

PEDIATRIC RENAL TUMOR EPIDEMIOLOGY: GLOBAL PERSPECTIVES, PROGRESS AND CHALLENGES

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Abbreviations:

AHOPCA	Asociación de Hemato-Oncología Pediátrica de Centro América
AIEOP	Associazione Italiana di Ematologia e Oncologia Pediatrica
AWT	Anaplastic Wilms tumor
ASR	Age-standardized incidence rates
BENCHISTA	Benchmarking International Survival by Toronto stage initiative
BWSp	Beckwith-Wiedemann spectrum
BWT	Bilateral Wilms tumor
CCSK	Clear cell sarcoma of kidney
COG	Children's Oncology Group
EFS	Event free survival
FHWT	Favorable histology Wilms tumor
GFAOP	Groupe Franco-Africain d'Oncologie Pédiatrique
HIC	High-income country
JWiTS	Japan Wilms tumor studies
LMIC	Low-Middle-Income country
LOH	Loss of heterozygosity
MRTK	Malignant rhabdoid tumor of kidney
NWTS	National Wilms tumor study
RCC	Renal cell carcinoma
RMC	Renal medullary carcinoma
RTSG	Renal Tumor Study Group
OS	Overall survival
SIOP	International Society of Pediatric Oncology
WAGR	Wilms tumor aniridia syndrome
WT	Wilms tumor

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Abstract

Pediatric renal tumors account for 3-11% of childhood cancers, the most common of which is Wilms Tumor or Nephroblastoma. Epidemiology plays a key role in cancer prevention and control by describing the distribution of cancer and discovering risk factors for cancer. Large pediatric research consortium trials have led to a clearer understanding of pediatric renal tumors, identification of risk factors and development of more risk-adapted therapies. These therapies have improved event free and overall survival for children. However, several challenges remain and not all children have benefited from the improved outcomes. In this article we review the global epidemiology of pediatric renal tumors, including key consortium and global studies. We identify current knowledge gaps and challenges facing both high and low-middle-income countries.

Introduction: Epidemiology of Renal Tumors

Renal tumors constitute from 3.2 to 11.1 percent (%) of pediatric cancers worldwide^(1, 2) and exhibit significant ethnic diversity. The lowest proportions occur in East Asia and the highest in Sub-Saharan Africa. Incidence and outcomes vary by diagnosis, age, sex, ethnicity and geography. The age-standardized incidence rates (ASR) per million person-years vary at 9.1-9.8 in North America and Europe, 6.7 in Central and South America and Caribbean countries and 4.1-5.4 for Asians and Pacific Islanders⁽³⁻⁵⁾. Black patients in the U.S. have the highest ASR (10.9) and Asians have the lowest ASR (4.4)⁽⁶⁾. The ASR for pediatric renal tumors in Sub-Saharan Africa ranges from 6.7 – 10.9, with variable reports due to limited registry data.^(7, 8) (Table 1). In 2019 there were 396,652 new childhood cancer cases (0-14), of these 20,978 (5.7%) were Wilms Tumor(WT).⁽⁹⁾ While WT is the most common malignant renal tumor of childhood worldwide, other etiologies include renal rhabdoid tumors, renal cell carcinomas (RCC), sarcomas and other rare malignancies.

Methods

Renal tumor experts from the International Society of Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) and the Children's Oncology Group (COG) Renal Tumor Committee performed a literature review of the epidemiology of pediatric malignant renal tumors globally. This collaborative - The HARMONICA (HARMONization and CollAboration) initiative, represents the joint renal tumor international effort. This review focused on systematic reviews, publications representing large cooperative group clinical trial data and international epidemiological publications. In low-middle-income countries (LMICs) where data is sparse, single institution studies were included. This data was evaluated to identify knowledge gaps that if resolved, may improve future survival outcomes.

