=5)	Truncation, Frameshift, Nonsense (n=63)
Clinical Phenotype				
WAGR	9 (43%)			
WT/AN/GU	5 (24%)			
WT/AN [2]	5 (24%)			
WT/GU	1 (5%)			32 (51%)
DDS diagnosis	1 (5%)	23 (92%)		5 (8%) [3]
WT, early-onset renal disease		1 (4%)		
WT only		1 (4%)	5 (100%)	26 (41%)
Laterality				
Bilateral	5 (24%)	4 (16%)	1	33 (52%)
Unilateral	16 (76%)	21 (84%)	4	30 (48%)
Age at Diagnosis				
Average	31.4 mo	17.0 mo	27.6 mo	14.8 mo
Range	12-87 mo	4-36 mo	8-55 mo	3-41 mo

Data taken with slight modification from Royer-Pokora et al 2004
WAGR = Wilms tumor, aniridia, genital anomalies, retardation
WT = Wilms tumor
AN = Aniridia
GU = Genitourinary abnormalities
DDS = Denys-Drash syndrome
1. Most are large contiguous gene deletions at 11p13.
2. Includes three females in whom GU phenotype is less penetrant
3. Includes cases reported as DDS, but ESRD (end-stage renal disease) may not have been noted

11p15 locus-related. The 11p15 locus is often referred to as "WT2," although a distinct Wilms tumor gene has not been isolated. The existence of a gene(s) at 11p15 that plays a role in Wilms tumorigenesis is inferred from two lines of evidence:

- Wilms tumor is observed in a small (<5%) but significant percentage of children with the Beckwith-Wiedemann syndrome, which has been mapped to chromosome 11p15.5, a region containing several imprinted genes [Koufos et al 1989, Ping et al 1989, DeBaun et al 1998].
- Loss of heterozygosity (LOH) or loss of imprinting (LOI) at 11p15 is observed in approximately 40% of Wilms tumors [Koufos et al 1985, Ogawa et al 1993, Moulton et al 1996]. Candidate genes in this region include *IGF2* and *H19* (telomeric) and *CDKN1C/p57^{kip2}* and *KCNQ1OT1/LIT1* (centromeric). Research on genotype-phenotype relationships is ongoing, but accumulating evidence indicates that uniparental isodisomy of 11p15 and hypermethylation of *H19* are associated with development of Wilms tumor, whereas alterations of *KCNQ1OT1* are associated with other tumors, macrosomia, and abdominal wall defects [Engel et al 2000, Tycko 2000, Bliek et al 2001, Weksberg et al 2001, DeBaun et al 2002]. Inherited microdeletions within the H19/IGF2 imprinting control region have been identified in two children with BWS and one family with BWS/WT, further strengthening the association between aberrant expression of IGF2 with WT development [Sparago et al 2004, Prawitt et al 2005].

Other disorders associated with Wilms tumor include:

- Autosomal dominant disorders: Li-Fraumeni syndrome, Sotos syndrome, hyperparathyroid-jaw tumor syndrome, and neurofibromatosis type 1
- Autosomal recessive disorders: Fanconi anemia syndrome (specifically the D1 subtype that is associated with biallelic *BRCA2* mutations), mosaic variegated aneuploidy, and Bloom's syndrome
- X-linked disorder: Simpson-Golabi-Behmel syndrome
- Perlman syndrome
- Trisomy 18

Nonsyndromic Causes—Familial Wilms tumor. Of individuals with Wilms tumor, 1-2% have at least one relative also diagnosed with Wilms tumor. Most often the affected relative (s) is a sib, parent, aunt/uncle, or close cousin [Breslow et al 1996]. Because of the very low incidence of Wilms tumor in the population and the lack of a strong environmental risk factor, the occurrence of more than one individual with Wilms tumor in a family is thought to be the result of a germline genetic alteration that predisposes to Wilms tumor development. Analyses of large families with many affected individuals have indicated that such predisposition is due to an autosomal dominant mutation with incomplete penetrance, although multigene models cannot be excluded. In general, a higher frequency of bilateral tumors and an earlier age of diagnosis are observed in families with Wilms tumor, although exceptions occur. The following genes/loci have been implicated in familial Wilms tumor:

