Received: 31 July 2022 | Revised: 28 August 2022 | Accepted: 29 August 2022

DOI: 10.1002/pbc.30343

Pediatric Blood & Cancer | SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY | aspho The American Society of Pediatric Hematology/Oncology | WILEY

SPECIAL REPORT

Pediatric renal tumor epidemiology: Global perspectives, progress, and challenges

Jaime Libes[1] | Janna Hol[2] | Joaquim Caetano de Aguirre Neto[3] | Kelly L. Vallance[4] | Harm van Tinteren[2] | Daniel J. Benedetti[5] | Gema Lucia Ramirez Villar[6] | Catriona Duncan[7] | Peter F. Ehrlich[8]

[1]Department of Pediatrics, University of Illinois College of Medicine, Peoria, Illinois, USA

[2]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

[3]Department of Oncology, Hospital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil

[4]Hematology and Oncology, Cook Children's Medical Center, Fort Worth, Texas, USA

[5]Department of Pediatrics, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[6]Hospital Universitario Virgen del Rocio, Pediatric Oncology Unit, University of Seville, Seville, Spain

[7]Great Ormond Street Hospital for Children (GOSH), NHS Foundation Trust, NIHR, Great Ormond Street Hospital Biomedical Research Centre, London, UK

[8]Department of Pediatric Surgery, C.S. Mott Children's Hospital, University of Michigan School of Public Health, Ann Arbor, Michigan, USA

Correspondence
Jaime Libes, Division of Pediatric Hematology-Oncology, Department of Pediatrics, University of Illinois College of Medicine, 530 NE Glen Oak Ave, Peoria, IL 61615, USA.
Email: libesjm@uic.edu

Article also appears in Pediatr Blood Cancer. 2023:70:e30006
https://doi.org/10.1002/pbc.30006

Jaime Libes and Janna Hol are co-first authors and Catriona Duncan and Peter Ehrlich are co-senior authors.

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-incomes countries.

KEYWORDS
clear cell sarcoma of kidney, epidemiology, global, pediatric renal cell carcinoma, rhabdoid tumor, Wilms tumor

1 | INTRODUCTION: EPIDEMIOLOGY OF RENAL TUMORS

Renal tumors constitute 3.2%–11.1% 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.

Abbreviations: ASR, age-standardized incidence rates; AWT, anaplastic Wilms tumor; 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; 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; OS, overall survival; RCC, renal cell carcinoma; RMC, renal medullary carcinoma; RTSG, Renal Tumor Study Group; SIOP, International Society of Pediatric Oncology; WAGR, Wilms tumor aniridia syndrome; WT, Wilms tumor.

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 United States 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 to 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.

2 | 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 are sparse, single-institution studies were included. These data were evaluated to identify knowledge gaps that, if resolved, may improve future survival outcomes.

TABLE 1 Renal tumor ASR per million person-years for children aged 0–14 years

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 United States	
Black	10.9
White	9.9
Hispanic	7.4
Native American	5.7
Asian and Pacific Islanders	4.4

Abbreviation: ASR, age-standardized incidence rates.

3 | RESULTS

3.1 | Wilms tumor

WT demonstrates significant ethnic diversity that parallels that of overall renal tumors, with the highest incidence in African and US 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 males with a peak incidence at 1 year compared to a 1–3-year peak for females.[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. Among the large clinical trial groups, SIOP stages after neoadjuvant chemotherapy and surgery, while COG stages after upfront nephrectomy. On the SIOP WT 2001 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, Ireland, Australia, and New Zealand).[12]

On the SIOP 93 and 2001 treatment protocols, 45.5% of patients had stage I disease, 22.6% stage II, and 16.9% stage III after preoperative chemotherapy, and 15.2% had stage IV.[13–15] Five percent to 8% of patients on SIOP protocols have BWT.[16,17] Postoperative 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 SIOP. Of 586 patients on the SIOP 2001 WT trial with stage I–IV disease, 167 (28%) had 1q gain, similar to the COG/National Wilms Tumor Study (NWTSG) studies. The 1q gain was a negative biomarker with an event-free survival (EFS) of 75.0% (95% CI: 68.5%–82.0%) versus 88.2% in patients without gain (95% CI: 85.0%–91.4%).[19] SIOP does not use combined loss of heterozygosity (LOH) 1p/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 1147 patients with stage I/II WT (4.27%), and 82 of 1364 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

TABLE 2 Stage and pathology at nephrectomy for unilateral favorable histology Wilms tumor for SIOP[a] and COG[b]

SIOP	SIOP 93 and 2001	COG	COG (AREN0 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%
LOH loss 1p16q	NA	Stage III and IV LOH loss 1p16 q	6.01%

[a]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.
[b]Children's Oncology Group: Most COG patients undergo primary nephrectomy where stage and pathology are then determined.

