

Protocol for the Examination of Specimens From Pediatric Patients With Wilms Tumors

Protocol applies to all renal tumors of childhood except renal cell carcinoma. Use the adult kidney protocol for renal cell carcinoma.

No AJCC/UICC TNM Staging System

The Children's Oncology Group Staging System is recommended.

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Procedures

- Partial Nephrectomy
- Radical Nephrectomy

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CAP Wilms Tumor Protocol Revision History

Version Code

The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: WilmsTumor 3.0.0.0

Summary of Changes

No changes have been made since the October 2009 release.

Important Note

First priority should always be given to formalin-fixed tissues for morphologic evaluation. The second priority for tissue processing may include snap-freezing up to 1 g (minimum of 100 mg) of tumor for molecular studies (**Note A**).

For more information, contact: The Children's Oncology Group Biopathology Center.
Phone: (614) 722-2890 or (800) 347-2486.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

KIDNEY: Resection for Pediatric Renal Tumor**Note: For bilateral tumors, complete a separate checklist for each kidney.****Select a single response unless otherwise indicated.****Procedure (Notes A and B)**

- Partial nephrectomy
 Radical nephrectomy
 Bilateral partial nephrectomies
 Other (specify): _____
 Not specified

Specimen Size

Kidney dimensions: ___ x ___ x ___ cm
 Weight: ___ g (**Note B**)

Specimen Laterality

- Right
 Left
 Not specified

***Tumor Site(s) (select all that apply)**

- * Upper pole
 * Middle
 * Lower pole
 * Other (specify): _____
 * Not specified

Tumor Size

Greatest dimension: ___ cm
 *Additional dimensions: ___ x ___ cm
 Cannot be determined (see "Comment")

For specimens with multiple tumors, specify greatest dimension of each additional tumor:

Greatest dimension tumor #2: ___ cm
 Greatest dimension tumor #3: ___ cm
 Other (specify): _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Tumor Focality

- Unifocal
 Multifocal
 Number of tumors in specimen (specify): _____
 Indeterminate
 Cannot be assessed

Macroscopic Extent of TumorGerota's Fascia

- Gerota's fascia intact
 Gerota's fascia disrupted
 Indeterminate
 Cannot be assessed

Renal Sinus (select all that apply)

- Renal sinus involvement by tumor not identified
 Tumor minimally extends into renal sinus soft tissue
 Tumor extensively involves renal sinus soft tissue
 Tumor involves lymph-vascular spaces in the renal sinus

Renal Vein

- Renal vein invasion present
 Renal vein invasion not identified
 Indeterminate
 Cannot be assessed

Adjacent Organ Involvement (select all that apply)

- Tumor extension into adjacent organ present (specify organ: _____)
 Tumor extension into adjacent organ not identified
 Indeterminate
 Cannot be assessed

Histologic Type (select all that apply) (Note C)

- Wilms tumor, favorable histology
 Wilms tumor, focal anaplasia
 Wilms tumor, diffuse anaplasia
 Congenital mesoblastic nephroma, classical
 Congenital mesoblastic nephroma, cellular
 Congenital mesoblastic nephroma, mixed
 Clear cell sarcoma
 Rhabdoid tumor
 Other (specify): _____
 Malignant neoplasm, type indeterminate

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

***Nephrogenic Rests (select all that apply) (Note D)**

- * ___ Nephrogenic rests not identified
- * ___ Nephrogenic rests present
 - * ___ Nephrogenic rests, intralobar
 - * ___ Nephrogenic rests, perilobar
 - * ___ Diffuse, hyperplastic
 - * ___ Multifocal
 - * ___ Focal
 - * ___ Nephrogenic rests, unclassified
- * ___ Cannot be assessed

Margins (select all that apply)

- ___ Cannot be assessed
- ___ Margin involvement by tumor not identified
 - Distance of tumor from closest margin: ___ mm or ___ cm
 - Specify margin: _____
- ___ Margin(s) involved by tumor
 - ___ Gerota's fascia
 - ___ Renal vein
 - ___ Inferior vena cava
 - ___ Ureter
 - ___ Other (specify: _____)

Lymph Nodes

- ___ No lymph nodes submitted
 - ___ Regional lymph node metastasis not identified
 - ___ Regional lymph node metastasis present (specify site [if known]: _____)
- Specify: Number of lymph nodes examined: ___
Number of lymph nodes involved: ___

Distant Metastasis

- ___ Not applicable
- ___ Distant metastasis present
 - *Specify site(s) if known: _____

Note: Distant metastasis category includes both hematogenous metastasis or lymph node metastasis outside the abdomen-pelvic region (beyond the renal drainage system).