Results

Wilms tumor (WT)

WT demonstrates significant ethnic diversity that parallels that of overall renal tumors, with the highest incidence in African and U.S. Black children and the lowest incidence in Asian children.⁽⁵⁻⁷⁾ The ASR globally is 7.5 per million person-years for patients 0-14 years of age and 0.3 per million person-years for patients 15-19 years of age.⁽¹⁾

The mean age at diagnosis is 36 months, with most children presenting between 12 and 48 months. Worldwide, WTs tend to occur earlier in boys with a peak incidence at 1 year compared to a 1-3 year peak for girls.⁽¹⁾ WT is less common under 6 months of age, but still comprises 20% of all renal tumors at this age. Bilateral WTs (BWT) occur in 4–13% of patients.^(6, 10, 11)

Variations in stage of presentation observed globally are impacted by age and time to diagnosis. Amongst the large clinical trial groups, SIOP stages after neoadjuvant chemotherapy and surgery, while COG stages after up-front nephrectomy. On the SIOPWT2001 trial, stage distribution varied significantly between countries, with the highest proportion of stage I disease (53.4%) observed in Germany and more metastatic disease

(18.2%) in the Children's Cancer and Leukaemia Group (CCLG) (United Kingdom (UK), Ireland, Australia and New Zealand).⁽¹²⁾

On the SIOF 93 and 2001 treatment protocols, 45.5% of patients had stage I disease, 22.6% stage II, and 16.9% stage III after pre-operative chemotherapy. 15.2% had stage IV.⁽¹³⁻¹⁵⁾

Five to 8 percent of patients on SIOF protocols have BWT.^(16, 17) Post-operative histological risk stratification resulted in low-risk disease in 5.6% (N = 315), intermediate risk in 82% (N = 4566), high-risk blastemal type in 8.3% (N = 466) and high-risk diffuse anaplastic in 4.9% (N = 278).⁽¹⁸⁾ Table 2 compares stage at the time of nephrectomy between COG and SIOF.

Of 586 patients on the SIOF 2001 WT trial with stage I-IV disease, 167 (28%) had 1q gain, similar to the COG/NWTSG studies. 1 q gain was a negative biomarker with an EFS of 75.0% (95% CI, 68.5% to 82.0%) versus 88.2% in patients without gain (95% CI, 85.0% to 91.4%).⁽¹⁹⁾ SIOF does not use combined loss of heterozygosity (LOH) 1 p/16q for risk stratification.

The COG AREN03B2 renal tumor biology and risk stratification protocol enrolled 6686 patients with renal tumors by February 2021.⁽¹¹⁾ Among patients who received an initial risk classification by September 2020, 91.3% were determined to have unilateral and 8.7% bilateral renal tumors.⁽¹¹⁾ Among those with unilateral renal tumors, 87.8% had WT (82% favorable histology Wilms tumor (FHWT): 21% stage I, 24% stage II, 33% stage III, and 22% stage IV) and 5.8% anaplastic WT (AWT)).⁽¹¹⁾ Combined LOH 1p/16q was detected in 49 of 1,147 patients with stage I/II WT (4.27%) and 82 of 1,364 patients with stage III/IV WT (6.01%) enrolled in AREN03B2.⁽²⁰⁾

The COG unilateral WT therapeutic protocols AREN0532, AREN0533, AREN0321 and BWT protocol AREN0534 enrolled a total of 1227 patients with FHWT and 84 patients with AWT.

⁽¹¹⁾ On AREN0321, there were 18 patients with stage I AWT (8 focal, 10 diffuse), 15 with stage II, 27 with stage III and 24 with stage IV AWT.^(11, 21, 22) On AREN0532, 116 patients were candidates for the nephrectomy only arm with very low risk, stage I FHWT, age under 2

years and tumor weight under 550 g.⁽²³⁾ On AREN0532, 32 patients had stage I-II FHWT with combined LOH 1p/16q and 533 patients had stage III FHWT without combined LOH 1p/16q.^(20, 24) On AREN0533, 124 patients had stage IV FHWT with only lung metastases with CR at 6 weeks, without combined LOH 1p/16q and 131 patients had stage IV FHWT with lung metastases only with an incomplete response, without combined LOH 1p/16q.⁽²⁵⁾ Fifty-one patients on AREN0533 presented with stage III and IV disease with LOH 1p/16q and 89 patients presented with stage IV disease with extra-pulmonary metastases.^(20, 24) Results are not yet published. Hepatic metastases are the most common extrapulmonary metastases in children with WT. In 2009 the NWTSG published results of 96 patients with FHWT with hepatic metastasis (NWTSG4 and 5).⁽²⁶⁾ EFS was 76% for lung metastases only (95% CI: 72%, 80%) (513 patients); 76% for liver only (95% CI: 58%, 87%) (34 patients), liver and lung 70% (95% CI: 57%, 80%) (62 patients), and other sites 64% (95% CI: 42%, 79%) (25 patients).⁽²⁶⁾ Regimen M improved outcome for those with pulmonary metastases only on AREN0533 and evaluation of those with hepatic metastases is pending. Of 1114 patients enrolled on NWTSG- 5, 28% had 1 q gain, with an 8-year EFS of 77% compared to 90% for those without ($P < .001$). On the upcoming COG studies, 1 q gain will be used for risk stratification.⁽²⁷⁾