AREN0321, there were 18 patients with stage I AWT (eight 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 extrapulmonary 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 (NWTS4 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 ARENO533 and evaluation of those with hepatic metastases is pending. Of 1114 patients enrolled on NWTS5, 28% had 1q gain, with an 8-year EFS of 77% compared to 90% for those without ($p < .001$). On the upcoming COG studies, 1q 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, nine had hemi-hypertrophy, seven Beckwith–Wiedemann spectrum (BWSp), six Wilms tumor aniridia syndrome (WAGR) syndrome, three Denys Drash syndrome, and 16 isolated anomalies. Of 189 total evaluable patients with BWT, 26 had at least one kidney with AWT (nine 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% 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, postsurgical SIOP staging demonstrated 21 stage I, four stage II, six 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 healthcare 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 healthcare system. In the United Kingdom, 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]

3.2 | Malignant rhabdoid tumors of kidney

Malignant rhabdoid tumors of kidney (MRTK) 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 = .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 are sparse from LMICs, in one retrospective report from sub-Saharan Africa, 80% of patients presented with stage III–IV disease.[39,40]

3.3 | Clear cell sarcoma of kidney

Clear cell sarcoma of kidney (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 NWTS5, 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 are 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]

3.4 | 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 United States, 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 United States 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 United States 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 United States, MiT-RCC and RMC both occur more frequently in the African American population compared to other ethnicities.[52,53] Incidence rates in LMICs are potentially influenced by underdiagnosis and/or underreporting. The incidence doubled worldwide from the 1970s to 2000s from 0.1 to 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 are 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 preoperative 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, make true evaluation of global and ethnic variation difficult. Collaborative global epidemiological studies, inclusive of LMICs, are needed for rare tumors.

TABLE 3 Currently identified WT predisposition genes

Gene[a]	References	Syndrome(s)	Inheritance	Estimated WT risk
WT1	61–69	Denys–Drash/Frasier syndrome: now referred to as *WT1* disorders. WT may be the first or only manifestation in children with germline *WT1* variants. WAGR[b] syndrome (11p13 deletion including *WT1* and PAX6)	AD	~50%–80%[c]
H19/IGF2	70–72	Beckwith–Wiedemann spectrum	Postzygotic	<1%–21%[d]
DIS3L2	73–75	Perlman syndrome	AR	~64%
PIK3CA	76,77	*PIK3CA*-related overgrowth spectrum	Postzygotic	1%–5%
GPC3	78	Simpson–Golabi Behmel syndrome	X-linked	~3%
TRIM28	55,79–82	*TRIM28*-related WT predisposition	AD	>50%
REST	83–85	*REST*-related WT predisposition	AD	>50%
CTR9	86,87	*CTR9*-related WT predisposition	AD	Appears high
NYNRIN	55	*NYNRIN*-related WT predisposition	AR	Unknown
BRCA2	88–92	Fanconi anemia type D1	AR	~20%
PALB2	88–92	Fanconi anemia type N	AR	~40%
TRIM37	93,94	Mulibrey nanism	AR	~6%–8%
BUB1B	95–97	MVA	AR	~50%
TRIP13		MVA	AR	~20%
MYCN	98–100	2p24.3 duplication syndrome	AD	Unknown
AMER1	101–103	Osteopathia striata with cranial sclerosis	X-linked	Appears >5%
BLM	104	Bloom syndrome	AR	~3%
DICER1	57,105,106	DICER1 syndrome	AD	<2%
TP53	57,107	Li–Fraumeni syndrome	AD	Low
NF1	108	Neurofibromatosis type 1	AD	<1%
CDC73	109,110	Hyperparathyroidism-jaw tumor syndrome	AD	<5%
ASXL1	111,112	Bohring–Opitz syndrome	AD	~7%

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MVA, mosaic variegated aneuploidy; WT, Wilms tumor.

[a]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.

[b]Wilms tumor, aniridia, genitourinary anomalies and range of developmental delays.

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

[d]Estimated WT risk depends on the molecular subtype.

3.5 | 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, BWSp is the most frequently diagnosed WT predisposition syndrome, affecting one 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 regions, 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 affected 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]

3.6 | 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 BWT, all with 11p15.5 tumor aberrations) compared to Western populations.[119] A higher prevalence of cancer predisposition syndromes in Black patients in the United States 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.

3.7 | 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 United States, 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.

3.8 | 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] RMC 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.