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Children's Oncology Group Staging System for pediatric renal tumors other than renal cell carcinoma (select all that apply under the appropriate stage) (Note E)

- Stage I: Tumor limited to kidney and completely resected
- Penetration of renal capsule by tumor not identified
 - Tumor involvement of extrarenal or renal sinus lymph-vascular spaces not identified
 - Tumor metastasis to lymph nodes not identified
- Stage II: Tumor extends beyond kidney but completely resected
- Tumor extends through the renal capsule but with negative resection margin
 - Tumor involvement of extrarenal or renal sinus lymph-vascular spaces present
 - Tumor involves renal vein but has not been transected and is not attached to vein wall at resection margin
 - Tumor extensively involves the renal sinus soft tissue
- Stage III: Residual tumor
- Tumor present at margin(s) of resection
 - Tumor capsular rupture identified
 - Tumor spill before or during surgery identified
 - Piecemeal excision of tumor (removal of tumor in more than 1 piece)
 - Metastatic tumor in regional lymph nodes identified
 - History of renal tumor biopsy before definitive surgery
- Stage IV: Metastatic disease
- Hematogenous metastases or lymph node metastases outside the abdomino-pelvic region (beyond renal drainage system, eg, lung, liver)
- Stage V
- Bilateral renal involvement at diagnosis (each side should also be staged separately, according to above criteria, as I to IV)
- Specify (both): Right kidney stage:
- Left kidney stage:

***Additional Pathologic Findings (Notes F and G)**

*Specify: _____

***Comment(s)**

Explanatory Notes

A. Frozen Section

Because of the high number of false-positives, intraoperative frozen sections should be avoided unless the operative procedure will be altered by the result. Biopsies of pediatric renal tumors present significant potential for diagnostic error, even on permanent section. However, frozen sections from the bivalved nephrectomy specimen—to ensure tumor viability or to prompt other differential diagnostic studies—may be of value.

For future potential molecular studies, viable tumor (up to 1 g or more) should be snap-frozen (liquid nitrogen or cold isopentane) in 2 or more vials, along with a separate portion of nonneoplastic kidney (at least 1 vial).¹ The latter serves as a useful control in molecular genetic studies and helps determine whether any detected genomic abnormalities are germline or intratumoral mutations. Nephrogenic rests may also be sampled and frozen for the same reasons.

B. Handling of Renal Specimens

With pediatric renal tumors, there are many issues that can interfere with making accurate diagnostic and staging decisions. The following guidelines are recommended to ensure that the necessary diagnostic features are preserved and properly examined²:

- *Nephrectomy specimens should be submitted intact by the surgeon.* The surface of the specimen should be photographed and inked before bivalving to facilitate the recognition of displacement artifacts from the smearing of tumor cells over the specimen surface during sectioning, as well as to evaluate margins. Bivalving will cause the capsule in a fresh kidney to retract, possibly altering the relationship between the tumor and the capsule or surgical margin.
- The capsule from nephrectomy specimens must *never* be stripped. Invasion of the tumor into the capsule is a criterion in staging. In addition, nephrogenic rests are often subcapsular in location. The medial sinus margin is defined as the medial end of soft tissues surrounding the renal artery and vein.
- Inspect the renal vein for tumor thrombus, because this is a common route by which Wilms tumor exits the kidney. Caution should be used in the evaluation of the margin of the renal vein that contains a thrombus. The vein often retracts after the surgeon sections it, leaving a protruding tumor thrombus, which may erroneously be considered a positive margin. If the thrombus itself is not transected, and if the margin of the vascular wall itself does not contain tumor, this surgical margin is interpreted as being negative.
- The exact site from which each section or paraffin block is obtained may be documented by photograph, photocopy, or drawing. Often, this documentation is critical for recognizing staging problems and for the evaluation of focal versus diffuse anaplasia.
- Take at least 1 microscopic section per centimeter of maximal tumor diameter, with additional sampling of any suspicious lesions. The majority of random tumor sections should be taken from the periphery of the tumor, because this is where the invasive pattern of the tumor can be identified and its interface with the capsule and native

