Changes for the Wilms Tumor and Other Childhood Kidney Tumors Treatment Summary

**Bold** = Proposed changes for Ed. Bd. review

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<tbody>
<tr>
<td>63</td>
<td>Added text on deaths related to congenital mesoblastic nephroma (cited Gooskens, p. 65).</td>
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General Information About Childhood Kidney Tumors

Cancer in children and adolescents is rare, although the overall incidence of childhood cancer has been slowly increasing since 1975.[1] Children and adolescents with cancer need to be referred to medical centers that have multidisciplinary teams of cancer specialists with experience treating the cancers that occur during childhood and adolescence. This multidisciplinary team approach incorporates the skills of the following health care professionals and others to ensure that children receive treatment, supportive care, and rehabilitation that will achieve optimal survival and quality of life:

- Primary care physicians.
- Pediatric surgical subspecialists.
- Radiation oncologists.
- Pediatric medical oncologists/hematologists.
- Rehabilitation specialists.
- Pediatric nurse specialists.
- Social workers.

(Refer to the PDQ Supportive and Palliative Care summaries for more information.)

Guidelines for pediatric cancer centers and their role in the treatment of pediatric patients with cancer have been outlined by the American Academy of Pediatrics.[2] At these pediatric cancer centers, clinical trials are available for most of the types of cancer...
that occur in children and adolescents, and the opportunity to participate in these trials is offered to most patients and their families. Clinical trials for children and adolescents with cancer are generally designed to compare potentially better therapy with therapy that is currently accepted as standard. Most of the progress made in identifying curative therapies for childhood cancers has been achieved through clinical trials under the auspices of cooperative groups such as the Children’s Oncology Group (COG), the Children's Cancer and Leukaemia Group (CCLG), and the Société Internationale d’Oncologie Pédiatrique (SIOP). Information about ongoing clinical trials is available from the NCI website.

Dramatic improvements in survival have been achieved for children and adolescents with cancer. Between 1975 and 2010, childhood cancer mortality decreased by more than 50%.[3] For children younger than 15 years with Wilms tumor, the 5-year survival rate has increased over the same time from 74% to 88%.[3] Childhood and adolescent cancer survivors require close monitoring because cancer therapy side effects may persist or develop months or years after treatment. (Refer to the PDQ summary on Late Effects of Treatment for Childhood Cancer for specific information about the incidence, type, and monitoring of late effects in childhood and adolescent cancer survivors.)

Childhood kidney cancers account for about 7% of all childhood cancers. Most childhood kidney cancers are Wilms tumor, but in the 15- to 19-year age group, most tumors are renal cell carcinoma. Wilms tumor can affect one kidney (unilateral) or both kidneys (bilateral). Less common types of childhood kidney tumors include rhabdoid tumors, clear cell sarcoma, congenital mesoblastic nephroma, Ewing sarcoma of the kidney, primary renal myoepithelial carcinoma, cystic partially differentiated nephroblastoma, multilocular cystic nephroma, primary renal synovial sarcoma, and anaplastic sarcoma. Nephroblastomatosis of the kidney is a type of nonmalignant neoplasia.[4, 5]

References:

Wilms Tumor

Incidence of Wilms Tumor

The incidence of Wilms tumor is 7.1 cases per 1 million children younger than 15 years. Approximately 650 cases of Wilms tumor are diagnosed in the United States each year. The incidence is substantially lower in Asians.

The male to female ratio in unilateral cases of Wilms tumor is 0.92 to 1.00, but in bilateral cases, it is 0.60 to 1.00. The mean age at diagnosis is 44 months in unilateral cases and 31 months in bilateral cases of Wilms tumor.[1, 2] About 10% of children with Wilms tumor have an associated congenital malformation syndrome.[3]

Syndromes and Other Conditions Associated With Wilms Tumor

Wilms tumor typically develops in otherwise healthy children without any predisposition to developing cancer; however, approximately 10% of children with Wilms tumor have been reported to have a congenital anomaly.[3, 4] Of 295 consecutive patients with Wilms tumor seen at the Institute Curie in Paris, 52 (17.6%) had anomalies or syndromes, 43 of which were considered major, and 14 of which were genetically proven tumor predisposition syndromes.[5]

Children with Wilms tumor may have associated hemihyperplasia and urinary tract anomalies, including cryptorchidism and hypospadias. Children may have recognizable phenotypic syndromes such as overgrowth, aniridia, genetic malformations, and others. These syndromes have provided clues to the genetic basis of the disease. The phenotypic syndromes and other conditions have been grouped into overgrowth and non-overgrowth categories. Overgrowth syndromes and conditions are the result of excessive prenatal and postnatal somatic growth.[6, 7]

It is important to recognize that the absolute risk of Wilms tumor varies with the underlying condition or anomaly (e.g., most patients with hemihypertrophy will not develop Wilms tumor).

Table 1. Syndromes and Conditions Associated With Wilms Tumor

<table>
<thead>
<tr>
<th>Syndrome/Condition</th>
<th>Gene</th>
<th>Overgrowth Phenotype</th>
<th>Non-Overgrowth Phenotype</th>
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<tbody>
<tr>
<td>9q22.3 microdeletion syndrome</td>
<td>9q22.3</td>
<td>X</td>
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<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>WT2</td>
<td>X</td>
<td></td>
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<tr>
<td>Isolated hemihyperplasia</td>
<td></td>
<td>X</td>
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<tr>
<td>Perlman syndrome</td>
<td>DIS3L2</td>
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<td>Syndrome</td>
<td>Gene(s)</td>
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<tr>
<td>Simpson-Golabi-Beohm syndrome</td>
<td>GPC3</td>
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<td>Sotos syndrome</td>
<td>NSD1</td>
<td>X</td>
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<td>Bloom syndrome</td>
<td>BLM</td>
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<tr>
<td>Denys-Drash syndrome</td>
<td>WT1</td>
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<tr>
<td>Familial Wilms tumor</td>
<td>FWT1</td>
<td>X</td>
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<td></td>
<td>FWT2</td>
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<td>Fanconi anemia with biallelic mutations</td>
<td>BRCA2</td>
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<td>in BRCA2 (FANCD1) or PALB2 (FANCN)</td>
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<td>Frasier syndrome</td>
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<td>Li-Fraumeni syndrome</td>
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<td>Trisomy 18</td>
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<tr>
<td>WAGR syndrome</td>
<td>WT1</td>
<td>X</td>
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WAGR = Wilms tumor, aniridia, genitourinary anomaly, and mental retardation.

For information about the genes associated with Wilms tumor, including Wilms tumor 1 (WT1) and Wilms tumor 2 (WT2), refer to the Genomics of Wilms Tumor section of this summary.

**Syndromic causes of Wilms tumor**

WT1-related syndromes include the following:

- **WAGR syndrome**. WAGR syndrome is characterized by the following:
  - Wilms tumor.
  - Aniridia.
  - Genitourinary anomaly.
  - Mental Retardation.

The constellation of WAGR syndrome occurs in association with an interstitial deletion on chromosome 11 (del(11p13)) (prevalence is about 0.4% of children with Wilms tumor).\[8, 9\] The incidence of bilateral Wilms tumor in children with
WAGR syndrome is about 15%.[10] (Refer to the Genomics of Wilms Tumor section of this summary for more information.)

- **Denys-Drash syndrome and Frasier syndrome.** Genitourinary anomalies such as hypospadias, undescended testis, and others are associated with WT1 mutations (prevalence is about 8%–10% of children with Wilms tumor). Children with pseudo-hermaphroditism and/or renal disease (glomerulonephritis or nephrotic syndrome) who develop Wilms tumor may have Denys-Drash or Frasier syndrome (characterized by male hermaphroditism, primary amenorrhea, chronic renal failure, and other abnormalities).[11] both of which are associated with mutations in the WT1 gene.[12] Specifically, germline missense mutations in the WT1 gene are responsible for most cases of Wilms tumor that occur as part of Denys-Drash syndrome.[13, 14] The risk of Wilms tumor is about 90% for children with Denys-Drash syndrome.[14]

**WT2-related syndromes include the following:**

- **Beckwith-Wiedemann syndrome.** Beckwith-Wiedemann syndrome is an overgrowth syndrome characterized by asymmetric growth of one or more parts of the body, large tongue, omphalocele or umbilical hernia at birth, creases or pits in the skin near the ears, kidney abnormalities, and hypoglycemia (in neonates). It is also characterized by the development of Wilms tumor, rhabdomyosarcoma, and hepatoblastoma in the first decade of life.

Beckwith-Wiedemann syndrome is caused by altered expression of two gene clusters involved in growth control and cell-cycle progression regulated by two independent Imprinting Control Regions (ICR1 [termed telomeric ICR] and ICR2 [termed centromeric ICR]) at chromosome 11p15.5. The two ICRs are characterized by differential methylation of maternal and paternal alleles. A variety of molecular mechanisms are implicated in Beckwith-Wiedemann syndrome pathogenesis, leading to unbalanced expression of imprinted genes within these two domains. Tumor predisposition results primarily from dysregulation at the telomeric domain of 11p15 (ICR1 Gain of Methylation [ICR1-GoM] and Paternal Uniparental Disomy [UPD]) rather than at the centromeric domain of 11p15 (ICR2 Loss of Methylation [ICR2-LoM] and Cyclin-Dependent Kinase Inhibitor 1C [CDKN1C] mutation).[15] Approximately 15% of cases with clear-cut phenotypes have no detectable molecular defect.[16, 17]

The molecular subtypes of the syndrome predispose patients to the development of different tumor histotypes.[18, 19, 20]

There are four main molecular subtypes of Beckwith-Wiedemann syndrome characterized by specific genotype-phenotype correlations, including tumor risk:

1. **ICR1-GoM.** Five percent to 10% of cases are caused by telomeric ICR1-GoM, which causes both biallelic expression of the insulin growth factor 2
gene (normally expressed by the paternal allele only) and reduced expression of the oncosuppressor \( H19 \) gene. The incidence of Wilms tumor is 22.8%.[21]

2. **ICR2-LoM.** Fifty percent of cases with Beckwith-Wiedemann syndrome are caused by ICR2-LoM, resulting in reduced expression of the \( CDKN1C \) gene, normally expressed by the maternal chromosome only. Tumor incidence is very low (2.5%).[21]

3. **UPD.** Altered expression at both imprinted gene clusters is observed in mosaic UPD of chromosome 11p15.5, accounting for 20% to 25% of the cases. The incidence of Wilms tumor is 6.2%, followed by hepatoblastoma (4.7%) and adrenal carcinoma of (1.5%).[21] Fewer than 1% of cases with Beckwith-Wiedemann syndrome are caused by chromosomal rearrangements involving the 11p15 region.

4. **CDKN1C mutation.** Maternally inheritable \( CDKN1C \) loss-of-function mutations account for approximately 5% of the cases. This type is associated with a 4.3% incidence of neuroblastoma.[21]

The prevalence of Beckwith-Wiedemann syndrome is about 1% of children with Wilms tumor.[22, 23, 24, 25] Approximately 10% of Beckwith-Wiedemann syndrome patients will develop Wilms tumor.[15] Beckwith-Wiedemann syndrome patients with hemihyperplasia have a fourfold increased tumor risk over that of Beckwith-Wiedemann syndrome patients without hemihyperplasia.[26] (Refer to the Genomics of Wilms Tumor section of this summary for more information.)

Other syndromic causes of Wilms tumor include the following:

- **Perlman syndrome.** Perlman syndrome—a rare, autosomal, recessively inherited, congenital overgrowth syndrome—is characterized by fetal gigantism, renal dysplasia and nephroblastomatosis, islet cell hypertrophy, multiple congenital anomalies, and mental retardation. Survivors have a high risk of developing Wilms tumor.[27]

Germline inactivating mutations in \( DIS3L2 \) on chromosome 2q37 are associated with Perlman syndrome. Preliminary data suggest that \( DIS3L2 \) plays a role in normal kidney development and in a subset of sporadic Wilms tumor cases.[28]

- **Simpson-Golabi-Behmel syndrome.** Simpson-Golabi-Behmel syndrome is characterized by macroglossia, macrosomia, renal and skeletal abnormalities, and increased risk of embryonal cancers.

The syndrome is caused by mutations in \( GPC3 \) and is believed to enhance the risk of Wilms tumor.[29]
• **Sotos syndrome.** Sotos syndrome is characterized by cerebral gigantism and learning disability, ranging from mild to severe. Sotos syndrome is associated with behavioral problems, congenital cardiac anomalies, neonatal jaundice, and renal anomalies such as Wilms tumor, scoliosis, and seizures.