4 | 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 six tumors to allow international benchmarking of population, based childhood survival. This project is designed to help maximize the availability, standardization, and comparability of cancer staging internationally.[131]

Other potential opportunities include: (a) development of low-cost tests and larger biomarker validation studies to standardize use of biomarkers LOH and 1q gain; (b) larger epigenetic studies are needed to advance our knowledge of etiology and outcomes; and (c) 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 noncancerous 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 are 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 multimodal 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.

ACKNOWLEDGMENTS

The authors would like to acknowledge HARMONICA, the joint initiative between the Children's Oncology Group Renal Tumor Committee and the International Society of Pediatric Oncology Renal Tumor Study Group. By combining efforts, we seek to find the best possible cures for global pediatric diseases for all children everywhere.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Jaime Libes https://orcid.org/0000-0001-5856-0180

REFERENCES

1. Nakata K, Colombet M, Stiller CA, Pritchard-Jones K, Steliarova-Foucher E, Contributors I. Incidence of childhood renal tumours: an international population-based study. *Int J Cancer*. 2020;147(12):3313-3327.
2. Qureshi SS, Bhagat M, Verma K, et al. Incidence, treatment, and outcomes of primary and recurrent non-Wilms renal tumors in children: report of 109 patients treated at a single institution. *J Pediatr Urol*. 2020;16(4):475.e1-475.e9.
3. Steliarova-Foucher E, Colombet M, Ries LAG, Hesseling P, Moreno F, Shin HY, Stiller CA, eds. 2017. International Incidence of Childhood Cancer, Volume III (electronic version). Lyon, France: International Agency for Research on Cancer. Accessed November 12, 2020. Available from: http://iicc.iarc.fr/results/
4. de Camargo B, de Oliveira Ferreira JM, de Souza Reis R, Ferman S, de Oliveira Santos M, Pombo-de-Oliveira MS. Socioeconomic status and the incidence of non-central nervous system childhood embryonic tumours in Brazil. *BMC Cancer*. 2011;11:160.
5. Stiller CA, Parkin DM. International variations in the incidence of childhood renal tumours. *Br J Cancer*. 1990;62(6):1026-1030.
6. Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms tumor. *Med Pediatr Oncol*. 1993;21:172-181.
7. Chu A, Heck JE, Ribeiro KB, et al. Wilms' tumour: a systematic review of risk factors and meta-analysis. *Paediatr Perinat Epidemiol*. 2010;24(5):449-469.
8. Scott RH, Stiller CA, Walker L, Rahman N. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. *J Med Genet*. 2006;43(9):705-715.
9. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. *Lancet Oncol*. 2019;20(4):483-493.
10. Coppes MJ, de Kraker J, van Dijken PJ. Bilateral Wilms' tumor: long-term survival and some epidemiological features. *J Clin Oncol*. 1989;7(3):310-315.
11. Dome JS, Mullen EA, Dix DB, et al. Impact of the first generation of Children's Oncology Group clinical trials on clinical practice for Wilms tumor. *J Natl Compr Canc Netw*. 2021;19(8):978-985.
12. de Aguirre-Neto JC, de Camargo B, van Tinteren H, et al. International comparisons of clinical demographics and outcomes in the International Society of Pediatric Oncology Wilms Tumor 2001 Trial and Study. *JCO Glob Oncol*. 2022;8:e2100425.
13. Hol JA, Lopez-Yurda MI, Van Tinteren H, et al. Prognostic significance of age in 5631 patients with Wilms tumour prospectively registered in International Society of Paediatric Oncology (SIOP) 93-01 and 2001. *PLoS One*. 2019;14(8):e0221373.
14. Reinhard H, Semler O, Bürger D, et al. Results of the SIOP 93-01/GPOH trial and study for the treatment of patients with unilateral nonmetastatic Wilms tumor. *Klin Padiatr*. 2004;216(3):132-140.
15. Pasqualini C, Furtwangler R, van Tinteren H, et al. Outcome of patients with stage IV high-risk Wilms tumour treated according to the SIOP2001 protocol: a report of the SIOP Renal Tumour Study Group. *Eur J Cancer*. 2020;128:38-46.
16. van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, et al. Position paper: rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. *Nat Rev Urol*. 2017;14(12):743-752.
17. van Peer SE, Hol JA, van der Steeg AFW, et al. Bilateral renal tumors in children: the first 5 years' experience of national centralization in the Netherlands and a narrative review of the literature. *J Clin Med*. 2021;10(23):5558.
18. Hol J, Lopez-Yurda M, Van Tinteren HI, et al. Prognostic significance of age in 5631 patients with Wilms tumour prospectively registered in International Society of Paediatric Oncology (SIOP) 93-01 and 2001. *PLoS One*. 2019;14(8):e0221373.
19. Chagtai T, Zill C, Dainese L, et al. Gain of 1q as a prognostic biomarker in Wilms tumors (WTs) treated with preoperative chemotherapy in the International Society of Paediatric Oncology (SIOP) WT 2001 trial: a SIOP Renal Tumours Biology Consortium Study. *J Clin Oncol*. 2016;34(26):3195-3203.
20. Dix DB, Fernandez CV, Chi YY, et al. Augmentation of therapy for favorable-histology Wilms tumor with combined loss of heterozygosity of chromosomes 1p and 16q: a report from the Children's Oncology Group studies AREN0532 and AREN0533. *J Clin Oncol*. 2015;33(s):1009.
21. Daw NC, Chi YY, Kalapurakal JA, et al. Activity of vincristine and irinotecan in diffuse anaplastic Wilms tumor and therapy outcomes of stage II to IV disease: results of the Children's Oncology Group AREN0321 study. *J Clin Oncol*. 2020;38(14):1558-1568.
22. Daw NC, Chi YY, Kim Y, et al. Treatment of stage I anaplastic Wilms' tumour: a report from the Children's Oncology Group AREN0321 study. *Eur J Cancer*. 2019;118:58-66.
23. Fernandez CV, Mullen EA, Chi YY, et al. Outcome and prognostic factors in stage III favorable-histology Wilms tumor: a report from the Children's Oncology Group study AREN0532. *J Clin Oncol*. 2018;36(3):254-261.
24. Dix DB, Gratias EJ, Seibel NL, et al. Treatment of stage IV favorable histology Wilms tumor with incomplete lung metastasis response after chemotherapy: a report from Children's Oncology Group study AREN0533. *J Clin Oncol*. 2014;32(15s):10001.
25. Dome J, Mullen E, Dix D, et al. Impact of the first generation of Children's Oncology Group clinical trials on clinical practice for Wilms tumor. *J Natl Compr Canc Netw*. 2021;19(8):978-985.