The first prospective BWT study, AREN0534, enrolled patients with bilateral tumors and unilateral tumors with bilaterally predisposed conditions, 41% of which were male and 59% female.⁽²⁸⁾ Of all 195 patients who enrolled on the trial initially, 9 had hemi-hypertrophy, 7 Beckwith-Wiedemann Syndrome(BWSp), 6 WAGR syndrome, 3 DDS and 16 isolated anomalies. Of 189 total evaluable patients with BWT, 26 had at least one kidney with AWT (9 focal and 17 diffuse). Twenty percent had discordant pathology between the two kidneys.

Thirty-four evaluable patients on AREN0534 had unilateral disease with a WT predisposing condition, 62% of which were female and 38% male.⁽²⁹⁾ Of these 34 patients, 76% were

Caucasian, 12% Black or African American, 3% American Indian or Alaskan and 9% unknown.⁽²⁹⁾ In this same group, 26% had BWSp, 3% Denys-Drash Syndrome, 26% Hemihypertrophy, 3% Simpson-Golabi-Behmel and 6% Wilms Tumor Aniridia Syndrome (WAGR). One third of these patients had a miscellaneous syndrome and one had a single kidney. The average age at diagnosis was 2.8 years. For the 32 patients who underwent a surgical procedure, post-surgical SIOP staging demonstrated 21 stage I, 4 stage II, 6 stage III and one stage IV. All patients had FHWT except a child with a congenital solitary kidney with stage I focal anaplasia.⁽²⁹⁾

The 5-year EFS is greater than 85% in high income countries (HICs),^(11, 16) impacted by stage, pathology and biology.⁽¹¹⁾ EFS is much lower in LMICs. On the last Collaborative Wilms Tumor Africa Project trial using adapted WT therapy, EFS improved, but remained substantially lower than HICs at 49.9%.⁽³⁰⁾ This disparity is multifactorial, influenced by characteristics of national health care systems, advanced stage at presentation, malnutrition and abandonment of therapy.⁽³¹⁻³⁴⁾ The stage at diagnosis in HICs can also be impacted by delays in the health care system. In the UK, patients must have referrals to specialists and presented with larger, higher staged tumors with an approximately 3% lower EFS and overall survival (OS) than German patients who have direct access to specialty care, despite being treated on the same regimens.⁽³⁵⁾

Malignant rhabdoid tumors of kidney (MRTK)

MRTKs are aggressive malignancies associated with SMARCB1/INI1 gene mutations and deletions on chromosome 22q. The incidence is highest in infancy and early childhood, representing approximately 2% of renal tumors^(1, 36-38), without reported international or ethnic variability. The male: female ratio on NWTs Studies 1-5 was 1.37 (p=0.01), with

10.6% of patients presenting with stage 1, 17.6% stage II, 40.8% stage III, 28.9% stage IV (including metastatic disease to the brain, potentially representing underappreciated second primaries, liver and lung) and 2.1% bilateral tumors. Four-year OS was 41.8% for stages I-II and 15.9% for stages III-V. Survival was highest for patients over 3 years of age at 46.2%, 41.1% over 2 years of age and dismal at 8.8% for infants 0-5 months of age.⁽³⁸⁾ Similar incidence and outcomes were noted on SIOP-93, SIOP-2001 and Japan Wilms tumor Studies (JWiTS). While data is sparse from LMICs, in one retrospective report from sub-Saharan Africa, 80% of patients presented with stage III-IV disease.^(39, 40)

Clear cell sarcoma of the kidney (CCSK)

CCSK accounts for 2-5% of childhood malignant renal tumors, most often presenting at 2-4 years of age with a 2:1 male predominance.⁽⁴¹⁻⁴³⁾ In NWTS 5, 11% of patients presented with stage I, 41% stage II, 42% stage III and 6% stage IV disease.^(41, 44) On SIOP 93-01/SIOP2001 trials, 42% of patients presented with stage I, 23% stage II, 28% stage 3 and 7% stage 4 disease.⁽⁴⁵⁾ Almost 75% of patients on JWITS2 presented with stage I-II disease (adjusted to match NWTS staging guidelines).⁽³⁹⁾ Prognosis is suboptimal in younger patients and those with metastatic and relapsed disease, 40% of which is to the central nervous system. OS at 5 years was 98-100% for patients with stage I disease, 86-90% for all patients included on NWTS5, SIOP 93-01/2001 and JWITS2 studies and 91% for stage I-III disease on the TW-2003 protocol of the Associazione Italiana di Ematologiae Oncologia Pediatrica (AIEOP).^(39, 44-46)