  \(NSD1\) is the only gene in which mutations are known to cause Sotos syndrome.\[30\]

• **9q22.3 microdeletion syndrome.** 9q22.3 microdeletion syndrome is characterized by craniofacial abnormalities, metopic craniosynostosis, hydrocephalus, macrosomia, and learning disabilities.

  Three patients presented with Wilms tumor in addition to a constitutional 9q22.3 microdeletion and dysmorphic/overgrowth syndrome. Although the size of the deletions was variable, all encompassed the \(PTCH1\) gene.\[31\]

• **Bloom syndrome.** Bloom syndrome is characterized by short stature and being thinner than other family members, sun-sensitive skin changes, and an increased risk of Wilms tumor.

  \(BLM\) is the only gene in which mutations are known to cause Bloom syndrome.\[32\]

• **Li-Fraumeni syndrome.** Li-Fraumeni syndrome is a rare disorder that greatly increases the risk of developing several types of cancer, particularly in children and young adults. The cancers most often associated with Li-Fraumeni syndrome include breast cancer, osteosarcoma, soft tissue sarcoma, brain tumor, leukemia, adrenocortical carcinoma, and Wilms tumor.

  The \(TP53\) gene mutation is present in most families with Li-Fraumeni syndrome. The \(CHEK2\) gene mutation is also known to cause Li-Fraumeni syndrome.\[33\]

• **Alagille syndrome.** Alagille syndrome includes congenital cardiopathy; facial dysmorphology; and vertebral, ocular, and renal abnormalities. It has been reported with Wilms tumor in two cases with identified mutations.\[34\]

• **Bohring-Opitz syndrome.** Bohring-Opitz syndrome is a rare genetic condition characterized by distinctive facial features, variable microcephaly, hypertrichosis, nevus flammeus, severe myopia, unusual posture, severe intellectual disability, and feeding issues.

  The syndrome is associated with \(ASXL1\) mutations and an estimated 7% incidence of Wilms tumor.\[35\]

**Nonsyndromic causes of Wilms tumor**
Nonsyndromic causes of Wilms tumor include the following:

- **Familial Wilms tumor.** Despite the number of genes that appear to be involved in the development of Wilms tumor, familial Wilms tumor is uncommon, with approximately 2% of patients having a positive family history for Wilms tumor. Siblings of children with Wilms tumor have a less-than-1% chance of developing Wilms tumor.\[36, 37, 38\] The risk of Wilms tumor among offspring of persons who have had unilateral (sporadic) tumors is less than 2%.\[39\]

Two familial Wilms tumor genes have been localized to *FWT1* (17q12-q21) and *FWT2* (19q13.4).\[40, 41, 42\] Occasional Wilms tumor families have a germline mutation in *WT1*. In these families, most, but not all, family members have genitourinary tract malformations.\[43, 44\]

Inactivating mutations in *CTR9* have been identified in 3 of 35 Wilms tumor families. *CTR9* is located at 11p15.3 and is a key component of the polymerase-associated factor 1 (PAF1) complex, which has multiple roles in RNA polymerase II regulation and transcriptional elongation and is implicated in embryonic organogenesis.\[45\]

- **Sporadic aniridia.** Sporadic aniridia may result from small germline deletions of one copy of the *PAX6* gene that includes part or all of the adjacent *WT1* gene but does not result in genitourinary abnormalities or retardation (i.e., not obviously WAGR syndrome). Therefore, many patients with sporadic aniridia develop Wilms tumor and are candidates for screening. The relative risk of Wilms tumor in sporadic aniridia is 67-fold.\[46\] About half of individuals with sporadic aniridia and *PAX6* and *WT1* deletions develop Wilms tumor.\[47\]

- **Constitutional 11p15 abnormalities.** Constitutional 11p15 abnormalities have been identified in 13 of 437 individuals (3%) with sporadic Wilms tumor without features of growth disorders, including 12% of bilateral cases. All were de novo abnormalities, except for one novel microdeletion in a child whose mother was not affected. This suggests that constitutional 11p15 analysis should be considered in all individuals with Wilms tumor.\[48\]

- **Isolated hemihyperplasia.** Hemihyperplasia is an asymmetric overgrowth of one or more body parts and is associated with Wilms tumor. It can also be associated with other predisposition syndromes such as Beckwith-Wiedemann syndrome. Clinical signs may not be very evident, and hemihyperplasia may be noted after tumor diagnosis.

The overall Wilms tumor incidence was 5.9% in a study of 168 patients with isolated hemihyperplasia, although this result may have been impacted by ascertainment bias.\[49\] The prevalence is about 2.5% of children with Wilms tumor.\[22, 49\]

- **Trisomy 18.**\[50\]
- Fanconi anemia with biallelic mutations in *BRCA2* (*FANCD1*) or *PALB2* (*FANCN*). *BRCA2* and *PALB2* play central roles in homologous recombination DNA repair. Biallelic mutations in either *BRCA2* or *PALB2* lead to Fanconi anemia and to increased risks of selected childhood cancers, including Wilms tumor.[51, 52, 53]

**Genomics of Wilms Tumor**

*[Permanent-Comment: Genomics of Wilms Tumor module begins here.]*

Wilms tumor is thought to arise from clonal expansion of a nephrogenic rest. Mutations in many genes can perturb renal development and lead to cancer. This is in contrast to retinoblastoma, for example, in which a mutation in a single gene (*RB1*) is the oncogenic driver. Approximately one-third of Wilms tumor cases involve mutations in *WT1*, *CTNNB1*, or *WTX*. Another subset of Wilms tumor cases result from mutations in miRNA processing genes (miRNAPG), including *DROSHA*, *DGCR8*, *DICER1*, and *XPO5*. Other genes that are recurrently mutated in Wilms tumor include *SIX1* and *SIX2* (transcription factors that play key roles in early renal development) and *MLLT1* (a gene involved in transcriptional elongation in early development). Anaplastic Wilms tumor is characterized by the presence of *TP53* mutations.

Elevated rates of Wilms tumor are observed in a number of genetic disorders, including WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) syndrome, Beckwith-Wiedemann syndrome, hemihypertrophy, Denys-Drash syndrome, and Perlman syndrome.[61] Other genetic causes that have been observed in familial Wilms tumor cases include germline mutations in *REST* and *CTR9*. [45, 62]

The genomic and genetic characteristics of Wilms tumor are summarized below.

**Wilms tumor 1 gene (*WT1*)**

The *WT1* gene is located on the short arm of chromosome 11 (11p13). *WT1* is a transcription factor that is required for normal genitourinary development and is important for differentiation of the renal blastema.[63] *WT1* mutations are observed in 10% to 20% of cases of sporadic Wilms tumor.[54, 63, 64]

Wilms tumor with a *WT1* mutation is characterized by the following:

- Evidence of WNT pathway activation by activating mutations in the *beta-catenin* gene (*CTNNB1*) is common.[64, 65, 66]
- Loss of heterozygosity at 11p15 is commonly observed, as paternal uniparental disomy for chromosome 11 represents a common mechanism for losing the remaining normal *WT1* allele.[64, 67]
Nephrogenic rests are benign foci of embryonal kidney cells that abnormally persist into postnatal life. Intralobar nephrogenic rests occur in approximately 20% of Wilms tumor cases. They are observed at high rates in cases with genetic syndromes that have WT1 mutations such as WAGR and Denys-Drash syndromes.\[68\] Intralobar nephrogenic rests are also observed in cases with sporadic WT1 and MLLT1 mutations.\[60, 69\]

WT1 germline mutations are uncommon (2%–4%) in nonsyndromic Wilms tumor.\[44, 70\]

WT1 mutations and 11p15 loss of heterozygosity were associated with relapse in patients with very low-risk Wilms tumor in one study of 56 patients who did not receive chemotherapy.\[71\] These findings need validation but may provide biomarkers for stratifying patients in the future.

Germline WT1 mutations are more common in children with Wilms tumor and one of the following:

- WAGR syndrome, Denys-Drash syndrome,\[14\] or Frasier syndrome.\[11\]
- Genitourinary anomalies, including hypospadias and cryptorchidism.
- Bilateral Wilms tumor.
- Unilateral Wilms tumor with nephrogenic rests in the contralateral kidney.
- Stromal and rhabdomyomatous differentiation.

Syndromic conditions with germline WT1 mutations include WAGR syndrome, Denys-Drash syndrome,\[14\] and Frasier syndrome.\[11\]

- **WAGR syndrome.** Children with WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) are at high risk (>30%) of developing Wilms tumor. WAGR syndrome results from deletions at chromosome 11p13 that involve a set of contiguous genes that includes the WT1 and PAX6 genes.

  Inactivating mutations or deletions in the PAX6 gene lead to aniridia, while deletion of WT1 confers the increased risk of Wilms tumor. Sporadic aniridia in which WT1 is not deleted is not associated with increased risk of Wilms tumor. Accordingly, children with familial aniridia, generally occurring for many generations, and without renal abnormalities, have a normal WT1 gene and are not at an increased risk of Wilms tumor.\[22, 72\]

  Wilms tumor in children with WAGR syndrome is characterized by an excess of bilateral disease, intralobar nephrogenic rests–associated favorable-histology (FH) tumors of mixed cell type, and early age at diagnosis.\[10\] The mental retardation in WAGR syndrome may be secondary to deletion of other genes, including SLC1A2 or BDNF.\[48\]
Germline WT1 point mutations produce genetic syndromes that are characterized by nephropathy, 46XY disorder of sex development, and varying risks of Wilms tumor.\cite{73,74}

- **Denys-Drash and Frasier syndromes.** Denys-Drash syndrome is characterized by nephrotic syndrome caused by diffuse mesangial sclerosis, XY pseudohermaphroditism, and increased risk of Wilms tumor. Frasier syndrome is characterized by progressive nephropathy caused by focal segmental glomerulosclerosis, gonadoblastoma, and XY pseudohermaphroditism.

WT1 mutations in Denys-Drash syndrome are most often missense mutations in exons 8 and 9, which code for the DNA binding region of WT1.\cite{14} By contrast, WT1 mutations in Frasier syndrome typically occur in intron 9 at the KTS site, and they affect an alternative splicing, thereby preventing production of the usually more abundant WT1 +KTS isoform.\cite{75}

Studies evaluating genotype/phenotype correlations of WT1 mutations have shown that the risk of Wilms tumor is highest for truncating mutations (14 of 17 cases, 82%) and lower for missense mutations (27 of 67 cases, 42%). The risk is lowest for KTS splice site mutations (1 of 27 cases, 4%).\cite{73,74} Bilateral Wilms tumor was more common in cases with WT1-truncating mutations (9 of 14 cases) than in cases with WT1 missense mutations (3 of 27 cases).\cite{73,74} These genomic studies confirm previous estimates of elevated risk of Wilms tumor for children with Denys-Drash syndrome and low risk of Wilms tumor for children with Frasier syndrome.

Late effects associated with WAGR syndrome and Wilms tumor include the following:

- Children with WAGR syndrome or other germline WT1 mutations are monitored throughout their lives because they are at increased risk of developing hypertension, nephropathy, and renal failure.\cite{76}
- Patients with Wilms tumor and aniridia without genitourinary abnormalities are at lower risk but are monitored for nephropathy or renal failure.\cite{77}
- Children with Wilms tumor and any genitourinary anomalies are also at increased risk of late renal failure and are monitored. Features associated with germline WT1 mutations that increase the risk of developing renal failure include the following:\cite{76}
  - Stromal predominant histology.
  - Bilateral disease.
  - Intralobar nephrogenic rests.
  - Wilms tumor diagnosed before age 2 years.
(Refer to the Late effects after Wilms tumor therapy section of the PDQ summary on Wilms Tumor and Other Childhood Kidney Tumors Treatment for more information about the late effects associated with Wilms tumor.)