26. Ehrlich PF, Ferrer F, Ritchey ML, et al. Hepatic metastasis at diagnosis in patients with Wilms tumor is not an independent adverse prognostic factor for stage V Wilms tumor. A report from the Childrens Oncology Group/National Wilms Tumor Study group. *Ann Surg*. 2009;250:642-648.
27. Gratias EJ, JS D, Jennings LJ, et al. Association of chromosome 1q gain with inferior survival in favorable histology Wilms tumor: a report from the Children's Oncology Group. *J Clin Oncol*. 2016;34(26):3189-3194.
28. Ehrlich P, Chi YY, Chintagumpala MM, et al. Results of the first prospective multi–institutional treatment study in children with bilateral Wilms tumor (AREN0534): a report from the Children's Oncology Group. *Ann Surg*. 2017;266(3):470-478.
29. Ehrlich PF, Chi YY, Chintagumpala MM, et al. Results of treatment for patients with multicentric or bilaterally predisposed unilateral Wilms tumor (AREN0534): a report from the Children's Oncology Group. *Cancer*. 2020;126(15):3516-3525.
30. Chagaluka G, Paintsil V, Renner L, et al. Improvement of overall survival in the Collaborative Wilms Tumour Africa Project. *Pediatr Blood Cancer*. 2020;67(9):e28383.
31. Axt J, Abdallah F, Axt M, et al. Wilms tumor survival in Kenya. *J Pediatr Surg*. 2013;48(6):1254-1262.
32. Libes J, Oruko O, Abdallah F, et al. Risk factors for abandonment of Wilms tumor therapy in Kenya. *Pediatr Blood Cancer*. 2015;62(2):252-256.
33. Davidson A, Hartley P, Desai F, Daubenton J, Rode H, Millar A. Wilms tumour experience in a South African centre. *Pediatr Blood Cancer*. 2006;46(4):465-471.
34. Valverde P. An analysis of treatment failure in Wilms tumor (WT): a report from the Central American Association of Pediatric Hematology/Oncology (AHOPCA). *J Global Oncol*. 2016;2(2):2s.
35. Pritchard-Jones K, Graf N, van TH, Craft A. Evidence for a delay in diagnosis of Wilms' tumour in the UK compared with Germany: implications for primary care for children. *Arch Dis Child*. 2016;101(5):417-420.
36. Vujanic G, Sandstedt B, Harms D. Rhabdoid tumour of the kidney: a clinicopathological study of 22 patients from the International Society of Paediatric Oncology (SIOP) nephroblastoma file. *Histopathology*. 1996;28:333-340.
37. Geller JI. Current standards of care and future directions for "high-risk" pediatric renal tumors: anaplastic Wilms tumor and rhabdoid tumor. *Urol Oncol*. 2016;34(1):50-56.
38. van den Heuvel-Eibrink MM, van Tinteren H, Rehorst H, et al. Malignant rhabdoid tumours of the kidney (MRTKs), registered on recent SIOP protocols from 1993 to 2005: a report of the SIOP renal tumour study group. *Pediatr Blood Cancer*. 2011;56(5):733-737.
39. Koshinaga T, Takimoto T, Oue T, et al. Outcome of renal tumors registered in Japan Wilms Tumor Study-2 (JWiTS-2): a report from the Japan Children's Cancer Group (JCCG). *Pediatr Blood Cancer*. 2018;65(7):e27056.
40. Saula PW, Hadley GP. Pediatric non-Wilms' renal tumors: a third world experience. *World J Surg*. 2012;36(3):565-572.
41. Argani P, Perlman EJ, Breslow N. Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms' Tumour Study Pathology Center. *Am J Surg Pathol*. 2000;24:4-18.
42. Gooskens SL, Furtwangler R, Vujanic GM, Dome JS, Graf N, van den Heuvel-Eibrink MM. Clear cell sarcoma of the kidney: a review. *Eur J Cancer*. 2012;48(14):2219-2226.
43. Gooskens SL, Graf N, Furtwangler R, et al. Position paper: rationale for the treatment of children with CCSK in the UMBRELLA SIOP-RTSG 2016 protocol. *Nat Rev Urol*. 2018;15(5):309-319.
44. Seibel NL, Chi YY, Perlman EJ, et al. Impact of cyclophosphamide and etoposide on outcome of clear cell sarcoma of the kidney treated on the National Wilms Tumor Study-5 (NWTS-5). *Pediatr Blood Cancer*. 2019;66(1):e27450.