- **FWT1 and FWT2 loci.** Genetic linkage analyses of families with Wilms tumor has mapped familial predisposition genes to a locus on 17q (called FWT1) and 19q (called FWT2) [Grundy et al 1988, Huff et al 1988, Rahman et al 1996, Diller et al 1998, Huff 1998, McDonald et al 1998]. Additionally, some families are not linked to WT1, 17q, or 19q, implying the existence of one or more other familial Wilms tumor genes [McDonald et al 1998].
- ***WT1*.** Mutations in *WT1* are not implicated in most families with Wilms tumor predisposition; however, a small number of families that have germline *WT1* mutations have been identified.
- ***BRCA2*.** Two siblings with Wilms tumor and brain tumors (glioblastoma multiforme in one and medulloblastoma in the other) have biallelic *BRCA2* mutations. Of 23 individuals with biallelic *BRCA2* mutations reported in the literature, five have had Wilms tumor [Reid et al 2005].

Isolated, simplex Wilms tumor

- **Germline *WT1* mutations.** *WT1* mutations are present in the germline of less than five percent of individuals with Wilms tumor. Some individuals with germline mutations do not exhibit features of any of the above syndromes [Huff et al 1991, Diller et al 1998, Huff 1998, Royer-Pokora et al 2004]. These are more likely to be individuals with a 46, XX karyotype. For example, 25 of the 32 (78%) individuals with "WT only" in Table 3 are female, consistent with the notion that germline *WT1* mutations have a greater effect on sex determination and genital tract development in males than females. Compared to individuals with sporadic Wilms tumor, those with germline *WT1* mutations are more likely to have bilateral or multicentric tumors and to develop tumors at an early age, although not all children with bilateral disease at an early age have *WT1* mutations [Perotti et al 2004]. In the absence of GU anomalies, renal mesangial sclerosis, or bilateral tumors, the likelihood

that a child with Wilms tumor has a *WT1* germline mutation is low, with reported frequencies of 2-5% [Huff 1998, Little et al 2004].

- **Somatic *WT1* mutations.** In individuals without GU anomalies or DDS, *WT1* mutations occur in approximately 20% of Wilms tumors. More than 70% of these mutations are somatic [Huff 1998].

Non-Heritable Causes

Some somatic mutations that have been detected in Wilms tumor samples presumably contribute to the pathogenesis of the tumor. The following genes/loci have been implicated in either the initiation or progression of Wilms tumor:

- ***CTNNB1* (β-catenin) gene.** Mutations in the *CTNNB1* gene have been identified in approximately 15% of Wilms tumors, but, as in other tumor types, mutations of this gene are tumor specific. *CTNNB1* mutations are almost invariantly coincident with *WT1* mutations [Koesters et al 1999, Maiti et al 2000, Li et al 2004].
- **Chromosome 7p.** Cytogenetic studies have detected both germline and acquired rearrangements of chromosome 7 in a subset of individuals with Wilms tumor. LOH studies have identified at least three regions at the 7p locus that may contain Wilms tumor-related genes [Grundy et al 1998, Powlesland et al 2000, Perotti et al 2001]. A candidate tumor suppressor gene at 7p14 called *POU6F2* has been identified; further work is underway to determine whether this candidate plays a role in Wilms tumor development [Perotti et al 2004].
- **Regions of LOH.** LOH and cytogenetic analyses of tumors have also implicated other genes at other loci, most notably at 16q and 1p [Maw et al 1992]; the genes have yet to be identified. A recent study from the NWTSG demonstrated that LOH at 1p and 16q is associated with adverse prognosis in individuals with favorable histology Wilms tumor [Grundy et al 2005]. Linkage studies of families with Wilms tumor have not provided any evidence for Wilms tumor predisposition genes in these regions [McDonald et al 1998].

Evaluation Strategy

Family history. A three-generation pedigree should be obtained with attention to individuals with Wilms tumor, renal abnormalities that may be nephrogenic rests, GU anomalies, and/or early-onset renal failure.

Clinical examination. Clinical examination should focus on those congenital anomalies suggestive of BWS (macroglossia, macrosomia, hemihypertrophy, omphalocele) or findings of a *WT1* mutation (aniridia, genital anomalies, evidence of early-onset renal failure).

Testing

- **Individuals with familial Wilms tumor.** Although several families with *WT1* mutations have been reported, most families with Wilms tumor do not have a *WT1* germline mutation. *WT1* molecular genetic testing in individuals with familial Wilms tumor is available on a clinical basis and can be considered, although the yield will be low.
- **Individuals with bilateral Wilms tumor**
  - If an individual with bilateral Wilms tumor has GU anomalies or renal failure, molecular genetic testing for *WT1* mutations is indicated.