**Beta-catenin gene (CTNNB1)**

Somatic activating mutations of the CTNNB1 gene have been reported to occur in 15% of patients with Wilms tumor.[55, 64, 66, 78] These CTNNB1 mutations result in activation of the WNT pathway, which plays a prominent role in the developing kidney.[79] CTNNB1 mutations commonly occur with WT1 mutations, and most cases of Wilms tumor with WT1 mutations have a concurrent CTNNB1 mutation.[64, 66, 78] Activation of beta-catenin in the presence of intact WT1 protein appears to be inadequate to promote tumor development because CTNNB1 mutations are rarely found in the absence of a WT1 or WTX mutation, except when associated with a MLLT1 mutation.[55, 80] CTNNB1 mutations appear to be late events in Wilms tumor development because they are found in tumors but not in nephrogenic rests.[69]

**Wilms tumor gene on the X chromosome (WTX)**

WTX, which is also called FAM123B, is located on the X chromosome at Xq11.1. It is altered in 15% to 20% of Wilms tumor cases.[81]-[54, 55, 64, 82] Germline mutations in WTX cause an X-linked sclerosing bone dysplasia, osteopathia striata congenita with cranial sclerosis (MIM300373).[83] Despite having germline WTX mutations, individuals with osteopathia striata congenita are not predisposed to tumor development.[83] The WTX protein appears to be involved in both the degradation of beta-catenin and in the intracellular distribution of APC protein.[80, 84] WTX is most commonly altered by deletions involving part or all of the WTX gene, with deleterious point mutations occurring less commonly.[54, 64, 81] Most Wilms tumor cases with WTX alterations have epigenetic 11p15 abnormalities.[64]

WTX alterations are equally distributed between males and females, and WTX inactivation has no apparent effect on clinical presentation or prognosis.[54]

**Imprinting Cluster Regions (ICRs) on chromosome 11p15 (WT2) and Beckwith-Wiedemann syndrome**

A second Wilms tumor locus, WT2, maps to an imprinted region of chromosome 11p15.5; when it is a germline mutation, it causes Beckwith-Wiedemann syndrome. About 3% of children with Wilms tumor have germline epigenetic or genetic changes at the 11p15.5 growth regulatory locus without any clinical manifestations of overgrowth. Like children with Beckwith-Wiedemann syndrome, these children have an increased incidence of bilateral Wilms tumor or familial Wilms tumor.[48]

Approximately 80% of patients with Beckwith-Wiedemann syndrome have a molecular defect of the 11p15 domain.[85] Various molecular mechanisms underlying Beckwith-Wiedemann syndrome have been identified. Some of these abnormalities are genetic
(germline mutations of the maternal allele of CDKN1C, paternal uniparental isodisomy of 11p15, or duplication of part of the 11p15 domain) but are more frequently epigenetic (loss of methylation of the maternal ICR2/KvDMR1 or gain of methylation of the maternal ICR1).[48, 86]

Several candidate genes at the WT2 locus comprise the two independent imprinted domains IGF2/H19 and KIP2/LIT1.[86] Loss of heterozygosity, which exclusively affects the maternal chromosome, has the effect of upregulating paternally active genes and silencing maternally active ones. A loss or switch of the imprint for genes (change in methylation status) in this region has also been frequently observed and results in the same functional aberrations.[48, 85, 86]

A relationship between epigenotype and phenotype has been shown in Beckwith-Wiedemann syndrome, with a different rate of cancer in Beckwith-Wiedemann syndrome according to the type of alteration of the 11p15 region.[87] The overall tumor risk in patients with Beckwith-Wiedemann syndrome has been estimated to be between 5% and 10%, with a risk between 1% (loss of imprinting at ICR2) and 30% (gain of methylation at ICR1 and paternal 11p15 isodisomy). Development of Wilms tumor has been reported in patients with only ICR1 gain of methylation, whereas other tumors such as neuroblastoma or hepatoblastoma were reported in patients with paternal 11p15 isodisomy.[15, 19, 88]

Loss of imprinting or gene methylation is rarely found at other loci, supporting the specificity of loss of imprinting at 11p15.5.[89] Interestingly, Wilms tumor in Asian children is not associated with either nephrogenic rests or IGF2 loss of imprinting.[90]

Approximately one-fifth of patients with Beckwith-Wiedemann syndrome who develop Wilms tumor present with bilateral disease, and metachronous bilateral disease is also observed.[22, 23, 24] The prevalence of Beckwith-Wiedemann syndrome is about 1% among children with Wilms tumor reported to the National Wilms Tumor Study (NWTS).[1, 24]

Other genes and chromosomal alterations

Additional genes and chromosomal alterations that have been implicated in the pathogenesis and biology of Wilms tumor include the following:

- 1q. Gain of chromosome 1q is associated with an inferior outcome and is the single most powerful predictor of outcome. In the presence of 1q gain, neither 1p nor 16q loss is significant.[91, 92] Gain of chromosome 1q is one of the most common cytogenetic abnormalities in Wilms tumor and is observed in approximately 30% of tumors.

In an analysis of FH Wilms tumor from 1,114 patients from NWTS-5 (COG-Q9401/NCT00002611), 28% of the tumors displayed 1q gain.[91]
The 8-year event-free survival (EFS) rate was 77% for patients with 1q gain and 90% for those lacking 1q gain ($P < .001$). Within each disease stage, 1q gain was associated with inferior EFS.

The 8-year overall survival (OS) rate was 88% for those with 1q gain and 96% for those lacking 1q gain ($P < .001$). OS was significantly inferior in cases with stage I disease ($P < .0015$) and stage IV disease ($P = .011$).

16q and 1p. Additional tumor-suppressor or tumor-progression genes may lie on chromosomes 16q and 1p, as evidenced by loss of heterozygosity for these regions in 17% and 11% of Wilms tumor cases, respectively.[93]

- In large NWTS studies, patients with tumor-specific loss of these loci had significantly worse relapse-free survival and OS rates. Combined loss of 1p and 16q are used to select FH Wilms tumor patients for more aggressive therapy in the current Children's Oncology Group (COG) study. However, a U.K. study of more than 400 patients found no significant association between 1p deletion and poor prognosis, but a poor prognosis was associated with 16q loss of heterozygosity.[94]
- An Italian study of 125 patients, using treatment quite similar to that in the COG study, found significantly worse prognosis in those with 1p deletions but not 16q deletions.[95]

These conflicting results may arise from the greater prognostic significance of 1q gain described above. Loss of heterozygosity of 16q and 1p loses significance as independent prognostic markers in the presence of 1q gain. However, in the absence of 1q gain, loss of heterozygosity of 16q and 1p retains their adverse prognostic impact.[91] The loss of heterozygosity of 16q and 1p appears to arise from complex chromosomal events that result in 1q loss of heterozygosity or 1q gain. The change in 1q appears to be the critical tumorigenic genetic event.[96]

miRNAPG. Mutations in selected miRNAPG are observed in approximately 20% of Wilms tumor cases.[56, 57, 58, 59] The products of these genes direct the maturation of miRNAs from the initial pri-miRNA transcripts to functional cytoplasmic miRNAs (refer to Figure 1).[97] The most commonly mutated miRNAPG is DROSHA, with a recurrent mutation (E1147K) affecting a metal-binding residue of the RNase IIIb domain, representing about 80% of DROSHA-mutated tumors. Other miRNAPG that are mutated in Wilms tumor include DGCR8, DICER1, TARBP2, DIS3L2, and XPO5. These mutations are generally mutually exclusive, and they appear to be deleterious and result in impaired expression of tumor-suppressing miRNAs. A striking sex bias was noted in mutations for DGCR8 (located on chromosome 22q11), with 38 of 43 cases (88%) arising in girls.[56, 57]

Germline mutations in miRNAPG are observed for DICER1 and DIS3L2, with mutations in the former causing DICER1 syndrome and mutations in the latter causing Perlman syndrome.
DICER1 syndrome is typically caused by inherited truncating mutations in *DICER1*, with tumor formation following acquisition of a missense mutation in a domain of the remaining allele of *DICER1* (the RNase IIIb domain) responsible for processing miRNAs derived from the 5p arms of pre-miRNAs.\[98\] Tumors associated with DICER1 syndrome include pleuropulmonary blastoma, cystic nephroma, ovarian sex cord–stromal tumors, multinodular goiter, and embryonal rhabdomyosarcoma.\[98\] Wilms tumor is an uncommon presentation of the DICER1 syndrome. In one study, three families with DICER1 syndrome included children with Wilms tumor, with two of the Wilms tumor cases showing the typical second *DICER1* mutation in the RNase IIIb domain.\[99\] Another study identified *DICER1* mutations in 2 of 48 familial Wilms tumor families.\[100\] Large sequencing studies of Wilms tumor cohorts have also observed occasional cases with *DICER1* mutations.\[57, 58\]

Perlman syndrome is a rare overgrowth disorder caused by mutations in *DIS3L2*, which encodes a ribonuclease that is responsible for degrading pre-let-7 miRNA.\[28, 101\] The prognosis of Perlman syndrome is poor, with a high neonatal mortality rate. In a survey of published cases of Perlman syndrome (N = 28), in infants who survived beyond the neonatal period, approximately two-thirds developed Wilms tumor, and all patients showed developmental delay. Fetal macrosomia, ascites, and polyhydramnios are frequent manifestations.\[102\]

**Figure 1.** The miRNA processing pathway is commonly mutated in Wilms tumor. Expression of mature miRNA is initiated by RNA polymerase–
mediated transcription of DNA-encoded sequences into pri-miRNA, which form a long double-stranded hairpin. This structure is then cleaved by a complex of Drospha and DGCR8 into a smaller pre-miRNA hairpin, which is exported from the nucleus and then cleaved by Dicer (an RNase) and TRBP (with specificity for dsRNA) to remove the hairpin loop and leave two single-stranded miRNAs. The functional strand binds to Argonaute (Ago2) proteins into the RNA-induced silencing complex (RISC), where it guides the complex to its target mRNA, while the nonfunctional strand is degraded. Targeting of miRNAs by this method results in mRNA silencing by mRNA cleavage, translational repression, or deadenylation. Let-7 miRNAs are a family of miRNAs highly expressed in ESCs with tumor suppressor properties. In cases in which LIN28 is overexpressed, LIN28 binds to pre-Let-7 miRNA, preventing DICER from binding and resulting in LIN28-activated polyuridylation by TUT4 or TUT7, causing reciprocal DIS3L2-mediated degradation of Let-7 pre-miRNAs. Genes involved in miRNA processing that have been associated with Wilms' tumor are highlighted in blue (inactivating) and green (activating) and include DROSHA, DGCR8, XPO5 (encoding exportin-5), DICER1, TARBP2, DIS3L2, and LIN28.

- **SIX1 and SIX2.** SIX1 and SIX2 are highly homologous transcription factors that play key roles in early renal development and are expressed in the metanephric mesenchyme, where they maintain the mesenchymal progenitor population. The frequency of SIX1 mutations is 3% to 4% in Wilms tumor, and the frequency of SIX2 mutations in Wilms tumor is 1% to 3%.[56, 57] Virtually all SIX1 and SIX2 mutations are in exon 1 and result in a glutamine-to-arginine mutation at position 177. Mutations in WT1, WTX, and CTNNB1 are infrequent in cases with SIX1/SIX2 or miRNAPG mutations. Conversely, SIX1/SIX2 mutations and miRNAPG mutations tend to occur together.

- **MLLT1.** Approximately 4% of Wilms tumor cases have mutations in the highly conserved YEATS domain of MLLT1 (ENL), a gene known to be involved in transcriptional elongation by RNA polymerase II during early development.[60] The mutant MLLT1 protein shows altered binding to acetylated histone tails. Patients with MLLT1-mutant tumors present at a younger age and have a high prevalence of precursor intralobar nephrogenic rests, supporting a model whereby activating MLLT1 mutations early in renal development result in the development of Wilms tumor.