45. Furtwangler R, Gooskens SL, van Tinteren H, et al. Clear cell sarcomas of the kidney registered on International Society of Pediatric Oncology (SIOP) 93-01 and SIOP 2001 protocols: a report of the SIOP Renal Tumour Study Group. *Eur J Cancer*. 2013;49(16):3497-3506.
46. Spreafico F, Gandola L, Melchionda F. Stage I clear cell sarcoma of the kidney: is it the time for a less intensive adjuvant treatment? *Transl Pediatr*. 2014;3(1):1-3. https://doi.org/10.3978/j.issn.2224-4336.2013.12.03
47. Geller JI, Ehrlich PF, Cost NG, et al. Characterization of adolescent and pediatric renal cell carcinoma: a report from the Children's Oncology Group study AREN03B2. *Cancer*. 2015;121(14):2457-2464.
48. van der Beek JN, Geller JI, de Krijger RR, et al. Characteristics and outcome of children with renal cell carcinoma: a narrative review. *Cancers (Basel)*. 2020;12(7):1776.
49. van der Beek J, Hol J, Coulomb-l'Hermine A, et al. Characteristics and outcome of pediatric renal cell carcinoma patients registered in the International Society of Pediatric Oncology (SIOP) 93-01, 2001 and UK-IMPORT database: a report of the SIOP-Renal Tumor Study Group. *Int J Cancer*. 2021;148:2724-2735.
50. Davis CJ, Mostofi FK, Sesterhenn IA. Renal medullary carcinoma. The seventh sickle cell nephropathy. *Am J Surg Pathol*. 1995;19:1-11.
51. Alvarez O, Rodriguez MM, Jordan L, Sarnaik S. Renal medullary carcinoma and sickle cell trait: a systematic review. *Pediatr Blood Cancer*. 2015;62(10):1694-1699.
52. Rao Q, Chen JY, Wang JD, et al. Renal cell carcinoma in children and young adults: clinicopathological, immunohistochemical, and VHL gene analysis of 46 cases with follow-up. *Int J Surg Pathol*. 2011;19(2):170-179.
53. Geller JI, Argani P, Adeniran A, et al. Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. *Cancer*. 2008;112(7):1607-1616.
54. Hol JA, Kuiper RP, van Dijk F, et al. Prevalence of (epi)genetic predisposing factors in a 5-year unselected National Wilms Tumor Cohort: a comprehensive clinical and genomic characterization. *J Clin Oncol*. 2022;40(17):1892-1902.
55. Mahamdallie S, Yost S, Poyastro-Pearson E, et al. Identification of new Wilms tumour predisposition genes: an exome sequencing study. *Lancet Child Adolesc Health*. 2019;3(5):322-331.
56. Treger TD, Chowdhury T, Pritchard-Jones K, Behjati S. The genetic changes of Wilms tumour. *Nat Rev Nephrol*. 2019;15(4):240-251.
57. Maciaszek JL, Oak N, Nichols KE. Recent advances in Wilms' tumor predisposition. *Hum Mol Genet*. 2020;29(R2):R138.
58. Ruteshouser EC, Huff V. Familial Wilms tumor. *Am J Med Genet C Semin Med Genet*. 2004;129C(1):29-34.
59. Rahman N, Arbour L, Tonin P. Evidence for a familial Wilms' tumour gene (FWT1) on chromosome 17q12-q21. *Nat Genet*. 1996;13:461-463.
60. Mussa A, Russo S, De Crescenzo A, et al. Prevalence of Beckwith–Wiedemann syndrome in North West of Italy. *Am J Med Genet A*. 2013;161A(10):2481-2486.
61. Chernin G, Vega-Warner V, Schoeb DS, et al. Genotype/phenotype correlation in nephrotic syndrome caused by WT1 mutations. *Clin J Am Soc Nephrol*. 2010;5(9):1655-1662.
62. Köhler B, Biebermann H, Friedsam V, et al. Analysis of the Wilms' tumor suppressor gene (WT1) in patients 46,XY disorders of sex development. *J Clin Endocrinol Metab*. 2011;96(7):E1131-E1136.
63. Lipska BS, Ranchin B, Iatropoulos P, et al. Genotype-phenotype associations in WT1 glomerulopathy. *Kidney Int*. 2014;85(5):1169-1178.
64. Lehnhardt A, Karnatz C, Ahlenstiel-Grunow T, et al. Clinical and molecular characterization of patients with heterozygous mutations in Wilms tumor suppressor gene 1. *Clin J Am Soc Nephrol*. 2015;10(5):825-831.