Ethnic variation in incidence has not been documented, although data is limited from LMICs.⁽¹⁾ In one Indian referral center, 22.5% of patients presented with metastatic disease.⁽²⁾ In a study from sub-Saharan Africa, 43.5% of patients presented with metastatic disease.⁽⁴⁰⁾

Renal cell carcinoma

RCC, a more common tumor in older age groups, has varying incidence in the African American and Oceanic populations.^(1, 47, 48) Several histological subtypes of RCC are included in the 2016 WHO classification system.

The SIOP RTSG reported RCC incidence from the SIOP 93-01, 2001 and UK IMPORT database showing 46% localized, 25% regionally advanced and 20% metastatic disease.⁽⁴⁹⁾

While patients with localized disease typically achieve cure with surgery alone, those with metastatic disease have poor outcomes. For patients with molecular testing, 56% had the MiT-RCC subtype. In the U.S, the MiT-RCC (translocation) subtype is the most predominant, accounting for 44% of pediatric patients with RCC under 25 years of age.⁽⁴⁸⁾ For patients without the MiT-RCC subtype on the AREN03B2 study, 38.4% presented with stage I-II disease, 35.8% stage III disease and 20.8% metastatic disease. Of the 47% of patients with the MiT-RCC subtype on AREN03B2, 30.4% presented with stage I-II disease, 51.8% stage III disease, and 10.7% metastatic disease. Cancer predisposition syndromes, aside from sickle cell trait associated with renal medullary carcinoma (RMC), were rare.^(47, 50, 51)

The ASR for children from Oceania was 0.4 compared to 0.1-0.3 for all other world regions and 0.2 for the world overall. African American children and adolescents aged 0-14 years in the U.S. experienced a higher ASR (0.7) compared to 0.3 for White non-Hispanic patients).⁽¹⁾ For adolescents aged 15-19 years, the ASR for Black patients in the U.S. was double the world rate and the ASR in Sub-Saharan Africa was 1.3, 0.7 for North Africa and 0.5 for Central America and the Caribbean. In the U.S., MiT-RCC and renal medullary carcinoma both occur more frequently in the African American population compared to other ethnicities.^(52, 53) Incidence rates in LMICs are potentially influenced by under-diagnosis and/or under-reporting. The incidence doubled worldwide from the 1970s-2000s from 0.1-0.2 per million and 1996-2010 by an average annual percentage change of 3.7% in male children and 3.2% in female adolescents.⁽¹⁾

Data is limited from LMIC settings, but at one Indian center, the translocation subtype was responsible for 70% of RCC cases.⁽²⁾ This has been associated with a worse prognosis.⁽⁵²⁾ Patients with localized, resectable disease had similar positive outcomes and those with metastatic disease had similarly poor outcomes to patients in HICs. However, patients with locally advanced disease did not respond to pre-operative immunotherapy. In a retrospective study from sub-Saharan Africa, 80% of patients with RCC, subtype unknown, presented with metastatic disease, with a survival of 40%.⁽⁴⁰⁾

Sparse data from LMICs, where accurate diagnostics are often a challenge, makes true evaluation of global and ethnic variation difficult. Collaborative global epidemiological studies, inclusive of LMICs, are needed for rare tumors.

Epidemiology of common predisposing syndromes and their risk of WT

(Epi)genetic factors play an important role in the pathogenesis of WT. In a Dutch study, epigenetic factors were identified in 33% of children with WT⁽⁵⁴⁾, with additional predisposition genes possibly remaining to be identified.⁽⁵⁴⁻⁵⁷⁾ Only 1-2% of WTs are familial with a large contribution of *de novo* (epi)genetic alterations.^(8, 58, 59)