- **TP53 (tumor suppressor gene).** Most anaplastic Wilms tumor cases show mutations in the TP53 tumor suppressor gene.[103, 104, 105] TP53 may be useful as an unfavorable prognostic marker.[103, 104] A study of 40 patients with
diffuse anaplastic Wilms tumor identified 25 patients with TP53 alterations (22 with TP53 mutations with or without 17p loss, and 3 with only 17p loss). The 25 cases with TP53 alterations had a significantly lower EFS and OS than did those without TP53 alterations.\[105\] Microdissection of focally anaplastic Wilms tumor demonstrated TP53 mutations in anaplastic but not nonanaplastic areas of the tumor, suggesting that acquisition of TP53 mutation may be inherent in the process of becoming anaplastic.\[106\]

- **FBXW7.** FBXW7, a ubiquitin ligase component, is a gene that has been identified as recurrently mutated at low rates in Wilms tumor. Mutations of this gene have been associated with epithelial-type tumor histology.\[107\]

- **9q22.3 microdeletion syndrome.** Patients with 9q22.3 microdeletion syndrome have an increased risk of Wilms tumor.\[31, 108\] The chromosomal region with germline deletion includes PTCH1, the gene that is mutated in Gorlin syndrome (nevoid basal cell carcinoma syndrome associated with osteosarcoma). 9q22.3 microdeletion syndrome is characterized by the clinical findings of Gorlin syndrome, as well as developmental delay and/or intellectual disability, metopic craniosynostosis, obstructive hydrocephalus, prenatal and postnatal macrosomia, and seizures.\[108\] Five patients who presented with Wilms tumor in the context of a constitutional 9q22.3 microdeletion have been reported.\[31, 109, 110\]

- **MYCN.** MYCN copy number gain was observed in approximately 13% of Wilms tumor cases, and it was more common in anaplastic cases (7 of 23 cases, 30%) than in nonanaplastic cases (11.2%).\[111\] Activating mutations at codon 44 (p.P44L) were identified in approximately 4% of Wilms tumor cases.\[111\] Germline copy number gain at MYCN has been reported in a bilateral Wilms tumor case, and germline MYCN duplication was also reported for a child with prenatal bilateral nephroblastomatosis and a family history of nephroblastoma.\[112\]

- **CTR9.** Inactivating CTR9 germline mutations were identified in 3 of 35 familial Wilms tumor pedigrees.\[45\] CTR9, which is located at chromosome 11p15.3, is a key component of the polymerase-associated factor 1 complex (PAF1c), which has multiple roles in RNA polymerase II regulation and is implicated in embryonic organogenesis and maintenance of embryonic stem cell pluripotency.

- **REST.** Inactivating germline mutations in REST (encoding RE1-silencing transcription factor) were identified in four familial Wilms tumor pedigrees.\[62\] REST is a transcriptional repressor that functions in cellular differentiation and embryonic development. Most REST mutations clustered within the portion of REST encoding the DNA-binding domain, and functional analyses showed that these mutations compromise REST transcriptional repression. When screened for REST mutations, 9 of 519 individuals with Wilms tumor who had no history of relatives with the disease tested positive for the mutation; some had parents who also tested positive.\[62\] These observations indicate that REST is a Wilms tumor predisposition gene associated with approximately 2% of Wilms tumor.
Figure 2 summarizes the genomic landscape of a selected cohort of Wilms tumor patients selected because they experienced relapse despite showing FH. The 75 FH Wilms tumor cases were clustered by unsupervised analysis of gene expression data, resulting in six clusters. Five of six MLLT1-mutant tumors with available gene expression data were in cluster 3, and two were accompanied by CTNNB1 mutations. This cluster also contained four tumors with a mutation or small segment deletion of WT1, all of which also had either a mutation of CTNNB1 or small segment deletion or mutation of WTX. It also contained a substantial number of tumors with retention of imprinting of 11p15 (including all MLLT1-mutant tumors). The miRNAPG-mutated cases clustered together and were mutually exclusive with both MLLT1 and with WT1/WTX/CTNNB1-mutated cases.

Approximately 5% to 10% of individuals with Wilms tumor have bilateral or multicentric tumors. The prevalence of bilateral involvement is higher in individuals with genetic predisposition syndromes than in those without predisposition syndromes; however,
85% of individuals with WAGR or Beckwith-Wiedemann syndrome have unilateral tumors.[25, 63]

Only 16% of persons with bilateral Wilms tumor have a WT1 germline mutation, and only 3% of persons with bilateral Wilms tumor have affected family members. Bilateral Wilms tumor with WT1 mutations are associated with early presentation in pediatric patients (age 10 months vs. age 39 months for those without a mutation) and a high frequency of WT1 nonsense mutations in exon 8.[113] The presence of bilateral or multifocal disease implies that a patient has a genetic predisposition for Wilms tumor.

**Screening Children Predisposed to Wilms Tumor**

Children with a significant increased predisposition to develop Wilms tumor (e.g., most children with Beckwith-Wiedemann syndrome or other overgrowth syndromes, WAGR syndrome, Denys-Drash syndrome, sporadic aniridia, or isolated hemihyperplasia) are usually screened with ultrasound every 3 months until they reach at least age 8 years.[6, 7, 22, 72] Early-stage, asymptomatic, small Wilms tumors may be discovered and potentially removed with renal-sparing surgery.[72]

Tumor screening programs for each overgrowth syndrome have been suggested, based on published age and incidence of tumor type.[7]

- **Beckwith-Wiedemann syndrome.** Approximately 10% of patients with Beckwith-Wiedemann syndrome will develop a malignancy, with the most common being either Wilms tumor or hepatoblastoma, although adrenal tumors can also occur.[21] Screening for hepatoblastoma or adrenal tumors with abdominal ultrasound and serum alpha-fetoprotein is suggested until age 4 years. After age 4 years, most hepatoblastomas will have occurred, and imaging may be limited to renal ultrasound, which is quicker and does not require fasting before the exam.[114]

Specific follow-up guidelines to screen for Wilms tumor are available for patients with Beckwith-Wiedemann syndrome who have undergone molecular subtyping [21] (refer to the Genomics of Wilms Tumor section of this summary for more information about the molecular subtypes). The four main molecular subtypes of Beckwith-Wiedemann syndrome (ICR1-GoM, ICR2-LoM, UPD, and CDKN1C mutation) are characterized by specific genotype-phenotype correlations, including tumor risk.

Screening for specific molecular subtypes of Beckwith-Wiedemann syndrome is as follows:

- Patients with a defect of the ICR1 region (ICR1-GoM and UPD) should have an abdominal ultrasound examination every 3 months until age 8 to 10 years; a clinical examination of the abdomen and muscle mass occurs...
monthly for the first year and then at 3-month intervals, between ultrasound scans, until age 6 years.

- For patients with loss of imprinting at ICR2 (ICR2-LoM), an abdominal ultrasound examination is performed at the time of clinical or molecular diagnosis; only patients with organomegaly or severe hemihyperplasia require surveillance by ultrasound scans. Monthly clinical examinations are performed for the first 2 years, followed by clinical examinations every 3 to 6 months until age 6 years.

- Patients with a CDKN1C mutation are not at high risk of developing Wilms tumor. There are no data to support routine screening.

- **Hemihyperplasia.** Children with hemihyperplasia are also at risk of developing liver and adrenal tumors. Screening with abdominal ultrasound and serum alpha-fetoprotein is suggested until age 4 years. After age 4 years, most hepatoblastomas will have occurred, and imaging may be limited to renal ultrasound, which is quicker and does not require fasting before the exam.[114]

- **Sporadic aniridia.** Newborns born with sporadic aniridia should undergo molecular testing for deletion analysis of PAX6 and WT1. If a deletion of WT1 is observed, the child should be screened with ultrasound every 3 months until age 8 years, and the parents should be educated about the need for early identification and treatment of Wilms tumor.[72, 115, 116]

- **Children of survivors of bilateral Wilms tumor.** Although the risk for Wilms tumor in the children of survivors of bilateral Wilms tumor is unknown and likely varies with the gene in which the mutation occurred, some experts recommend screening such children with serial ultrasound examinations every 3 months until age 8 years.[61]

- **Bohring-Opitz syndrome.** Bohring-Opitz syndrome is a rare genetic condition associated with ASXL1 mutations. Screening with abdominal ultrasounds every 3 to 4 months in the first 8 years of life has been suggested because of the 7% incidence of a renal neoplastic process in patients with Bohring-Opitz syndrome.[35]

- **Simpson-Golabi-Behmel syndrome.** Affected males with Simpson-Golabi-Behmel syndrome with GPC3 mutations or deletions have an approximate 10% risk of Wilms tumor. Regular age-dependent screening for tumors, including abdominal ultrasound, urinalysis, and biochemical markers, is recommended for males with Simpson-Golabi-Behmel syndrome, although the true benefit has not been determined. Carrier females are not at increased risk of Wilms tumor and do not require surveillance. Individuals without GPC3 mutations have a less than 5% risk of developing Wilms tumor and do not require surveillance.[72]

- **Klippel-Trénaunay syndrome.** The risk of Wilms tumor in children with Klippel-Trénaunay syndrome (a unilateral limb overgrowth syndrome) was no different than the risk in the general population when assessed using the NWTS database. Routine ultrasound surveillance is not recommended.[117]
Genetic counseling

The frequency of malformations observed in patients with Wilms tumor underlines the need for genetic counseling, molecular and genetic explorations, and follow-up.

A French study [5] concluded that patients need to be referred for genetic counseling if they have one of the following:

- One major abnormality such as:
  - Beckwith-Wiedemann symptoms (macroglossia, neonatal or postnatal macrosomia, abdominal wall defects, or visceromegaly); or
- One condition such as:
  - Hemihyperplasia.
  - Overgrowth syndrome.
  - Mental retardation.
  - Aniridia.
  - Diffuse mesangial sclerosis.
- Two or more minor malformations such as:
  - Inguinal or umbilical hernia.
  - Hypospadias.
  - Renal abnormalities.
  - Ectopic testis.

Simple oncological follow-up is indicated when there is no malformation or when there is only one minor malformation.[5]

After genetic counseling takes place, a search for WT1 mutations should be considered for patients who have the following:

- Bilateral Wilms tumor.
- Familial Wilms tumor.
- Wilms tumor and age younger than 6 months.
- Genitourinary abnormality.
- Mental retardation association.

A search for an 11p15 abnormality should be considered for patients exhibiting any symptoms of Beckwith-Wiedemann syndrome, hemihyperplasia, or bilateral or familial Wilms tumor.
Clinical Features of Wilms Tumor

Most Wilms tumor patients present asymptomatically with an abdominal mass noticed by a parent or pediatrician on a well-child visit. In children with known predisposing clinical syndromes, renal tumors can be found during routine screening.

- A lump, swelling, or pain in the abdomen. Most children present with an asymptomatic mass that is noted when they are bathed or dressed. Abdominal pain is present in 40% of children.
- Blood in the urine. Gross hematuria occurs in about 18% of children with Wilms tumor at presentation, and microscopic hematuria is seen in 24% of patients.[118]
- Hypertension. About 25% of children have hypertension at presentation, which is attributed to activation of the renin-angiotensin system.
- Hypercalcemia. Symptomatic hypercalcemia can sometimes be seen at presentation of rhabdoid tumors.
- Constitutional symptoms such as fever, anorexia, and weight loss occur in 10% of cases.

Children with Wilms tumor or other renal malignancies may also come to medical attention as a result of the following:

- Vascular obstruction or metastasis, including pulmonary symptoms due to lung metastasis.
- Abdominal pain due to liver metastasis, prominent abdominal wall vessels, or varicocele due to inferior vena cava obstruction.
- Pulmonary embolus (rare).

Diagnostic and Staging Evaluation for Wilms Tumor

Tests and procedures used to diagnose and stage Wilms tumor and other childhood kidney tumors include the following:

1. Physical exam and history.
2. Complete blood count (CBC).
3. Liver function test.
4. Renal function test.
5. Urinalysis.
6. Abdominal imaging.
   - Abdominal x-ray.
- Ultrasound exam of the abdomen. Ultrasound exam of the abdomen is often performed before a more definitive computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI) with contrast of the abdomen is done. This procedure is unnecessary after the definitive diagnostic study has been performed.

- CT scan with contrast or MRI of abdomen.[119]
  - About 4% of Wilms tumor patients present with inferior vena cava or atrial involvement and 11% with renal vein involvement. Embolization of a caval thrombus to the pulmonary artery is rare but can be lethal, and the presence of a thrombus must be identified preoperatively to prevent this occurrence and guide treatment. CT scan of the abdomen will confirm the renal origin of the mass and determine whether there are bilateral tumors. A report from the COG shows that CT can accurately identify cavoatrial thrombus, obviating the need for ultrasound if CT has already been performed.[120]
  - Review of children with bilateral WT demonstrated that only 0.25% of bilateral tumors were missed with modern helical CT scans, all of which were small tumors.[121]

7. Chest x-ray

8. CT scan of chest. The common sites of metastases for Wilms tumor are the lung and liver. Approximately 15% of patients will present with pulmonary metastases. CT scanning provides the most sensitive method of detecting metastatic lung nodules.

9. 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT. Wilms tumor is 18F-FDG avid, and 18F-FDG-PET-CT imaging adds clinically applicable information to conventional imaging, which may be particularly helpful in patients with bilateral disease or those receiving preoperative chemotherapy. 18F-FDG-PET-CT highlights FDG-avid areas in the tumor and metastases, which corresponds to histologically confirmed active disease.[122]

10. von Willebrand disease work-up. About 1% to 8% of patients presenting with Wilms tumor have acquired von Willebrand disease, although many are asymptomatic. von Willebrand multimers bind to Wilms tumor, reducing the plasma concentration to low levels.[123] Some clinicians recommend evaluation for von Willebrand disease before surgery.