65. Sun S, Xu L, Bi Y, et al. Early diagnosis of WT1 nephropathy and follow up in a Chinese multicenter cohort. *Eur J Med Genet*. 2020;63(11):104047.
66. Muto R, Yamamori S, Ohashi H, Osawa M. Prediction by FISH analysis of the occurrence of Wilms tumor in aniridia patients. *Am J Med Genet*. 2002;108(4):285-289.
67. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. WAGR syndrome: a clinical review of 54 cases. *Pediatrics*. 2005;116(4):984-988.
68. van Heyningen V, Hoovers JM, de Kraker J, Crolla JA. Raised risk of Wilms tumour in patients with aniridia and submicroscopic WT1 deletion. *J Med Genet*. 2007;44(12):787-790.
69. Marakhonov AV, Vasilyeva TA, Voskresenskaya AA, et al. LMO2 gene deletions significantly worsen the prognosis of Wilms' tumor development in patients with WAGR syndrome. *Hum Mol Genet*. 2019;28(19):3323-3326.
70. Maas SM, Vansenne F, Kadouch DJ, et al. Phenotype, cancer risk, and surveillance in Beckwith–Wiedemann syndrome depending on molecular genetic subgroups. *Am J Med Genet A*. 2016;170(9):2248-2260.
71. Brioude F, Kalish JM, Mussa A, et al. Expert consensus document: clinical and molecular diagnosis, screening and management of Beckwith–Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol*. 2018;14(4):229-249.
72. Coktu S, Spix C, Kaiser M, et al. Cancer incidence and spectrum among children with genetically confirmed Beckwith+Wiedemann spectrum in Germany: a retrospective cohort study. *Br J Cancer*. 2020;123(4):619-623.
73. Perlman M, Goldberg GM, Bar-Ziv J, Danovitch G. Renal hamartomas and nephroblastomatosis with fetal gigantism: a familial syndrome. *J Pediatr*. 1973;83(3):414-418.
74. Henneveld HT, van Lingen RA, Hamel BC, Stolte-Dijkstra I, van Essen AJ. Perlman syndrome: four additional cases and review. *Am J Med Genet*. 1999;86(5):439-446.
75. Neri G, Martini-Neri ME, Katz BE, Opitz JM. The Perlman syndrome: familial renal dysplasia with Wilms tumor, fetal gigantism and multiple congenital anomalies. *Am J Med Genet*. 1984;19(1):195-207.
76. Postema FAM, Hopman SMJ, Deardorff MA, et al. Correspondence to Gripp et al. Nephroblastomatosis or Wilms tumor in a fourth patient with a somatic PIK3CA mutation. *Am J Med Genet A*. 2017;173(8):2293-2295.
77. Peterman CM, Fevurly RD, Alomari AI, et al. Sonographic screening for Wilms tumor in children with CLOVES syndrome. *Pediatr Blood Cancer*. 2017;64:e26684.
78. Brioude F, Toutain A, Giabicani E, Cottereau E, Cormier-Daire V, Netchine I. Overgrowth syndromes - clinical and molecular aspects and tumour risk. *Nat Rev Endocrinol*. 2019;15(5):299-311.
79. Halliday BJ, Fukuzawa R, Markie DM, et al. Germline mutations and somatic inactivation of TRIM28 in Wilms tumour. *PLoS Genet*. 2018;14(6):e1007399.
80. Armstrong AE, Gadd S, Huff V, Gerhard DS, Dome JS, Perlman EJ. A unique subset of low-risk Wilms tumors is characterized by loss of function of TRIM28 (KAP1), a gene critical in early renal development: a Children's Oncology Group study. *PLoS One*. 2018;13(12):e0208936.
81. Diets IJ, Hoyer J, Ekici AB, et al. TRIM28 haploinsufficiency predisposes to Wilms tumor. *Int J Cancer*. 2019;145(4):941-951.
82. Moore C, Monforte H, Teer JK, et al. TRIM28 congenital predisposition to Wilms' tumor: novel mutations and presentation in a sibling pair. *Cold Spring Harb Mol Case Stud*. 2020;6(4):a004796.
83. Mahamdallie SS, Hanks S, Karlin KL, et al. Mutations in the transcriptional repressor REST predispose to Wilms tumor. *Nat Genet*. 2015;47(12):1471-1474.