  - A few individuals with bilateral Wilms tumor without GU anomalies, a positive family history, or renal failure have been found to have *WT1* mutations, so molecular genetic testing may be considered, although the yield will be low [Huff 1998, Perotti et al 2005].

- **Individuals with unilateral Wilms tumor.** Individuals with unilateral Wilms tumor and no congenital anomalies are unlikely to have germline *WT1* mutations; in three large studies, the frequency of *WT1* mutations in such individuals was 0%, 1.3%, and 1.4% [Diller 1998, Huff 1998, Little et al 2004]
- **Individuals with known or suspected Denys-Drash syndrome (DDS) or Frasier syndrome.** Sequence analysis of *WT1* to detect intragenic mutations can be considered. Germline *WT1* mutations identified to date are predominantly deletions or insertions, truncation mutations, or missense mutations in exons 8 or 9 (DDS) or IVS9 mutations that affect splicing (Frasier syndrome).
- **Individuals with aniridia.** (See Aniridia GeneReview for testing issues.)
- **Individuals with BWS or hemihypertrophy.** (See Beckwith-Wiedemann Syndrome GeneReview for testing issues.)

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Wilms tumor may occur as a part of a syndrome (syndromic Wilms tumor) or as an isolated finding (i.e., not in association with any other medical findings) (nonsyndromic Wilms tumor).

Syndromic Wilms tumor. If a proband is found to have syndromic Wilms tumor (e.g., WAGR, a *WT1*-related syndrome, Beckwith-Wiedemann syndrome), genetic counseling for the specific syndrome is appropriate.

Nonsyndromic Wilms tumor. This most frequently occurs in a single individual of a family; however, nonsyndromic Wilms tumor may occur in more than one family member (familial Wilms tumor) and may be inherited in an autosomal dominant manner with reduced penetrance. In both of these situations, Wilms tumor predisposition is usually not due to a germline *WT1* mutation.

Individuals with a known *WT1* germline mutation

- *WT1* germline mutations are inherited in an autosomal dominant manner with variable expressivity and reduced penetrance.
- The majority of individuals with a *WT1* germline mutation have a *de novo* mutation; their parents are unlikely to have had Wilms tumor or to have the *WT1* mutation.
- When the *WT1* disease-causing mutation identified in the proband cannot be detected in the DNA of either parent, the risk to the sibs of a proband is likely to be low; however, the rate of parental germline mosaicism is unknown [Huff 1994 & unpublished data].

- Offspring of an individual with a known *WT1* mutation have a 50% risk of inheriting the mutation. The risk of Wilms tumor developing in a child with a known *WT1* alteration depends on the penetrance of the specific mutation.

Familial Wilms tumor

- Most individuals diagnosed with nonsyndromic Wilms tumor do not have an affected parent; some may have another affected family member (familial Wilms tumor).
- Familial Wilms tumor may be caused by a *WT1* germline mutation that is inherited in an autosomal dominant manner with variable expressivity and reduced penetrance [Zirn et al 2005]; however, in most families, Wilms tumor predisposition is not caused by a *WT1* mutation [Huff 1998].
- Empiric risks to the sibs of a proband who does not have an identified *WT1* mutation to develop Wilms tumor are unknown.

Nonsyndromic Wilms tumor in a single individual in a family

- The vast majority of individuals with Wilms tumor have no family history of Wilms tumor nor do they have associated congenital anomalies.
- Empiric risks to the sibs of a proband who is the only affected family member are unknown but likely low.
- Empiric risks to the offspring of a proband who is the only affected family member are not increased.
  - No Wilms tumor was observed in the 179 offspring of 96 long-term survivors who had been diagnosed with unilateral, non-familial Wilms tumor [Li et al 1988].
  - In the absence of an identified *WT1* mutation in the proband, molecular genetic testing or ultrasound screening of the offspring of such individuals is not warranted.

Related Genetic Counseling Issues

Genetic cancer risk assessment and counseling. For comprehensive descriptions of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see:

- Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors
- Elements of Cancer Genetics Risk Assessment and Counseling (part of PDQ®, National Cancer Institute)

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at 50% risk for inheriting a *WT1* mutation from a parent is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12

weeks' gestation. The *WT1* mutation in the parent must be identified before prenatal testing can be performed. The risk of Wilms tumor developing in a child with a known *WT1* alteration depends on the penetrance of the specific mutation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

Because Wilms tumor can spread to the lungs, pre-operative chest radiography is imperative. Although plain films of the chest have been recommended on past National Wilms Tumor Studies, many physicians in North America favor chest CT scans because they provide increased sensitivity. However, the prognostic significance of small pulmonary nodules detected by CT scan and not chest x-ray is unclear and is a subject of active investigation [Green et al 1991, Meisel et al 1999].