11. Biopsy or resection. In children with a renal mass that clinically appears to be stage I or stage II Wilms tumor, biopsy is not performed so that tumor cells are not spread during the biopsy. A biopsy would upstage such a patient to stage III. Nephrectomy (in North America) or chemotherapy (in Europe) is performed instead. Therefore, the diagnostic pathology is first seen when the nephrectomy specimen is examined.
Biopsy of a renal mass may be indicated if the mass is atypical by radiographic appearance for Wilms tumor, and the patient is not going to undergo immediate nephrectomy. Biopsy tissue from inoperable Wilms tumor obtained before chemotherapy may be used for histologic review and initial treatment decisions. The use of biopsy to determine histology in an inoperable tumor remains controversial because biopsy may cause local tumor spread.\footnote{124} It is important to recognize that data from NWTS-4 and NWTS-5 (COG-Q9401/NCT00002611) have shown that, because of the histologic heterogeneity of Wilms tumor, a significant number of patients have unfavorable histology that is missed during an upfront biopsy but revealed at the time of definitive surgery after chemotherapy.

Detection of a contralateral renal lesion in a child with Wilms tumor can change the stage and initial management of the patient, indicating a role for a renal-sparing approach without up-front surgery. The detection of contralateral renal lesions is important at baseline imaging because routine intraoperative exploration of the contralateral kidney is no longer recommended on the basis of the results of the NWTS-4 study.\footnote{119, 121} If the initial imaging studies suggested a possible lesion on the contralateral kidney, the contralateral kidney is formally explored to rule out bilateral involvement. This is done to exclude bilateral Wilms tumor before nephrectomy.

Biopsy is also controversial in patients with bilateral tumors because biopsy rarely detects anaplasia in bilateral Wilms tumor,\footnote{125} and the incidence of bilateral tumors being other than Wilms is very low. The now closed COG AREN0534 (NCT00945009) study of bilateral Wilms tumor and of patients with unilateral Wilms tumor predisposed to developing bilateral tumors tried to avoid initial biopsy and mandated biopsy only after 6 weeks of three-drug chemotherapy if there was less than a 50% reduction in size and the tumor remained unresectable.

12. Lymph node sampling is required to locally stage all Wilms tumor patients.

Children with a renal mass are carefully assessed for signs of associated syndromes such as aniridia, developmental delay, hypospadias, cryptorchidism, pseudohermaphroditism, overgrowth, and hemihyperplasia. About 5% of renal masses thought to be Wilms tumor on the basis of clinical and radiological findings are diagnosed as another condition.\footnote{126}

For patients with suspected Wilms tumor, additional preoperative staging studies are performed to assess intravascular extension or rupture of Wilms tumor.\footnote{127}

- Intravascular extension of the Wilms tumor. Preoperative assessment of intravascular extension of Wilms tumor is essential to guide management. The presence of intravenous tumor thrombus in the lumen of the renal vein, inferior
vena cava, and right atrium has been reported in up to 11.3% of Wilms tumor patients and may lead to differences in management.

In North America, local staging of Wilms tumor is performed with CT or MRI of the abdomen and pelvis. Contrast-enhanced CT for Wilms tumor patients has high sensitivity and specificity for detection of cavoatrial tumor thrombus that may impact surgical approach. Routine Doppler evaluation after CT has been performed but is not necessarily required.[120] Before surgical approach to the renal mass is performed, large tumor thrombi need to be controlled, especially when they extend above the hepatic vein, to avoid embolization of the tumor.

- Wilms tumor rupture. Based on their similar diagnostic performances, either CT or MRI can be used for initial staging.[119] Ascites beyond the cul-de-sac is most predictive of preoperative Wilms tumor rupture, irrespective of attenuation. In the presence of ascites, fat stranding around the tumor and the presence of retroperitoneal fluid are highly predictive of rupture.[128]

**Prognosis and Prognostic Factors for Wilms Tumor**

Wilms tumor is a curable disease in most affected children. Since the 1980s, the 5-year survival rate for Wilms tumor with favorable histology (FH) has been consistently above 90%.[129] This favorable outcome occurred despite reductions in the length of therapy, dose of radiation, extent of fields irradiated, and the percentage of patients receiving radiation therapy.[130]

The prognosis for patients with Wilms tumor depends on the following:[131, 132, 133, 134]

- Histopathologic features of the tumor (FH vs. anaplastic histology). (Refer to the Histologic Findings in Wilms Tumor section of this summary for more information.)
- Stage of disease at diagnosis.
- Molecular features of the tumor such as 1q gain and loss of heterozygosity of 1p and 16q. 1q gain is the most powerful predictor of outcome and is associated with an adverse outcome.[91, 92, 93]
- Age. Older age is associated with adverse prognosis.[135]

**Adolescents and young adults with Wilms tumor**

In an analysis of Wilms tumor patients in the Surveillance, Epidemiology, and End Results (SEER) database, adults (n = 152) had a statistically worse OS (69% vs. 88%, P < .001) than did pediatric patients (n = 2,190),[136] despite previous studies showing comparable outcome with treatment on protocol.[137, 138] The inferior outcome of the adult patients on this study may be the result of differences in tumor biology between
children and adults, incorrect diagnosis, inadequate staging (e.g., more likely to be staged as localized disease or to not receive lymph node sampling), or undertreatment (e.g., not receiving radiation therapy). Additional factors in this SEER report that may have contributed to a worse OS in adult patients include the size of the study and lack of central review of pathology.[136] Adolescent and young adult patients up to age 30 years are now eligible for treatment on the COG Wilms tumor protocols.

The inferior outcome of older patients is not explained entirely by inadequate treatment or not being treated according to the pediatric Wilms tumor protocol. In a U.K. study looking at the outcome of patients aged 10 to 16 years (N = 50) registered on the U.K. Wilms Tumor 3 and Société Internationale d’Oncologie Pédiatrique (SIOP) 2001 Wilms tumor trials, patients in this age group had a higher percentage of diffuse anaplastic tumors. The overall 5-year survival was 63% for patients aged 10 to 16 years (43% for anaplastic tumors), which is significantly lower than the outcome for younger patients with FH Wilms tumor.[135] However, SEER 5-year relative survival of nephroblastoma between 2003 and 2009 did not show differences among age groups from younger than 1 year to age 10 to 14 years.[139]

Histologic Findings in Wilms Tumor

Although most patients with a histologic diagnosis of Wilms tumor do well with current treatment, approximately 10% of patients have histopathologic features that are associated with a worse prognosis, and in some types, with a high incidence of relapse and death. Wilms tumor can be separated into the following two prognostic groups on the basis of tumor and kidney histopathology:

- **Favorable histology (FH).**
- **Anaplastic histology.**

**Favorable histology (FH)**

Histologically, Wilms tumor mimics the triphasic development of a normal kidney consisting of blastemal, epithelial (tubules), and stromal cell types. Not all tumors are triphasic, and monophasic patterns may present diagnostic difficulties.

While associations between histologic features and prognosis or responsiveness to therapy have been suggested, with the exception of anaplasia, none of these features have reached statistical significance in North American treatment algorithms, and therefore, do not direct the initial therapy.[140]

**Anaplastic histology**

Anaplastic histology accounts for about 10% of Wilms tumor cases. Anaplastic histology is the single most important histologic predictor of response and survival in patients with Wilms tumor. Tumors occurring in older patients (aged 10–16 years) have a higher
incidence of anaplastic histology.\cite{135} In bilateral tumors, 12% to 14% have been reported to have anaplastic histology in one kidney.\cite{141,142}

The following two histologic criteria must be present to confirm the diagnosis of anaplasia:

- Presence of multipolar polyploid mitotic figures with marked nuclear enlargement.
- Hyperchromasia.

Changes on 17p consistent with mutations in the \texttt{p53TP53} gene have been associated with foci of anaplastic histology.\cite{103} Focal anaplasia is defined as the presence of one or more sharply localized regions of anaplasia in a primary tumor. All of these factors lend support to the hypothesis that anaplasia evolves as a late event from a subpopulation of Wilms tumor cells that have acquired additional genomic lesions.\cite{143} Focal anaplasia does not confer as poor a prognosis as does diffuse anaplasia.\cite{133,144,145}

Anaplasia correlates best with responsiveness to therapy rather than to tumor aggressiveness. It is most consistently associated with poor prognosis when it is diffusely distributed and when identified at advanced stages. These tumors are more resistant to the chemotherapy traditionally used in children with FH Wilms tumor.\cite{133}

**Nephrogenic rests**

Nephrogenic rests are abnormally retained embryonic kidney precursor cells arranged in clusters. Nephrogenic rests are found in about 1% of unselected pediatric autopsies, 35% of kidneys with unilateral Wilms tumor, and nearly 100% of kidneys with bilateral Wilms tumor.\cite{146,147}

The term \texttt{nephroblastomatosis} is defined as the presence of diffuse or multifocal nephrogenic rests. Nephrogenic rests can be subclassified according to the category of rest (intralobar or perilobar nephrogenic rests) and their growth phase (incipient or dormant nephrogenic rests, hyperplastic nephrogenic rests, and regressing or sclerosing nephrogenic rests). \texttt{Diffuse hyperplastic perilobar nephroblastomatosis} represents one unique category of nephroblastomatosis that forms a thick rind around one or both kidneys and is considered a preneoplastic condition. Distinguishing between Wilms tumor and diffuse hyperplastic perilobar nephrogenic rests may be a challenge, and it is critical to examine the juncture between the lesion and the surrounding renal parenchyma. Incisional biopsies are of no diagnostic value unless they include the margin between the lesion and the normal renal parenchyma.\cite{148}

The type and percentage of nephrogenic rests vary in patients with unilateral or bilateral disease. Patients with bilateral Wilms tumor have a higher proportion of perilobar rests (52%) than of intralobar or combined rests (32%) and higher relative proportions of
rests, compared with patients with unilateral tumors (18% perilobar and 20% intralobar or both).[76]

Patients with any type of nephrogenic rest in a kidney removed for nephroblastoma are considered at increased risk for tumor formation in the remaining kidney. This risk decreases with patient age.[42]

Bilateral diffuse hyperplastic perilobar nephroblastomatosis is generally treated with chemotherapy to reduce the risk of developing Wilms tumor; however, the risk of developing Wilms tumor remains high. Patients who have been treated with chemotherapy for a prolonged period of time remain at high risk of developing Wilms tumor. If these patients develop Wilms tumor, they have a poorer prognosis than do other bilateral Wilms patients, perhaps as a result of the development and selection of anaplasia in the surviving abnormal kidney cells.[148, 149]

Extrarenal nephrogenic rests are rare and may develop into extrarenal Wilms tumor.[150]

**Stage Information for Wilms Tumor**

Both the results of the imaging studies and the surgical and pathologic findings at nephrectomy are used to determine the stage of disease. The stage is the same for tumors with FH or anaplastic histology. Thus, the stage information is characterized by a statement of both criteria (for example, stage II, FH or stage II, anaplastic histology).[140, 151]

The staging system was originally developed by the NWTS Group and is still used by the COG. The staging system used in North America and incidence by stage are outlined below.[140]

**Stage I**

In stage I Wilms tumor (43% of patients), all of the following criteria must be met:

- Tumor is limited to the kidney and is completely resected.
- The renal capsule is intact.
- The tumor is not ruptured or biopsied before being removed.
- No involvement of renal sinus vessels.
- No evidence of the tumor at or beyond the margins of resection.
- All lymph nodes sampled are negative.

For a tumor to qualify for certain therapeutic protocols such as very low-risk stage I, regional lymph nodes must be examined microscopically. Lymph node sampling is
strongly recommended for all patients, even in the absence of clinical abnormal nodes, to achieve the most accurate stage.

Stage II

In stage II Wilms tumor (20% of patients), the tumor is completely resected, and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond the kidney as evidenced by any one of the following criteria:

- There is regional extension of the tumor (i.e., penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below).
- Blood vessels in the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor cells. Margins are clear.
- Vascular extension of tumor is considered stage II only if it is completely removed en bloc in the nephrectomy specimen.

All lymph nodes sampled are negative.