84. Cullinan N, Villani A, Mourad S, et al. An eHealth decision-support tool to prioritize referral practices for genetic evaluation of patients with Wilms tumor. *Int J Cancer*. 2020;146(4):1010-1017.
85. Hyder Z, Fairclough A, Groom M, et al. Constitutional de novo deletion CNV encompassing REST predisposes to diffuse hyperplastic perilobar nephroblastomatosis (HPLN). *J Med Genet*. 2021;58(9):581-585.
86. Hanks S, Perdeaux ER, Seal S, et al. Germline mutations in the PAF1 complex gene CTR9 predispose to Wilms tumour. *Nat Commun*. 2014;5:4398.
87. Martins AG, Pinto AT, Domingues R, Cavaco BM. Identification of a novel CTR9 germline mutation in a family with Wilms tumor. *Eur J Med Genet*. 2018;61(5):294-299.
88. Reid S, Renwick A, Seal S, et al. Biallelic BRCA2 mutations are associated with multiple malignancies in childhood including familial Wilms tumour. *J Med Genet*. 2005;42(2):147-151.
89. Reid S, Schindler D, Hanenberg H, et al. Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. *Nat Genet*. 2007;39(2):162-164.
90. Wagner JE, Tolar J, Levran O, et al. Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. *Blood*. 2004;103(8):3226-3229.
91. Alter BP, Rosenberg PS, Brody LC. Clinical and molecular features associated with biallelic mutations in FANCD1/BRCA2. *J Med Genet*. 2007;44(1):1-9. https://doi.org/10.1136/jmg.2006.043257
92. Xia B, Dorsman JC, Ameziane N, et al. Fanconi anemia is associated with a defect in the BRCA2 partner PALB2. *Nat Genet*. 2007;39(2):159-161.
93. Karlberg N, Karlberg S, Karikoski R, Mikkola S, Lipsanen-Nyman M, Jalanko H. High frequency of tumours in Mulibrey nanism. *J Pathol*. 2009;218(2):163-171.
94. Sivunen J, Karlberg S, Lohi J, Karlberg N, Lipsanen-Nyman M, Jalanko H. Renal findings in patients with Mulibrey nanism. *Pediatr Nephrol*. 2017;32(9):1531-1536.
95. Jacquemont S, Bocéno M, Rival JM, Méchinaud F, David A. High risk of malignancy in mosaic variegated aneuploidy syndrome. *Am J Med Genet*. 2002;109(1):17-21, discussion 16.
96. Hanks S, Coleman K, Reid S, et al. Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. *Nat Genet*. 2004;36(11):1159-1161.
97. Yost S, de Wolf B, Hanks S, et al. Biallelic TRIP13 mutations predispose to Wilms tumor and chromosome missegregation. *Nat Genet*. 2017;49(7):1148-1151.
98. Micale MA, Embrey B 4th, Macknis JK, Harper CE, Aughton DJ. Constitutional 560.49 kb chromosome 2p24.3 duplication including the MYCN gene identified by SNP chromosome microarray analysis in a child with multiple congenital anomalies and bilateral Wilms tumor. *Eur J Med Genet*. 2016;59(12):618-623.
99. Williams RD, Chagtai T, Alcaide-German M, et al. Multiple mechanisms of MYCN dysregulation in Wilms tumour. *Oncotarget*. 2015;6(9):7232-7243.
100. Fievet A, Belaud-Rotureau MA, Dugay F, et al. Involvement of germline DDX1-MYCN duplication in inherited nephroblastoma. *Eur J Med Genet*. 2013;56(12):643-647.
101. Bach A, Mi J, Hunter M, et al. Wilms tumor in patients with osteopathia striata with cranial sclerosis. *Eur J Hum Genet*. 2021;29(3):396-401.
102. Sperotto F, Bisogno G, Opocher E, et al. Osteopathia striata with cranial sclerosis and Wilms tumor: coincidence or consequence? *Clin Genet*. 2017;92(6):674-675.
103. Fukuzawa R, Holman SK, Chow CW, Savarirayan R, Reeve AE, Robertson SP. WTX mutations can occur both early and late in the pathogenesis of Wilms tumour. *J Med Genet*. 2010;47(11):791-794.
104. Cunniff C, Djavid AR, Carrubba S, et al. Health supervision for people with Bloom syndrome. *Am J Med Genet A*. 2018;176(9):1872-1881.