kidney can be evaluated. Peripheral sections also demonstrate invasion of vessels within the intrarenal extension of the renal sinus. The renal sinus is that area in the hilum of the kidney occupied by the renal pelvis, as well as hilar vessels and fat. The renal cortex at the sinus lacks a capsule. The most important sections are those taken from regions of the sinus adjacent to the tumor to demonstrate involvement (or lack of involvement) of sinus vessels.

- For Wilms tumors that are multicentric, sample each nodule. More than 30% of Wilms nephrectomy specimens contain nephrogenic rests. Nephrogenic rests often appear paler than the typical nonneoplastic kidney parenchyma. These areas should be sampled. Nephrogenic rests have important implications concerning the risk of contralateral Wilms tumor development and may have other syndromic implications. At least 1 random section of normal kidney and possibly more may be taken to detect nephrogenic rests microscopically (Note D).
- Nephrectomy weight may be an eligibility factor for some clinical trial protocols. Hence, this measurement is critical.
- In addition to the capsular, vascular, and sinus sampling already described, routine sections taken for margins should include sampling of the distal ureter.

C. Microscopic Examination

Favorable Histology Wilms Tumor

Classic Wilms tumors present with a mixture of blastemic, stromal, and epithelial cell types. A common difficulty faced by pathologists interpreting a pediatric renal mass is the distinction between a hyperplastic perilobar nephrogenic rest and a Wilms tumor because these may be cytologically identical. The most helpful histologic feature is the absence of a peritumoral fibrous capsule in perilobar nephrogenic rests.

Many other neoplasms may have a histologic appearance similar to blastemal-predominant Wilms tumors. The most common tumors misdiagnosed as Wilms tumors are undifferentiated neuroblastoma, primitive neuroectodermal tumor, and synovial sarcoma. The most helpful feature that favors the diagnosis of Wilms tumor is the presence of overlapping nuclei with finely dispersed chromatin. Similarly, epithelial-predominant Wilms tumors show considerable histologic overlap with papillary renal cell carcinoma and metanephric adenoma. A more detailed differential diagnosis of pediatric renal tumors is provided elsewhere.^{1,3}

Anaplastic Wilms Tumor

Once a tumor has been diagnosed as Wilms tumor, it is necessary to determine whether it is of favorable histology or if anaplasia is present. Although anaplasia is present in only 5% of all cases,² it is the major prognostic indicator and will place a tumor in an unfavorable histological category.

The presence of anaplasia is a significant prognostic factor in Wilms tumor and places the tumor in an unfavorable category. Although the mechanism for unfavorable prognosis is unclear, anaplasia may be a marker of chemotherapy resistance. A diagnosis of anaplasia requires both (1) gigantic polyploid nuclei with increased chromatin content and major diameters at least 3 times those of adjacent cells and

(2) the presence of multipolar or otherwise recognizably polyploid mitotic figures. On a small biopsy, a single multipolar mitotic figure or an unequivocally gigantic tumor cell nucleus may be sufficient criteria for diagnosis. *Severe nuclear unrest* is defined as nuclear pleomorphism or atypia approaching the criteria of anaplasia.

Criteria for focal versus diffuse anaplasia have been defined topographically and are rigorous.⁴ This topographic definition of focal anaplasia makes it mandatory that pathologists carefully document the exact site from which every section is obtained (eg, on a diagram, specimen photocopy, and/or photograph of the gross specimen).

Focal Anaplasia

Diagnosis of focal anaplasia is warranted if *all* of the following are true:

- No anaplasia should be present in tumor within renal vessels or outside the kidney.
- Random biopsies are free of anaplasia.
- Anaplasia must be confined to 1 or more sharply localized regions within the primary intrarenal tumor site.
- Each focus of anaplasia must be surrounded on all sides by nonanaplastic tissue. This may require mapping of the tumor during submission.
- The remaining nonanaplastic tumor must not show severe nuclear unrest. (The same criteria applies to posttreatment nephrectomies.)