Rupture or spillage confined to the flank, including biopsy of the tumor, is now included in stage III by the COG Renal Tumor Committee; however, data to support this approach are controversial.[124, 152]

Stage III

In stage III Wilms tumor (21% of patients), there is postsurgical residual nonhematogenous tumor that is confined to the abdomen. Any one of the following may occur:

- Lymph nodes in the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax or other extra-abdominal sites is a criterion for stage IV.)
- The tumor has penetrated through the peritoneal surface.
- Tumor implants are found on the peritoneal surface.
- Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination).
- The tumor is not completely resectable because of local infiltration into vital structures.
- Tumor spillage occurs either before or during surgery.
- Any biopsy is performed, regardless of type—Tru-cut biopsy, open biopsy, or fine-needle aspiration—before the tumor is removed.
- The tumor is removed in more than one piece (e.g., tumor cells are found in a separately excised adrenal gland; a tumor thrombus in the renal vein is removed
separately from the nephrectomy specimen). Extension of the primary tumor in the vena cava into the thoracic vena cava and heart is considered stage III, rather than stage IV, even though outside the abdomen—and it can even be stage II if completely resected en bloc with the nephrectomy specimen.

Lymph node involvement and microscopic residual disease are reported as highly predictive of outcome in patients with stage III FH Wilms tumor.[153]

**Stage IV**

In stage IV Wilms tumor (11% of patients), one of the following is present:

- Hematogenous metastases (lung, liver, bone, brain).
- Lymph node metastases outside the abdominopelvic region.

The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present. According to the criteria described above, the primary tumor is assigned a local stage, which determines local therapy. For example, a patient may have stage IV, local stage III disease.

**Stage V**

In stage V Wilms tumor (5% of patients), bilateral involvement by tumor is present at diagnosis. A previous attempt was made to stage each side according to the previously described criteria on the basis of the extent of local disease. In these patients, renal failure rates approach 15% at 15 years posttreatment, although standard approaches have not been accepted for renal-sparing treatment.[154]

**Treatment of Wilms Tumor**

**Treatment option overview for Wilms tumor**

Because of the relative rarity of Wilms tumor, all patients with this tumor should be considered for entry into a clinical trial. Treatment planning by a multidisciplinary team of cancer specialists (pediatric surgeon and/or pediatric urologist, pediatric radiation oncologist, and pediatric oncologist) who have experience treating children with Wilms tumor is necessary to determine and implement optimal treatment.

Most randomized clinical studies for treatment of children with Wilms tumor have been conducted by two large clinical groups (COG Renal Tumor Committee [COG RTC] and SIOP). Differences between the two groups affect staging and classification.

- **COG RTC** (includes the previous NWTS Group): The NWTS Group established standard treatment for Wilms tumor in North America, consisting of initial nephrectomy (when feasible) followed by chemotherapy and, in some patients,
radiation therapy.[155, 156, 157] This approach allows for early and accurate histologic diagnosis, collection of biologic materials unaltered by therapy, and staging information, such as the presence of tumor spill or tumor involvement in lymph nodes, before chemotherapy is administered.

- **SIOP**: SIOP is a European consortium whose trials provide preoperative chemotherapy before definitive resection for patients with renal tumors. This results in fewer tumor ruptures during surgery and lower postoperative stage.[158]

This summary focuses on the NWTS (now COG RTC) results and studies.

The major treatment and study conclusions of NWTS-1, NWTS-2, NWTS-3, NWTS-4, and NWTS-5 are as follows:

1. Routine, postoperative radiation therapy of the flank is not necessary for children with stage I tumors or stage II tumors with FH when postnephrectomy combination chemotherapy consisting of vincristine and dactinomycin is administered.[157]

2. The prognosis for patients with stage III FH is best when treatment includes either (a) dactinomycin, vincristine, doxorubicin, and 10.8 Gy of radiation therapy to the flank; or (b) dactinomycin, vincristine, and 20 Gy of radiation therapy to the flank. Whole abdominal radiation is indicated for extensive intraperitoneal disease or widespread intraperitoneal tumor spill with possible boost to gross residual disease.[157]

3. The addition of cyclophosphamide at the protocol dose (10 mg/kg/d for 3 days every 6 weeks) to the combination of vincristine, dactinomycin, and doxorubicin does not improve prognosis for patients with stage IV FH tumors.[157]

4. A single dose of dactinomycin per course (stages I–II FH, stage I anaplastic, stage III FH, stages III–IV, or stages I–IV clear cell sarcoma of the kidney) is equivalent to the divided-dose courses, results in the same EFS, achieves greater dose intensity, and is associated with less toxicity and expense.[159]

5. Eighteen weeks of therapy is adequate for patients with stage I and II FH, and stage III and IV patients can be treated with 6 months of therapy instead of 15 months.[130, 155, 159, 160, 161]

6. Gain of 1q is associated with inferior survival in unilateral FH Wilms tumor. It is the single most powerful predictor of outcome, and in the presence of 1q gain, neither 1p nor 16q loss is significant. In the absence of 1q gain in unilateral FH Wilms tumor, 1p and/or 16q loss retain some prognostic significance and are associated with a higher risk of recurrence.[91, 93]

**Surgery**

The following operative principles have also evolved from NWTS trials:
1. The most important role for the surgeon is to ensure complete tumor removal without rupture and assess the extent of disease. Radical nephrectomy and lymph node sampling via a transabdominal or thoracoabdominal incision is the procedure of choice.[162] A flank incision is not performed because it provides limited exposure to the kidney.

For patients with resectable tumors, preoperative biopsy or intraoperative biopsy is not performed because either would upstage the tumor in the current COG staging system.[162]

2. Routine exploration of the contralateral kidney is not necessary if technically adequate imaging studies do not suggest a bilateral process. If the initial imaging studies suggest bilateral kidney involvement, treatment approaches should facilitate renal-sparing surgery.[121]

3. About 2% of Wilms tumor cases have ureteral involvement. The presence of gross hematuria, nonfunctioning kidney, or hydronephrosis suggests the tumor may extend into the ureter, and cystoscopy is recommended. En bloc resection to avoid tumor spill is recommended.[163]

4. The surgeon needs to be aware of the risk of intraoperative spill, especially in patients who have right-sided and large tumors, as noted in a review of cases of intraoperative spill among 1,131 patients registered on COG study AREN03B2 (NCT00898365).[164]

5. Even if stage IV disease (e.g., pulmonary metastases) is evident on imaging, resection of the renal tumor should be considered. Treatment of local stage I or II Wilms tumor in the setting of distant metastasis does not require local radiation therapy.

Renal-sparing surgery remains controversial and is not recommended, except for children with the following:[165, 166]; [167][Level of evidence: 3iiB]

- A solitary kidney.
- Predisposition to bilateral tumors. Some children who are predisposed to bilateral tumors and who have very small tumors detected by ultrasound screening may be considered for renal-sparing surgery to preserve renal tissue.[165]
- Horseshoe kidney. Wilms tumor arising in a horseshoe kidney is rare, and accurate preoperative diagnosis is important for planning the operative approach. Primary resection is possible in most cases. Inoperable cases can usually be resected after chemotherapy.[168]
- Wilms tumor in infants with Denys-Drash or Frasier syndrome (to delay the need for dialysis).

Renal-sparing surgery does not appear to be feasible for most patients at the time of diagnosis because of the location of the tumor within the kidney, even in patients with
very low risk.\cite{169} In North America, renal-sparing surgery (partial nephrectomy) of unilateral Wilms tumor after administration of chemotherapy to shrink the tumor mass is considered investigational.\cite{170,171}

Hilar and periaortic lymph node sampling is appropriate even if the nodes appear normal.\cite{162,172} Furthermore, any suspicious node basin is sampled. Margins of resection, residual tumor, and any suspicious node basins are marked with titanium clips.

Wilms tumor rarely invades adjacent organs; therefore, resection of contiguous organs is seldom indicated. There is an increased incidence of complications occurring in more extensive resections that involve removal of additional organs beyond the diaphragm and adrenal gland. This has led to the recommendation in current COG protocols that these patients should be considered for initial biopsy, neoadjuvant chemotherapy, and then secondary resection.\cite{173} Primary resection of liver metastasis is not recommended.\cite{174}

**Chemotherapy**

Preoperative chemotherapy before nephrectomy is indicated in the following situations: [162, 173, 175, 176, 177, 178]

- Wilms tumor in a solitary kidney.
- Synchronous bilateral Wilms tumor.
- Extension of tumor thrombus in the inferior vena cava above the level of the hepatic veins. About 4% of Wilms tumor patients present with inferior vena cava or atrial involvement, and 11% of patients present with renal vein involvement. Embolization of a caval thrombus to the pulmonary artery is rare but can be lethal, and the presence of a thrombus must be identified preoperatively to prevent this occurrence and guide treatment.\cite{120}
- Tumor involves contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structures (e.g., spleen, pancreas, or colon but excluding the adrenal gland).
- Inoperable Wilms tumor.
- Pulmonary compromise due to extensive pulmonary metastases.

Preoperative chemotherapy follows a biopsy. The biopsy may be performed through a flank approach.\cite{179,180,181,182,183,184} Adequate tissue is essential for accurate histological assessment and molecular studies. Preoperative chemotherapy includes doxorubicin in addition to vincristine and dactinomycin unless anaplastic histology is present; in such cases, chemotherapy then includes treatment with regimen I (refer to Table 2 below). The chemotherapy generally makes tumor removal easier by decreasing the size and vascular supply of the tumor; it may also reduce the frequency of surgical complications.\cite{124,173,175,184,185,186}
In North America, the use of preoperative chemotherapy in patients with evidence of a contained preoperative rupture has been suggested to avoid intraoperative spill, but this is controversial.[187, 188] The preoperative diagnosis of a contained retroperitoneal rupture on CT is difficult, even for experienced pediatric radiologists.[128]

Newborns and all infants younger than 12 months who will be treated with chemotherapy require a 50% reduction in chemotherapy dose compared with the dose given to older children.[189] Dosing for infants (younger than 12 months) will be calculated per kilogram of weight, not body surface area. This reduction diminishes the toxic effects reported in children in this age group enrolled in NWTS studies while maintaining an excellent overall outcome.[190]

Liver function tests in children with Wilms tumor are monitored closely during the early course of therapy because hepatic toxic effects (sinusoidal obstructive syndrome, previously called veno-occlusive disease) have been reported in these patients.[191, 192] Dactinomycin or doxorubicin should not be administered during radiation therapy. Patients who develop renal failure while undergoing therapy can continue receiving chemotherapy with vincristine, dactinomycin, and doxorubicin. Vincristine and doxorubicin can be given at full doses; however, dactinomycin is associated with severe neutropenia. Reductions in dosing these agents may not be necessary, but accurate pharmacologic and pharmacokinetic studies are needed while the patient is receiving therapy.[193, 194]

Postoperative radiation therapy to the tumor bed is required when a biopsy is performed or in the setting of local tumor stage III.

Table 2 describes the standard chemotherapy regimens used to treat Wilms tumor.

<table>
<thead>
<tr>
<th>Regimen Name</th>
<th>Regimen Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen EE-4A [93]</td>
<td>Vincristine, dactinomycin × 18 weeks postnephrectomy</td>
</tr>
<tr>
<td>Regimen DD-4A [93]</td>
<td>Vincristine, dactinomycin, doxorubicin × 24 weeks; baseline nephrectomy or biopsy with subsequent nephrectomy</td>
</tr>
<tr>
<td>Regimen I [133]</td>
<td>Vincristine, doxorubicin, cyclophosphamide, etoposide × 24 weeks postnephrectomy</td>
</tr>
</tbody>
</table>

**Table 2. Standard Chemotherapy Regimens for Wilms Tumor**

**Treatment of stage I Wilms tumor**

Table 3 provides an overview of the standard treatment options and survival data for stage I Wilms tumor, based on published results.
Table 3. Overview of Standard Treatment Options for Stage I Wilms Tumor

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>4-Year RFS or EFS</th>
<th>4-Year OS</th>
<th>Treatment (refer to Table 2 for chemotherapy regimen descriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>FH &lt;24 mo/tumor weight &lt;550g</td>
<td>85%</td>
<td>98%</td>
<td>Surgery including lymph node biopsy only (not standard treatment; should be done only in the context of a clinical trial)</td>
</tr>
<tr>
<td></td>
<td>FH &gt;24 mo/tumor weight &gt;550g</td>
<td>94% RFS</td>
<td>98%</td>
<td>Nephrectomy + lymph node sampling followed by regimen EE-4A</td>
</tr>
<tr>
<td></td>
<td>FA</td>
<td>68%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89%</td>
<td>Nephrectomy + lymph node sampling followed by regimen EE-4A and XRT</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>68% EFS</td>
<td>79% (n = 10)</td>
<td>Nephrectomy + lymph node sampling followed by regimen EE-4A and XRT</td>
</tr>
</tbody>
</table>

DA = diffuse anaplastic; EFS = event-free survival; FA = focal anaplastic; FH = favorable histology; OS = overall survival; RFS = relapse-free survival; XRT = radiation therapy.