In Western populations, Beckwith-Wiedemann spectrum (BWSp) is the most frequently diagnosed WT predisposition syndrome, effecting 1 in 10,500 children.⁽⁶⁰⁾ (Table 3)^(55,57,61-112) BWSp is caused by genetic and/or epigenetic changes at the 11p15.5 imprinted region, which are frequently mosaic. Standard diagnostic tests do not detect low-level mosaic aberrations and clinical features can be subtle, risking missed diagnoses. The risk of WT depends on the molecular subtype, ranging from ~0.2% for patients with maternal IC2 loss of methylation to ~21% in patients with gain of methylation at the maternal IC1 locus. With paternal uniparental disomy of 11p15.5, the cumulative WT risk is estimated to be ~8%.⁽⁷⁰⁾ In a Dutch cohort of children with WT, which included mosaic and clinical diagnoses, BWSp was identified in 16% of patients.⁽⁵⁴⁾

The overall prevalence of *WT1* aberrations in the general population is unknown, with fewer than 500 effected individuals reported worldwide.⁽¹¹³⁾ The risk of WT can range from ~2% in patients with variants located in the intron 9 region, to >50% in patients with truncating variants or deletions, including children with WAGR syndrome.⁽¹¹⁴⁾ Germline *WT1* aberrations account for 2-11% of all WT cases.⁽¹¹⁵⁻¹¹⁸⁾ Other syndromes have been associated with an increased risk of WT development and genomic sequencing studies identified additional WT predisposition genes such as *TRIM28*, *CTR9* and *REST*, that each account for ≤1% of WT cases.^(55,79,81,83,86)

Global differences in WT predisposing factors

Global differences in the prevalence of predisposing factors have been identified for WT patients, but epidemiological data are limited and difficult to compare. In different settings, germline genetic testing varies in availability.⁽⁸⁴⁾ Moreover, the extent of genetic testing ranges from targeted to genome-wide approaches.⁽⁵⁵⁾ Although confirmation is needed, the prevalence of BWSp among Japanese children with WT appears to be lower (0/13 patients with bilateral WT, all with 11p15.5 tumor aberrations) compared to Western populations.⁽¹¹⁹⁾ A higher prevalence of cancer predisposition syndromes in Black patients in the U.S. has been suggested as one reason for higher WT incidence.⁽¹²⁰⁾ Germline testing is not readily accessible in LMIC countries. Future studies implementing this testing would likely help with screening and earlier cancer diagnoses.

Global differences in WT specimens

Despite the lack of global germline genetic data, (epi)genetic and peptide studies have demonstrated global differences in WT specimens. In accordance with the lower prevalence of BWSp, 11p15.5 epimutations were identified as much less common in WTs from Japanese children compared to children from Western countries or New Zealand.^(121,122) Libes et al evaluated molecular disparities between WT of different race groups from the COG biobank and Kenyan WT specimen bank.⁽¹²³⁾ Using imaging mass spectrometry,

different peptide profiles were identified for black and white children in the U.S., although these were more similar than those of Kenyan children. This might explain the disparate incidences and biological behavior of the tumors and may also identify novel therapeutic targets. In a study of genetic and chromosomal alterations in Kenyan tumors, 25% of specimens had *TP53* mutations, 23% had *CTNNB1* mutations, 18% had *MYCN* mutations, 11% had *AMER1* mutations, 9% had *WT1* and *TOP2A* mutations and 7% had *IGF2* mutations. Copy number gain of 1q was detected in 32% of tumors and LOH at 11q was found in 32% of tumors.⁽¹²⁴⁾ Three of 11 tumors with *TP53* mutations had unfavorable histology. Given how advanced the disease often is prior to presentation, this raises the question of whether peptide profiles and genetic mutations change over time or are reflective of true differences in original tumor biology. Due to concurrent illness, malnutrition and drug toxicity resulting in on-therapy mortality, late presentation and treatment abandonment, biology is difficult to correlate with treatment outcomes in LMICs.

Predisposing factors in non-Wilms renal tumors

(Epi)genetic predisposing factors have not been well characterized for most non-Wilms pediatric renal tumors except MRTK, which is strongly associated with pathogenic germline variants in the *SMARCB1* gene, and to a lesser extent the *SMARCA4* gene.⁽¹²⁵⁾ Cystic nephromas and anaplastic sarcoma of the kidney are associated with pathogenic germline variants in the *DICER1* gene, which predispose to various benign and malignant tumors.⁽¹²⁶⁾ The childhood onset of RCC warrants genetic evaluation.⁽¹²⁷⁾ Although most RCCs in children are MIT-family translocation-type RCCs which are typically sporadic, the diagnosis of rare RCC subtypes should trigger awareness for an underlying syndrome.⁽¹²⁸⁻¹²⁹⁾ The most common RCC-associated syndromes, including hereditary leiomyomatosis, von Hippel-Lindau disease and Birt-Hogg-Dube syndrome, typically predispose to adult-onset RCC and are well defined as a rare cause of RCC in children. General cancer predisposition syndromes may also present in children.⁽¹³⁰⁾ Renal medullary carcinomas are almost

exclusively reported in patients with sickle cell trait.⁽⁵¹⁾ Mesoblastic nephroma, CCSK and other rare renal tumor types have not been clearly associated with predisposing factors.