Diffuse Anaplasia

Diagnosis of diffuse anaplasia is warranted if *any* of the following are true:

- Anaplasia is present in tumor in any extrarenal site, including vessels of the renal sinus, extracapsular infiltrates, or nodal or distant metastases. Also, anaplasia is present in intrarenal vascular involvement by tumor.
- Anaplasia is present in a random biopsy.
- Anaplasia is unequivocally expressed in 1 region of the tumor, but with extreme nuclear pleomorphism approaching the criteria of anaplasia (extreme nuclear unrest) elsewhere in the lesion.

Congenital Mesoblastic Nephroma

There is a growing appreciation that congenital mesoblastic nephroma (CMN), a tumor of infancy, represents 2 genetically distinct tumors: the “classic” CMN (24% of cases), which corresponds to infantile fibromatosis; and “cellular” CMN (66% of cases), which corresponds to infantile fibrosarcoma and contains the characteristic t(12;15), resulting in a fusion product detectable by reverse transcriptase polymerase chain reaction.¹ Occasional cases (10%) are classified as “mixed” CMN, owing to the presence of both histologic types. Currently, there is no consensus regarding the pathways through which mixed CMN may arise.

Approximately 10% of CMNs recur. The substantial majority of CMNs that recur are of the cellular subtype. Recurrences occur very rapidly, often within the first month of diagnosis. Virtually all recurrences occur by 1 year of age. More than half are local recurrences; however, pulmonary metastases have been identified in 20% of patients who relapse. Preliminary evidence suggests that renal sinus vascular involvement may be closely associated with lung metastasis. However, the primary determinant of outcome is the completeness of excision. Surgeons should be educated and encouraged to secure wide margins, particularly medial margins, when resecting renal tumors in infants. Nonetheless, one can rarely be sure that the medial margin is clear;

therefore, all patients should be followed closely. Monthly abdominal ultrasounds should be performed for 1 year, with the hope of catching recurrences early enough to surgically excise them. Adjuvant chemotherapy is required when there is gross residual tumor. Radiation has no demonstrable effect.

Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) is capable of mimicking, or being mimicked by, every other major neoplastic entity in the pediatric kidney. A genetic or histochemical feature specific to CCSK has been elusive. Immunohistochemical stains other than vimentin are inconsistent, but these negative results can help rule out other neoplasia in the differential diagnosis.

The histologic spectrum and clinical outcome of patients with CCSK have recently been reported by the National Wilms Tumor Study Group.⁵ Nearly all patients with stage I CCSK survive. Conversely, patients with more advanced disease have a propensity for local recurrence and metastasis. Recurrences can occur from years to decades after initial presentation, sometimes demonstrating a bland histology that differs from the primary tumor. The metastatic pattern tends to be more widespread than that of Wilms tumor and includes bone, brain, and soft tissue. There is a high recurrence rate and death rate even when treated by combination chemotherapy, but survival can be greatly improved after treatment with doxorubicin,⁵ which underscores the importance of identifying this neoplasia to facilitate early administration of more effective chemotherapy regimens.

There are several variants of CCSK, among which the following are most important:

Classical Pattern

The classical pattern of CCSK presents an evenly dispersed network of fine, arborizing vessels accompanied by a variable amount of spindle-cell stroma, subdividing the tumor into nests or cords of regular size, usually about 8 to 12 cells in width. The tumor cells are of regular size, usually with stellate cytoplasm, which often surrounds clear vacuoles. The nuclei are notably regular in size, with finely dispersed chromatin and usually inconspicuous nucleoli. Mitotic activity may be sparse. Scattered pre-existent tubules or glomeruli often are dispersed through the peripheral regions of the tumor. This pattern of growth, which isolates and separates individual nephronic units or collecting tubules, is an important clue that one is not dealing with a Wilms tumor. The latter almost always has a sharply defined, “pushing” border.

Hyalinizing Pattern

The hyalinizing pattern of CCSK often has an osteoid-like, nonbirefringent matrix that separates tumor cells, giving an appearance reminiscent of osteosarcoma. A similar change maybe seen in rhabdoid tumor of the kidney (RTK).