<sup>a</sup>Fewer than five patients have survived 4 years; therefore, results should be interpreted with caution.

The COG addressed the question of whether a subset of stage I Wilms tumor patients could be treated with surgery alone. The NWTS-5 trial investigated this approach for children younger than 2 years at diagnosis with stage I FH Wilms tumor that weighed less than 550 g.

Evidence (surgery only for children younger than 24 months at diagnosis with stage I FH tumor that weighed <550 g):

1. In the NWTS-5 study, the omission of adjuvant chemotherapy was tested for children younger than 2 years at diagnosis with stage I FH Wilms tumor that weighed less than 550 g.<sup>[134]</sup> Stringent stopping rules were designed to ensure closure of the study if the 2-year RFS rate was 90% or lower. The expectation was that approximately 50% of the surgery-only children would be salvaged after recurrence, thus attaining the 95% predicted survival of children with very low-risk Wilms tumor treated with standard chemotherapy according to regimen EE-4A.

   - The study was discontinued in 1998 when the predicted 2-year EFS fell below 90%.[195]
• Long-term follow-up of this study’s surgery-only cohort and the EE-4A group with a median follow-up of 8.2 years reported the estimated 5-year EFS for surgery-only patients was 84% (95% CI, 73%–91%); for the EE-4A patients, it was 97% (95% CI, 92%–99%, \( P = .002 \)). One death was observed in each treatment group. The estimated 5-year OS was 98% (95% CI, 87%–99%) for surgery only and 99% (95% CI, 94%–99%) for EE-4A (\( P = .70 \)).[134]

• Investigators observed that the children who relapsed were more successfully retreated than prior stage I/FH children, probably because they were naïve to both radiation therapy and chemotherapy.[134]

**Treatment of stage II Wilms tumor**

Table 4 provides an overview of the standard treatment options and survival data for stage II Wilms tumor, based on published results.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>4-Year RFS or EFS</th>
<th>4-Year OS</th>
<th>Treatment (refer to Table 2 for chemotherapy regimen descriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II [93, 133]</td>
<td>FH</td>
<td>86% RFS</td>
<td>98%</td>
<td>Nephrectomy + lymph node sampling followed by regimen EE-4A</td>
</tr>
<tr>
<td></td>
<td>FA</td>
<td>80% EFS</td>
<td>80% (n = 5)</td>
<td>Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>83% EFS</td>
<td>82%</td>
<td>Nephrectomy + lymph node sampling followed by abdominal XRT and regimen I</td>
</tr>
</tbody>
</table>

DA = diffuse anaplastic; EFS = event-free survival; FA = focal anaplastic; FH = favorable histology; OS = overall survival; RFS = relapse-free survival; XRT = radiation therapy.

On NWTS-3, NWTS-4, and NWTS-5, patients with intraoperative spill were divided into two groups: (1) those with diffuse spillage involving the whole abdominal cavity; and (2) those with local spillage confined to the flank. Patients with diffuse spillage were treated with radiation therapy to the entire abdomen and three-drug chemotherapy (vincristine, dactinomycin, and doxorubicin), whereas patients with local spillage were treated with vincristine and dactinomycin only. On the basis of an analysis of patients treated on NWTS-3 and NWTS-4 indicating that patients with stage II disease and local spillage had inferior OS compared with patients with stage II disease without local spillage, COG studies treat patients with local spillage with doxorubicin and flank radiation.[196] This
approach is controversial and has not been tested; therefore, it should not be considered standard.

In a review of 499 patients from NWTS-4 with stage II, FH Wilms tumor, 95 of the patients experienced tumor spill. The 8-year RFS and OS for patients who experienced tumor spill and were treated with vincristine and dactinomycin without flank radiation therapy were lower, at 75.7% and 90.3%, than the 85% and 95.6% rates for those who did not experience tumor spill. None of these differences achieved statistical significance.\[152\\]

**Treatment of stage III Wilms tumor**

*Table 5* provides an overview of the standard treatment options and survival data for stage III Wilms tumor, based on published results.

**Table 5. Overview of Standard Treatment Options for Stage III Wilms Tumor**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>4-Year RFS or EFS</th>
<th>4-Year OS</th>
<th>Treatment (refer to Table 2 for chemotherapy regimen descriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td>FH</td>
<td>87% RFS</td>
<td>94%</td>
<td>Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A</td>
</tr>
<tr>
<td></td>
<td>FA</td>
<td>88% RFS</td>
<td>100% (n = 8)</td>
<td>Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A</td>
</tr>
<tr>
<td></td>
<td>FA (preoperative treatment)</td>
<td>71% RFS</td>
<td>71% (n = 7)</td>
<td>Preoperative treatment with regimen DD-4A followed by nephrectomy + lymph node sampling and abdominal XRT</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>46% EFS</td>
<td>53% (n = 16)</td>
<td>Preoperative treatment with regimen I followed by nephrectomy + lymph node sampling and abdominal XRT</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>65% EFS</td>
<td>67%</td>
<td>Immediate nephrectomy + lymph node sampling followed by abdominal XRT and regimen I</td>
</tr>
</tbody>
</table>

*DA = diffuse anaplastic; EFS = event-free survival; FA = focal anaplastic; FH = favorable histology; OS = overall survival; RFS = relapse-free survival; XRT = radiation therapy.*
The outcome of patients with peritoneal implants treated with gross resection, three-
drug chemotherapy, and total-abdominal radiation (10.5 Gy) is similar to that of other
stage III patients.[197] [Level of evidence: 2A]

For patients classified as stage III purely on the basis of local spill, refer to the Standard
treatment options for stage II Wilms tumor section of this summary.

Treatment of stage IV Wilms tumor

Table 6 provides an overview of the standard treatment options and survival data for
stage IV Wilms tumor, based on published results.

Table 6. Overview of Standard Treatment Options for Stage IV Wilms Tumor

<table>
<thead>
<tr>
<th>Stage</th>
<th>Histology</th>
<th>4-Year RFS or EFS</th>
<th>4-Year OS</th>
<th>Treatment (refer to Table 2 for chemotherapy regimen descriptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IV</td>
<td>FH</td>
<td>76% RFS</td>
<td>86%</td>
<td>Nephrectomy + lymph node sampling, followed by abdominal XRT,\textsuperscript{a} radiation to sites of metastases, bilateral pulmonary XRT,\textsuperscript{b} and regimen DD-4A</td>
</tr>
<tr>
<td></td>
<td>FA</td>
<td>61% EFS</td>
<td>72%</td>
<td>(n = 11) Nephrectomy + lymph node sampling, followed by abdominal XRT,\textsuperscript{a} radiation to sites of metastases, bilateral pulmonary XRT,\textsuperscript{b} and regimen DD-4A</td>
</tr>
<tr>
<td></td>
<td>DA</td>
<td>33% EFS</td>
<td>33%</td>
<td>(n = 15) Immediate nephrectomy + lymph node sampling followed by abdominal XRT,\textsuperscript{a} radiation to sites of metastases, whole-lung XRT,\textsuperscript{b} and regimen I</td>
</tr>
<tr>
<td></td>
<td>DA (preoperative treatment)</td>
<td>31% EFS</td>
<td>44%</td>
<td>(n = 13) Preoperative treatment with regimen I followed by nephrectomy + lymph node sampling, followed by abdominal XRT,\textsuperscript{a} radiation to sites of metastases, and whole-lung XRT\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\( \text{DA} = \text{diffuse anaplasia}; \text{EFS} = \text{event-free survival}; \text{FA} = \text{focal anaplasia}; \text{FH} = \text{favorable histology}; \text{OS} = \text{overall survival}; \text{RFS} = \text{relapse-free survival}; \text{XRT} = \text{radiation therapy}. \)

\textsuperscript{a}Abdominal XRT is planned according to local stage of renal tumor.

\textsuperscript{b}Pulmonary XRT is reserved for patients with chest x-ray/chest CT evidence of pulmonary metastases.
Stage IV disease is defined by the presence of hematogenous metastases to the lung, liver, bone, brain, or other sites, with the lung being the most common site. Historically, chest x-rays were used to detect pulmonary metastases. The introduction of CT created controversy because many patients had lung nodules detected by chest CT scans that were not seen on chest x-rays. Management of newly diagnosed patients with FH Wilms tumor who have lung nodules detected only by CT scans (with negative chest x-ray) has elicited controversy as to whether they need to be treated with additional intensive treatment that is accompanied by acute and late toxicities.

Evidence (treatment of pulmonary nodules detected by chest CT scan only):

1. A retrospective review of 186 patients from NWTS-4 and NWTS-5 with CT-only–detected lung nodules reported on the use of doxorubicin, vincristine, and dactinomycin with or without lung radiation versus the use of two drugs.[198]
   - Patients who received doxorubicin, vincristine, and dactinomycin with or without lung radiation had a 5-year EFS of 80% versus an EFS of 56% for patients receiving only two drugs ($P = .004$).
   - There was no difference in the 5-year OS (87% vs. 86%).

Retrospective studies from Europe have examined the impact of omitting pulmonary radiation in patients with pulmonary metastases diagnosed by chest x-ray. European investigators omitted radiation from the treatment of most patients with Wilms tumor and pulmonary metastases as identified on chest x-ray who were treated on the SIOP-93-01 (NCT00003804) trial. The European approach to renal tumors differs from the approach used in North America. All patients who were shown to have a renal tumor by imaging underwent 9 weeks of prenephrectomy chemotherapy consisting of vincristine, dactinomycin, and doxorubicin.

Evidence (treatment of pulmonary nodules detected by chest x-ray):

1. In a retrospective SIOP study, 234 newly diagnosed patients with Wilms tumor presenting with pulmonary metastases were treated according to the response of the pulmonary metastases to the prenephrectomy chemotherapy.[199]
   a. Patients who were in complete remission after 9 weeks of therapy continued with the same chemotherapy and did not require radiation to their lungs.
      - The 5-year EFS was 77%, and the OS was 88%.
   b. Patients who had residual pulmonary metastases were evaluated for metastasectomy.
      - Thirty-seven patients obtained complete remission with surgery, and their outcome was similar to that of the group of patients who were treated with chemotherapy. Tumor viability in the resected
pulmonary metastases was not a factor for omitting radiation therapy.

- The 5-year EFS was 84%, and the OS was 92%.

c. Patients with residual pulmonary metastases that were incompletely resected or inoperable received more aggressive chemotherapy consisting of ifosfamide/anthracycline alternating with carboplatin/etoposide for 9 weeks.

- Patients showing a complete remission at that time were spared pulmonary radiation and continued with chemotherapy, whereas patients with residual pulmonary metastases continued with additional chemotherapy (to complete 34 weeks) and pulmonary irradiation. The 5-year OS was 48%, compared with the OS for patients who responded to chemotherapy alone (88%) and those who underwent metastasectomy (92%) \((P < .001)\).

- Patients with high-risk histologies, such as anaplastic Wilms tumor, were treated with more aggressive chemotherapy but had a poorer outcome, compared with that of patients with nonanaplastic histologies (5-year OS, 87% vs. 33%; \(P < .001)\).

It is important to note that patients in Europe receive higher cumulative doses of dactinomycin and doxorubicin before their pulmonary metastases are reevaluated than do patients in North America. The European experience cannot be directly applied to North America. It suggests that for patients with nonanaplastic histology who are in a complete remission with chemotherapy, radiation may be omitted without impacting outcome. However, the duration and quantity of therapy appropriate to make this determination is unknown.

The presence of liver metastases at diagnosis is not an independent adverse prognostic factor in patients with stage IV Wilms tumor.\([174]\)

**Treatment of stage V Wilms tumor and those predisposed to developing bilateral Wilms tumor**

Currently, there is not a standard approach for the treatment of stage V Wilms tumor (bilateral Wilms tumor at diagnosis) and those predisposed to developing Wilms tumor.