Discussion

Great advances have been made in the understanding and treatment of renal tumors in children, but several challenges remain, including global discrepancies in advances in care. HICs have benefited from over 50 years of consortium research resulting in large cancer registries and specimen banks. Cancer control studies have identified risk groups, predisposition syndromes, and genetic and epigenetic factors allowing for targeted risk-based therapy and improved outcomes. However, groups of patients with EFS below 75% still exist. These are rare tumors that are difficult to study. One method to overcome this barrier is to conduct international studies, which would require datapoints and definitions to be the same.

The two largest research consortiums, SIOP and COG, have definition differences, such as the pathological definition of stage I WT. Efforts are underway to bridge the differences and allow future international research collaborations. The Pediatric Cancer Data Commons project is applying uniform clinical data standards, collection, and linkage of data from different sources. The Benchmarking International Survival by Toronto stage initiative, BENCHISTA, aims to retrospectively use the Toronto guidelines to collect stage at diagnosis and outcomes of 6 tumors to allow international benchmarking of population – based childhood survival. This project is designed to help maximise the availability, standardization and comparability of cancer staging internationally.⁽¹³¹⁾

Other potential opportunities include: 1. Development of low-cost tests and larger biomarker validation studies to standardize use of biomarkers LOH and 1 q gain. 2. Larger epigenetic studies are needed to advance our knowledge of etiology and outcomes. 3. Larger studies are needed to confirm suggested findings that use of circulating tumor DNA is promising for WT.⁽¹³²⁾ This could potentially help distinguish pathological subtypes, cancerous from non-

cancerous lesions, and nephrogenic rests from tumors. This would be particularly helpful for children with BWT.

Children in LMICs have not fully benefited from advances in renal tumor care due to issues including political instability, late diagnoses, difficulty accessing care, inexperienced and/or improperly trained healthcare providers and non-inclusive healthcare systems. Outside of North America, Europe, and Japan, renal tumor specific registries are rare, but needed to improve cancer control. India has recently developed a national renal tumors committee to run studies which may lead to substantial advances. Consistent access to high quality multi-modal care is also needed. Central review of tumors with feedback and training for pathologists, tumor board reviews and continued efforts to reduce treatment abandonment and mortality would all contribute to higher survival rates for patients in LMICs. Survival on Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA), Groupe Franco-Africain d'Oncologie Pédiatrique (GFAOP) and African WT collaborative studies is improving, but would likely improve further with development of specimen banks, germline genetic testing, tumor genetic testing and screening to assess epi-clinical correlations and clinical nuances (racial, ethnic, pharmacogenomic). Finally, global tissue banks and registries would not only help LMICs but would provide valuable racial and ethnic data that has the potential to guide therapy in HICs as well.

Future epidemiological studies of children with renal tumors will benefit from more international collaboration, standardization, and data sharing, especially for those with poor EFS and OS.

Conflicts of Interest

None of the authors have any conflicts of interest to report.

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TABLE 1 Renal Tumor ASR¹ per million person years for children aged 0-14

Region	ASR
Globally	8.3
Sub-Saharan Africa	6.7-10.9
North America	9.1-9.8
Europe	9.1-9.8
Central and South America and the Caribbean	6.7
Brazil	8.4
Asia	4.1-5.4
West Asia	6.7
Ethnicity in the U.S.	
Black	10.9
White	9.9
Hispanic	7.4
Native American	5.7
Asian and Pacific Islanders	4.4

¹ Age-standardized incidence rates

TABLE I2. Stage and pathology at nephrectomy for unilateral FH² Wilms tumor for SIOP³ and COG⁴