Epithelioid Pattern

The epithelioid pattern is the most deceptive of the patterns of CCSK, in which the tumor cells align themselves along vessels in a manner mimicking the tubules of Wilms tumor. Often these cells form filigree-like strands.

Rhabdoid Tumor of the Kidney

This distinctive renal neoplasm most commonly is encountered in infants younger than 1 year of age and is extremely uncommon in patients older than 5 years. It is extremely

aggressive and is the most prognostically unfavorable neoplasm of the kidney in early life. Rhabdoid tumors continue to present significant diagnostic challenges, particularly when they do not show overt rhabdoid features. However, the growing appreciation that this tumor arises in sites other than the kidney and the central nervous system, and the increased appreciation of the wide histologic spectrum of rhabdoid tumors have contributed to a marked increase in their correct diagnosis. Rhabdoid tumor of the kidney should not be confused with the true myogenic cells, which are often found in Wilms tumors.

The most distinctive features of rhabdoid tumor of the kidney (RTK) are rather large cells with large vesicular nuclei, a prominent single nucleolus, and the presence in at least some cells of globular eosinophilic cytoplasmic inclusions composed of whorled masses of intermediate filaments. Another distinctive feature is the extremely aggressive, invasive pattern of this lesion. RTK has a diverse immunohistochemical profile. Tumors may be positive for many supposedly incompatible epitopes for epithelial, myogenous, neural, and mesenchymal cell types. Epithelial membrane antigen (EMA) should be included in the routine panel applied to small blue cell tumors, largely because of the typical focal strong positivity for EMA (as well as a multitude of other markers) that rhabdoid tumors demonstrate.

Rapid advances in our understanding of the genetic events leading to the development of rhabdoid tumors have been made recently. It now is clear that both renal and extrarenal rhabdoid tumors carry homozygous deletions and/or mutations of the *hSNF5/INI1* gene located at 22q11.2.⁶ Furthermore, germline mutations have been identified in individuals with both renal and central nervous system rhabdoid tumors. The *INI1* gene causes conformational changes in the nucleosome, thereby altering histone-DNA binding and facilitating transcription factor access. The *INI1* deletion can be evaluated with immunohistochemistry using the BAF47 antibody.³ This antibody shows strong nuclear staining in virtually all cell types except rhabdoid tumor cells. Important exceptions are renal medullary carcinoma and epithelioid sarcoma, which also often show loss of INI-1 protein.

Renal Sinus Vascular Invasion

True tumor invasion is easy to confirm when the tumor fills the lumen or invades the vascular wall. Displacement artifact is also readily identified when it is present in arterial lumina, when it is accompanied by abundant displacement artifact elsewhere, or when ink is present within the aggregates. More difficult are foci of unattached tumor intermingling with fibrin and red cells, or free-floating rounded tumor fragments that are not associated with other displacement artifact. The presence of these foci in children with small, otherwise stage I tumors not treated with adjuvant chemotherapy are biologically significant and should upstage the patient. Intrarenal vascular invasion does not upstage a renal tumor.

D. Nephrogenic Rests⁷

Nephrogenic rests are regions of persistent embryonal tissue in the renal parenchyma and can be found in 30% to 44% of kidneys removed for Wilms tumor, 4% of kidneys removed for dysplasia or urinary tract malformations, and 0.21% to 0.87% of kidneys in pediatric autopsy series (higher incidence in infants <3 months of age). The term nephroblastomatosis refers to multiple or diffusely distributed nephrogenic rests. The 2 fundamental categories of nephrogenic rests are based on the topography of the lesion. *Perilobar nephrogenic rests* (PLNR) are located at the periphery of the lobule and are