Treatment of Manifestations

The management of Wilms tumor involves multi-modal therapy including surgery, chemotherapy, and, for selected individuals, radiation therapy [Metzger & Dome 2005, Wu et al 2005].

Surgery is a cornerstone of Wilms tumor treatment, though there is disagreement about the optimal timing of tumor resection summarized below. Either approach yields excellent results.

- The NWTSG in North America advocates performing surgery at the time of diagnosis to achieve the most accurate staging information.
- The International Society of Pediatric Oncology (SIOP) in Europe administers 4-8 weeks of pre-operative chemotherapy to shrink the tumor and facilitate surgical resection.
- Nephron-sparing surgery is advocated for individuals with bilateral Wilms tumor but not routinely recommended for those with unilateral Wilms tumor. In persons with unilateral Wilms tumor, the risk of renal failure is less than 1% after nephrectomy, so nephron-sparing surgery should be considered only if the tumor is very small and can be resected with clean margins [Ritchey 2005].

Chemotherapy. Serial studies starting in the 1960s by the NWTSG, SIOP, and other groups have led to the development of the modern Wilms tumor chemotherapy regimens.

- In North America, individuals with stage I and II favorable histology Wilms tumor are treated with vincristine and dactinomycin.
- Individuals with stage III or IV favorable histology disease are treated with vincristine, dactinomycin, and doxorubicin.

Note: All chemotherapy for favorable histology Wilms tumors may be given on an outpatient basis.

Treatment of anaplastic Wilms tumor requires more intensive therapy. Although the optimal regimen has not been established, treatment for anaplastic Wilms tumor typically includes the agents vincristine, doxorubicin, cyclophosphamide or ifosfamide, etoposide, and carboplatin.

Radiation therapy. After surgery, radiation therapy is administered to individuals with advanced disease (stage III or IV).

Survival. The treatment results from the most recently reported National Wilms Tumor Studies (NWTS) are summarized in Table 5. Children with BWS and Wilms tumor have an excellent prognosis with modern treatment regimens [Porteus et al 2000]. Individuals with WAGR syndrome are usually cured of Wilms tumor, but have decreased long-term survival rates due to the risk of end-stage renal disease (Table 3) [Breslow et al 2003].

Table 5. Outcomes from NWTS-4 and -5 Studies

Histology	Stage	Relapse-Free Survival (%)	Overall Survival (%)
Favorable NWTS-4	I	94.9 (2-year)	98.7 (2-year)
	II	83.6 (8-year)	93.8 (8-year)
	III	88.9 (2-year)	93.0 (8-year)
	IV	80.6 (2-year)	89.5 (2-year)
	V	Not yet reported	81.7 (4-year) [1]
Anaplastic NWTS-5	I [2]	69.5 (4-year)	82.6 (4-year)
	II	82.1 (4-year)	81.2 (4-year)
	III	68.3 (4-year)	72.0 (4-year)
	IV	37.5 (4-year)	37.5 (4-year)
	V	43.8 (4-year)	55.2 (4-year)

Horwitz et al 1996, Green et al 1998, Breslow et al 2004, Dome et al 2005

1. Includes only individuals who underwent renal-sparing surgery
2. Individuals with stage I anaplastic Wilms tumor received less therapy than those with the other stages.

Bilateral Wilms tumor. The aim of therapy is to eradicate the tumors while preserving as much kidney tissue as possible. The modern approach is to perform pre-operative chemotherapy to shrink the tumors followed by nephron-sparing surgery [Horwitz et al 1996].

Relapsed Wilms tumor. Only 10-15% of individuals with Wilms tumor experience recurrence, the majority of which occur within two years of diagnosis. Although the survival after Wilms tumor recurrence historically has been only 20-30% [Wilimas et al 1985, Grundy et al 1989], modern intensive treatment regimens, with or without autologous transplantation, have improved survival to the 50-60% range [Garaventa et al 1994, Pein et al 1998, Dome et al 2002, Kremens et al 2002, Campbell et al 2004].