SIOP	SIOP 93 and 2001	COG	COG (ARENO studies)
Stage I	45.5%	Stage I	22.6%
Low Risk	6%	Favorable Histology	21%
Intermediate Risk	84%	Diffuse Anaplasia	1.6%
High Risk	10%		
Stage II	22.6%	Stage II	25.4%
Low Risk	0.8%	Favorable Histology	24%
Intermediate Risk	83.8%	Diffuse Anaplasia	1.4%
High Risk	15.4%		
Stage III	16.9%	Stage III	35.5%
Low Risk	3.4%	Favorable Histology	33%
Intermediate Risk	75.8%	Diffuse Anaplasia	2.5%
High Risk	20.8%		
Stage IV	15.2%	Stage IV	24.2%
Low Risk	11.6%	Favorable Histology	22%
Intermediate Risk	74.1%	Diffuse Anaplasia	2.2%
High Risk	14.3%		
LOH loss 1p16q	NA	Stage I and II LOH loss 1p16q	4.27%

² Favorable histology

³ International Society of Pediatric Oncology - All SIOP patients over 7 months receive neoadjuvant therapy first. The stage and pathology are determined after neoadjuvant therapy and surgery.

⁴ Children's Oncology Group - Most COG patients undergo primary nephrectomy where stage and pathology are then determined.

LOH loss 1p16q	NA	Stage III and IV LOH loss 1p16 q	6.01%
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Table 3. Currently identified WT⁵ predisposition genes.

Gene ⁶	References	Syndrome(s)	Inheritance	Estimated WT risk
<i>WT1</i>	[1-9]	- Denys-Drash / Frasier syndrome: now referred to as <i>WT1</i> disorders. WT may be the first or only manifestation in children with germline <i>WT1</i> variants. - WAGR ⁷ syndrome (11p13 deletion including <i>WT1</i> and <i>PAX6</i>).	AD ⁸	~50-80% ⁹
<i>H19/IGF2</i>	[10-12]	Beckwith-Wiedemann spectrum	Postzygotic	<1%-21% ¹⁰
<i>DIS3L2</i>	[13-15]	Perlman syndrome	AR ¹¹	~64%
<i>PIK3CA</i>	[16, 17]	<i>PIK3CA</i> -related overgrowth spectrum	Postzygotic	1-5%
<i>GPC3</i>	[18]	Simpson-Golabi Behmel syndrome	X-linked	~3%
<i>TRIM28</i>	[19-23]	<i>TRIM28</i> -related WT predisposition	AD	>50%
<i>REST</i>	[24-26]	<i>REST</i> -related WT predisposition	AD	>50%
<i>CTR9</i>	[27, 28]	<i>CTR9</i> -related WT predisposition	AD	Appears high
<i>NYNRIN</i>	[19]	<i>NYNRIN</i> -related WT predisposition	AR	Unknown
<i>BRCA2</i>	[29-33]	Fanconi anemia type D1	AR	~20%
<i>PALB2</i>	[29-33]	Fanconi anemia type N	AR	~40%
<i>TRIM37</i>	[34, 35]	Mulibrey Nanism	AR	~6-8%
<i>BUB1B</i>	[36-38]	MVA ¹²	AR	~50%
<i>TRIP13</i>		MVA ⁸	AR	~20%
<i>MYCN</i>	[39-41]	2p24.3 duplication syndrome	AD	Unknown
<i>AMER1</i>	[42-44]	Osteopathia striata with cranial sclerosis	X-linked	Appears >5%
<i>BLM</i>	[45]	Bloom syndrome	AR	~3%
<i>DICER1</i>	[46-48]	<i>DICER1</i> syndrome	AD	<2%

⁵ Wilms tumor

⁶ Genes with somatic WT driver variants are included in this table if such variants were reported in more than one publication, or at least three times in a single publication.

⁷ Wilms tumor, aniridia, genitourinary anomalies and range of developmental delays

⁸ Autosomal dominant

⁹ Estimated WT risk depends on the location of the variant. *WT1* intron 9 variants are associated with low WT risk.

¹⁰ Estimated WT risk depends on the molecular subtype.

¹¹ Autosomal recessive

¹² Mosaic variegated aneuploidy

<i>TP53</i>	[46, 49]	Li Fraumeni syndrome	AD	Low
<i>NF1</i>	[50]	Neurofibromatosis type 1	AD	<1%
<i>CDC73</i>	[51, 52]	Hyperparathyroidism-jaw tumor syndrome	AD	<5%
<i>ASXL1</i>	[53, 54]	Bohring-Opitz syndrome	AD	~7%

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