Management of a child with bilateral Wilms tumor is very challenging. The goals of therapy are to eradicate all tumor and to preserve as much normal renal tissue as possible, with the hope of decreasing the risk of chronic renal failure among these children.\([154]\)

In the NWTS-4 trial, bilateral Wilms tumor patients had a lower EFS and OS than did patients with localized Wilms tumor (including anaplastic histology), except for stage IV disease, in which OS was higher for patients with bilateral Wilms. The NWTS-4 study
reported that the 8-year EFS for patients with bilateral FH Wilms tumor was 74% and
the OS was 89%; for patients with anaplastic histology, the EFS was 40% and the OS
was 45%.[142] The NWTS-5 study reported the 4-year EFS for bilateral Wilms tumor
patients was 61% and the OS was 81%; for patients with anaplastic histology, the EFS
was 44% and the OS was 55%.[133, 200] Similar outcomes for patients with bilateral
Wilms tumor have been reported in Europe.[141, 201] In a single-institution experience
in the Netherlands (N = 41), there was significant morbidity in terms of renal failure
(32%) and secondary tumors (20%).[201] The incidence of end-stage renal failure in the
Dutch study may be a reflection of a longer follow-up period.

Treatment options for stage V Wilms tumor may include the following:

1. **Preoperative chemotherapy and resection for bilateral Wilms tumor.**
2. **Renal transplantation.**

**Preoperative chemotherapy and resection for bilateral Wilms tumor**

Traditionally, patients have undergone bilateral renal biopsies, with staging of each
kidney followed by preoperative chemotherapy. In COG trials, pretreatment biopsies are
not required if results of imaging tests are consistent with Wilms tumor. This approach
was taken because the bilateral occurrence of rhabdoid tumors and clear cell sarcoma
of the kidney is very low. Also, core-needle and wedge biopsies are not highly
successful in identifying anaplasia in Wilms tumor.[125] In one study, zero of seven
patients with anaplastic tumor present at nephrectomy had it diagnosed on initial core-
needle biopsy, and an open-wedge biopsy demonstrated anaplasia in only three of nine
cases. In the past, the surgical approach varied according to the size of the tumor; small
tumors were resected and larger tumors were biopsied, and then patients were given
prenephrectomy chemotherapy.

For patients who are treated with preoperative chemotherapy, the tumor pathology
needs to be evaluated after 4 to 8 weeks. For patients not treated in a clinical trial, the
ideal time to perform a biopsy or resection is unknown because minimal shrinkage may
reflect chemotherapy-induced differentiation or anaplastic histology. A planned attempt
at resection or biopsy of apparently unresectable tumor is undertaken no later than 12
weeks from diagnosis. Continuing therapy without evaluating tumor pathology in a
patient with bilateral Wilms tumor may miss anaplastic histology or chemotherapy-
induced differentiation (including rhabdomyomatous differentiation) and thus increase
toxicity for the patient without providing additional benefit for tumor control. Anaplastic
histology occurs in 10% of patients with bilateral Wilms tumor, and these tumors
respond poorly to chemotherapy.[142]

Once the diagnosis is confirmed, a complete resection is performed. Histologic
confirmation of the diagnosis is not straightforward. In a series of 27 patients from
NWTS-4, discordant pathology (unilateral anaplastic tumor) was seen in 20 cases
(74%), which highlights the need to obtain tissue from both kidneys. Seven children who
were later diagnosed with diffuse anaplastic tumors had core biopsies performed to establish the diagnosis; however, anaplasia was not found. Anaplasia was identified in only three of the nine patients when an open-wedge biopsy was performed and in seven of nine patients who had a partial or complete nephrectomy.[142]

The decision to administer chemotherapy and/or radiation therapy after biopsy or second-look operation is dependent on the tumor’s response to initial therapy. More aggressive therapy is required for patients with inadequate response to initial therapy observed at the second procedure or in the setting of anaplasia.[151, 200, 202]

At this time, there is no standard evidence-based approach to treat bilateral Wilms tumor. Several approaches that are being used are described below.

Evidence (preoperative chemotherapy and resection for bilateral Wilms tumor):

1. In a series of 49 patients with Wilms tumor who received preoperative therapy according to the SIOP-93-01 (NCT00003804) guidelines, the timing of surgery was determined when there was no longer imaging evidence of tumor regression. The mean treatment duration was 80 days before renal-sparing surgery.[203]
   - The 5-year EFS rate was 83.4%, and the OS rate was 89.5%.
   - All but one of the patients had renal-sparing surgery in at least one kidney.
   - Despite the good survival, 14% of the patients developed end-stage renal disease.

2. In a retrospective review from St. Jude Children's Research Hospital, investigators described their experience with preoperative chemotherapy followed by renal-sparing procedures in children with bilateral FH Wilms tumor.[204]
   - In a series, 39 of 42 patients with bilateral FH Wilms tumor underwent successful bilateral renal-sparing procedures after receiving preoperative chemotherapy. Three patients underwent unilateral nephrectomy with contralateral nephron-sparing surgery. Three patients required early (within 4 months) repeat nephron-sparing surgery for residual tumor. In the long term, seven patients had local tumor recurrence, and three patients had intestinal obstruction.
   - OS was 86% (mean follow-up, 4.1 years). Of the six patients who died, five had diffuse anaplastic histology.
   - All of the patients had an estimated glomerular filtration rate of more than 60 mL/min/1.73m² at the last follow-up; none of the patients developed end-stage renal disease.
   - The authors concluded that bilateral renal-sparing surgery is almost always feasible and can be done safely with good oncologic outcomes in
patients with synchronous, bilateral Wilms tumor. It should be considered even if preoperative imaging studies suggest that the lesions are unresectable. Sparing of renal parenchyma is likely to help preserve renal function in children who are at significant risk of chronic renal insufficiency. Careful long-term follow-up is required to fully assess the potential progression of renal dysfunction.

Renal transplantation

Renal transplantation for children with stage V Wilms tumor is usually delayed until 1 to 2 years have passed without evidence of malignancy because most relapses occur within 2 years of diagnosis.\[205\] Similarly, renal transplantation for children with Denys-Drash syndrome and Wilms tumor, all of whom require bilateral nephrectomy, is generally delayed 1 to 2 years after completion of initial treatment.\[205\]

Treatment options under clinical evaluation

There is no current standard treatment for children with stage V Wilms tumor and for those predisposed to developing Wilms tumor. Information about ongoing clinical trials is available from the NCI website.

Follow-up after treatment

For patients who have completed therapy for Wilms tumor and exhibit features consistent with genetic predisposition, such as bilateral Wilms tumor, screening involves renal ultrasound examination every 3 months for metachronous tumors during the risk period for that particular syndrome (5 years for WT1-related syndromes; 8 years for Beckwith-Wiedemann syndrome).

Late effects after Wilms tumor therapy

Children treated for Wilms tumor are at increased risk of developing the following:

- **Premature mortality after Wilms tumor diagnosis.** In 1,441 5-year survivors of Wilms tumor, a substantial increase in cumulative mortality from 5.4% to 22.7% was noted from 30 to 50 years after Wilms tumor diagnosis. Excess deaths after 30 years were attributed to subsequent malignant neoplasms (50%) and cardiac-related causes (25%).\[206\] Radiation therapy was a risk factor for both outcomes.

- **Subsequent malignant neoplasms.**\[206, 207, 208\] Digestive cancers and breast cancer are the most frequent subsequent neoplasms, and radiation therapy is a risk factor. Women treated with lower doses of radiation to large volumes of breast tissue for a childhood cancer have a risk of breast cancer that is higher than previously recognized. The cumulative incidence of invasive breast
cancer in Wilms tumor survivors who had received pulmonary radiation for metastatic Wilms tumor is nearly 15% by age 40 years.[209]

- **Congestive heart failure.** The risk of congestive heart failure is influenced by dose of doxorubicin received, radiation to the heart, and female gender.[208, 210]
- **Complications of pregnancy.**[211]
- **End-stage renal disease.** The cumulative incidence of end-stage renal disease caused by chronic renal failure at 20 years from diagnosis of Wilms tumor is low, at 3.1% for patients with bilateral Wilms tumor and less than 1% for those with unilateral Wilms tumor.[76] Efforts, therefore, have been aimed toward reducing the intensity of therapy when possible.

(Refer to the PDQ summary on Late Effects of Treatment for Childhood Cancer for a full discussion of the late effects of cancer treatment in children and adolescents.)

**References:**


35. Russell B, Johnston JJ, Biesecker LG, et al.: Clinical management of patients with ASXL1 mutations and Bohring-Opitz syndrome, emphasizing the need for


Congenital Mesoblastic Nephroma

General Information About Congenital Mesoblastic Nephroma
Mesoblastic nephroma comprises about 5% of childhood kidney tumors, and more than 90% of cases appear within the first year of life. It is the most common kidney tumor found in infants younger than 3 months. The median age of diagnosis is 1 to 2 months. Twice as many males as females are diagnosed. The diagnosis should be questioned when applied to individuals older than 2 years.[1]

When patients are diagnosed in the first 7 months of life, the 5-year event-free survival rate is 94%, and the overall survival rate is 96%.[2] In a report from the United Kingdom of 50 children with mesoblastic nephroma studied on clinical trials and 80 cases from the national registry in the same time period, there were no deaths.[1] However, in a comprehensive review of the literature, 12 deaths were reported, 7 from surgical mishaps in infants.[3][Level of evidence: 3iiiDii] [Comment: Gooskens text from CFrantz. 3/5/17]

Grossly, mesoblastic nephromas appear as solitary, unilateral masses indistinguishable from nephroblastoma. Microscopically, they consist of spindled mesenchymal cells. Mesoblastic nephroma can be divided into the following two major types:

- **Classic.** Classic mesoblastic nephroma is often diagnosed by prenatal ultrasound or within 3 months after birth and closely resembles infantile fibromatosis.[4]

- **Cellular.** A potential linkage between infantile fibrosarcoma and cellular mesoblastic nephroma is suggested because both contain the same t(12;15)(p13;q25) translocation, which results in the ETV6/NTRK3 fusion.[5]

The risk of recurrence for patients with mesoblastic nephroma is closely associated with the presence of a cellular component and with stage.[4]

(Refer to the Clinical Features of Wilms Tumor and Diagnostic and Staging Evaluation for Wilms Tumor sections of this summary for more information about the clinical features and diagnostic evaluation of childhood kidney tumors.)

**Treatment of Congenital Mesoblastic Nephroma**

Standard treatment options for congenital mesoblastic nephroma include the following:

1. **Nephrectomy.**
2. **Adjuvant chemotherapy.**

**Nephrectomy**

Evidence (nephrectomy):

1. A prospective clinical trial enrolled 50 patients with congenital mesoblastic nephroma.[4]
The results confirmed that complete surgical resection, which includes the entire capsule, is adequate therapy for most patients with mesoblastic nephroma.

- Only 2 of 50 patients died.
- Patients were at increased risk of local and eventually metastatic recurrence if there was stage III disease (incomplete resection and/or histologically positive resection margin), cellular subtype, and age 3 months or older at diagnosis. Because of the small numbers of patients and the overlapping incidence of these characteristics (5 of 50 patients), the significance of the individual characteristics could not be discerned.

**Adjuvant chemotherapy**

Adjuvant chemotherapy has been recommended for patients with stage III cellular subtype who are aged 3 months or older at diagnosis. However, the benefit of adjuvant therapy remains unproven, given the low incidence of disease.[4] Infants younger than 2 months with incompletely resected, stage III disease may not need chemotherapy.[1]

**Treatment Options Under Clinical Evaluation for Congenital Mesoblastic Nephroma**

Consideration should be given to targeted therapy for patients with recurrent or refractory disease containing the *ETV6/NTRK3* fusion. The following are examples of national and/or institutional clinical trials that are currently being conducted. Information about ongoing clinical trials is available from the NCI website.

- **LOXO-TRK-15003 (NCT02637687)** (Oral TRK Inhibitor LOXO-101 for Treatment of Advanced Pediatric Solid or Primary Central Nervous System [CNS] Tumors): This is a multicenter, open-label, phase I study of pediatric patients with advanced solid or primary CNS tumors. LOXO-101 will be administered orally twice daily, with the dose adjusted by body surface area.

- **RXDX-101-03 (NCT02650401)** (Study of RXDX-101 in Children With Recurrent or Refractory Solid Tumors and Primary CNS Tumors): This is a four-part, open-label, phase I/Ib, dose-escalation study in pediatric patients with relapsed or refractory solid tumors, primary CNS tumors, neuroblastoma, and non-neuroblastoma, extracranial solid tumors with NTRK1/2/3, ROS1, or ALK gene rearrangements. The study is designed to explore the safety, maximum tolerated dose or recommended phase II dose, pharmacokinetics, and antitumor activity of entrectinib (RXDX-101).

**References:**