usually subcapsular. They are often multiple and can be diffuse (diffuse perilobar nephrogenic rests or DPLN). Microscopically, perilobar rests are well demarcated but not encapsulated. They are typically composed of blastema and tubules with little intervening stroma. Similarly, tumors arising in association with PLNR are more likely to be blastemal or epithelial predominant. PLNR are associated with higher birthweights and overgrowth syndromes, including Beckwith-Wiedemann syndrome. PLNR serve as a marker of loss of imprinting or loss of heterozygosity for *IGF-2*. Intralobar nephrogenic rests (ILNR) are located deep within the lobule and are usually solitary. They have indistinct margins with respect to the normal kidney. ILNR contain blastemal, tubular, and prominent stromal elements interspersed among normal glomerular and tubular elements. ILNR are also more often associated with early-onset, stromal-predominant Wilms tumor or Wilms tumor showing divergent (teratomatous) differentiation. ILNR are a morphologic indicator of WT1 mutation and are strongly associated with WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) and Denys-Drash syndromes. It is thought that ILNR result from an error earlier in nephrogenesis as compared with PLNR, explaining the typical ILNR location deep within the lobule.

The presence of nephrogenic rests has clinical implications for their association with genetic syndromes as well as the risk for development of contralateral Wilms tumor, particularly in patients whose tumors are diagnosed in the first year of life.⁸

E. Staging

The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) TNM staging systems currently do not apply to Wilms tumor. The Children's Oncology Group staging system for Wilms tumors is recommended and shown below.⁹

Stage I

- Tumor limited to kidney and completely resected
- Renal capsule intact
- Tumor not ruptured or biopsied before removal
- No residual tumor apparent beyond margins of resection
- Renal vein and renal sinus vessels contain no tumor (intrarenal vessel involvement may be present)
- No lymph node involvement or distant metastases

Stage II

- Tumor extends beyond kidney but is completely resected
- Regional extension of tumor (vascular invasion outside the renal parenchyma or within the renal sinus, extensive renal sinus soft tissue invasion, and/or capsular penetration with negative excision margin)

Stage III

- Nonhematogenous metastases confined to the abdomen (eg, tumor in regional lymph nodes), including tumor implants on or penetrating the peritoneum
- Gross or microscopic tumor remains postoperatively (tumor at margins of resection)
- Tumor spill before or during surgery not confined to flank
- Piecemeal excision of the tumor (removal in more than 1 piece)
- Operative tumor spill confined to flank (no peritoneal contamination)

- Tumor biopsy before surgery

Stage IV

- Hematogenous metastases or lymph node metastases outside the abdomino-pelvic region (beyond renal drainage system, eg, lung, liver)

Stage V

- Bilateral renal involvement at diagnosis (each side should also be staged separately, according to above criteria, as I through IV)

F. Special Studies

The diagnosis of primary renal tumors in children remains largely based on examination of hematoxylin-eosin (H&E)-stained sections. Although some studies suggest that p53 immunostaining may be a more sensitive predictor of poor outcome than histologic assessment of anaplasia,¹⁰ such studies are fraught with difficulties in interpreting the outside limits of “positivity” as well as with interinstitutional variability in immunostaining techniques. Confirmation in larger studies using multiple techniques is needed.

No single cytogenetic or molecular abnormality has been consistently abnormal in Wilms tumor or its host, but constitutional deletions of the *WT-1* tumor suppressor gene at 11p13 often predispose the patient to development of Wilms tumors. WAGR syndrome and Denys-Drash syndrome are characterized by the deletion or mutation of this gene. ILNR are associated with WAGR and Denys-Drash syndromes. PLNR are associated with Beckwith-Weidemann syndrome, Perlman syndrome, and hemihypertrophy.^{7,11}

Genetic tests are often quite useful in the evaluation of several pediatric tumors arising in the kidney that mimic Wilms tumor. These include the characteristic translocation of cellular mesoblastic nephroma, t(12;15); and peripheral primitive neuroectodermal tumor (PNET), t(11;22). Fluorescence in situ hybridization (FISH) study to detect the 22q11.2 deletion of malignant RTK may also be diagnostically useful. Neuroblastomas not infrequently present as renal primaries, and *MYCN* amplification detected by FISH may be important in such cases.

G. Syndromes Associated with Wilms Tumor

The following syndromes are associated with Wilms tumor^{7,11}:

- Beckwith-Wiedemann syndrome
- Perlman familial nephroblastomatosis syndrome
- Denys-Drash syndrome
- Trisomy 18
- Neurofibromatosis
- Bloom syndrome
- WAGR syndrome

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