Renal transplantation. Individuals with bilateral Wilms tumor or Denys-Drash Syndrome are at risk for renal failure. Individuals with renal failure are treated initially with dialysis and are candidates for renal transplantation. Most oncologists and transplant surgeons recommend performing the renal transplant one to two years following the end of chemotherapy treatment, which is the time period during which most Wilms tumor relapses occur. A recent study from the North American Pediatric Renal Transplant Cooperative Study demonstrated that the outcomes of renal transplantation in individuals with Wilms tumor or DDS are comparable to outcomes in children with other renal disorders [Kist-van Holthe et al 2005].

Surveillance

For relapse of Wilms tumor. See Table 6.

Table 6. COG Guidelines for Surveillance of Relapse in Individuals with Wilms Tumor

Histology	Imaging Study	Schedule
Favorable	Chest x-ray or CT chest	• Every 6 weeks until complete remission is documented, then • Every 3 months x 8, then • Every 6 months x 4
	Abdominal ultrasound	• Postoperatively after 6 weeks, then • After 3 months, then • Every 3 months x 8, then • Every 6 months x 4
Anaplastic	CT chest	• Every 6 weeks until complete remission is documented, then • Every 3 months x 8
	CT abdomen/pelvis	• Postoperatively after 6 weeks, then • After 3 months, then • Every 3 months x 8
	Abdominal ultrasound/chest x-ray	• Starting two years from end of therapy: every 6 months x 4

Recommendations from the COG Renal Tumors Committee [Dome et al 2005]

- **Individuals with Beckwith-Wiedemann syndrome or isolated hemihypertrophy.** Individuals with BWS or isolated hemihypertrophy have a 5% to 7.5% risk of developing Wilms tumor or other malignancies (mainly hepatoblastoma, adrenocortical carcinoma, neuroblastoma, and rhabodmyosarcoma). It is generally accepted that screening every three months with abdominal ultrasound examination is warranted until the child is eight years old. Among individuals with BWS and Wilms tumor, 81% develop the tumor by age five years and 93% develop the tumor by age eight years [Beckwith 1998a].
- **Individuals with WAGR**. Because the risk of Wilms tumor is high, regular screening by abdominal ultrasound examination is recommended until age five to seven years. Among individuals with Wilms tumor and WAGR syndrome, 90% develop a tumor by age four years and 98% by age seven years [Beckwith 1998b]. Because Wilms tumors can double in size every week [Beckwith 1998a], evaluation every three months is optimal.
- **Familial Wilms tumor.** Screening siblings of the affected individual with renal ultrasound examination until the age of five to seven years is recommended.
- **Bilateral Wilms tumor.** After completion of therapy for Wilms tumor, individuals with bilateral or multifocal Wilms tumors should be screened by renal ultrasound examination every three months for metachronous tumors until they are seven years old. It is assumed that most individuals with bilateral Wilms tumor have a germline mutation in a gene predisposing to Wilms tumor. Although the risk of Wilms tumor in the children of survivors of bilateral Wilms tumor is unknown, the authors recommend screening such children with serial ultrasound examinations until the age of five to seven years.

For end-stage renal disease (ESRD). Individuals with DDS, WAGR syndrome, and GU anomalies are at increased risk for ESRD [Breslow et al 2005]. Guidelines for surveillance of ESRD have not been published, but it is prudent to perform urinalysis, blood pressure measurement, and serum chemistries (including BUN and creatinine) at least annually in such

individuals. If abnormalities or changes are detected, further testing of renal function should be pursued.

Testing of Relatives at Risk

Although the risk of Wilms tumor in the children of survivors of bilateral Wilms tumor is unknown, the authors recommend screening such children with serial ultrasound examinations until the age of five to seven years.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Medline Plus
Wilms' Tumor

National Cancer Institute
Wilms' Tumor and Other Childhood Kidney Tumors

Candlelighters Childhood Cancer Foundation
PO Box 498
Kensington, MD 20895-0498
Phone: 800-366-2223; 301-962-3520
Fax: 301-962-3521
Email: info@candlelighters.org
www.candlelighters.org

Kidney Cancer Association
1234 Sherman Avenue, Suite 203
Evanston, IL 60202-1375
Phone: 800-850-9132; 847-332-1051
Fax: 847-332-2978
Email: office@kidneycancerassociation.org
CureKidneyCancer.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Chapter Notes

Revision History

- 10 April 2006 (me) Comprehensive update posted to live Web site
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