105. Foulkes WD, Bahubeshi A, Hamel N, et al. Extending the phenotypes associated with DICER1 mutations. *Hum Mutat*. 2011;32(12):1381-1384.
106. Khan NE, Ling A, Raske ME, et al. Structural renal abnormalities in the DICER1 syndrome: a family-based cohort study. *Pediatr Nephrol*. 2018;33(12):2281-2288.
107. Kratz CP, Achatz MI, Brugières L, et al. Cancer screening recommendations for individuals with Li–Fraumeni syndrome. *Clin Cancer Res*. 2017;23(11):e38-e45.
108. Stay EJ, Vawter G. The relationship between nephroblastoma and neurofibromatosis (Von Recklinghausen's disease). *Cancer*. 1977;39(6):2550-2555.
109. Szabó J, Heath B, Hill VM, et al. Hereditary hyperparathyroidism-jaw tumor syndrome: the endocrine tumor gene HRPT2 maps to chromosome 1q21-q31. *Am J Hum Genet*. 1995;56(4):944-950.
110. Kakinuma A, Morimoto I, Nakano Y, et al. Familial primary hyperparathyroidism complicated with Wilms' tumor. *Intern Med*. 1994;33(2):123-126.
111. Brunner HG, van Tintelen JP, de Boer RJ. Bohring syndrome. *Am J Med Genet*. 2000;92(5):366-368.
112. Russell B, Johnston JJ, Biesecker LG, et al. Clinical management of patients with ASXL1 mutations and Bohring–Opitz syndrome, emphasizing the need for Wilms tumor surveillance. *Am J Med Genet A*. 2015;167(9):2122-2131.
113. Lipska-Ziętkiewicz BS. In: Adam MP, ed. *GeneReviews. WT1 Disorder*. University of Washington; 1993.
114. Hol JA, Jewell R, Chowdhury T, et al. Wilms tumour surveillance in at-risk children: literature review and recommendations from the SIOP-Europe Host Genome Working Group and SIOP Renal Tumour Study Group. *Eur J Cancer*. 2021;153:51-63.
115. Huff V. Wilms tumor genetics. *Am J Med Genet*. 1998;79(4):260-267.
116. Diller L, Ghahremani M, Morgan J, et al. Constitutional WT1 mutations in Wilms' tumor patients. *J Clin Oncol*. 1998;16(11):3634-3640.
117. Segers H, Kersseboom R, Alders M, Pieters R, Wagner A, van den Heuvel-Eibrink MM. Frequency of WT1 and 11p15 constitutional aberrations and phenotypic correlation in childhood Wilms tumour patients. *Eur J Cancer*. 2012;48(17):3249-3256.
118. Wang H, Shen Y, Sun N, Jiang YP, Li ML, Sun L. Identification and analysis of mutations in WTX and WT1 genes in peripheral blood and tumor tissue of children with Wilms' tumor. *Chin Med J (Engl)*. 2012;125(10):1733-1739.
119. Kaneko Y, Okita H, Haruta M, et al. A high incidence of WT1 abnormality in bilateral Wilms tumours in Japan, and the penetrance rates in children with WT1 germline mutation. *Br J Cancer*. 2015;112(6):1121-1133.
120. Kramer S, Meadows AT, Jarrett P. Racial variation in incidence of Wilms' tumor: relationship to congenital anomalies. *Med Pediatr Oncol*. 1984;12(6):401-405.
121. Haruta M, Arai Y, Watanabe N, et al. Different incidences of epigenetic but not genetic abnormalities between Wilms tumors in Japanese and Caucasian children. *Cancer Sci*. 2012;103(6):1129-1135.
122. Fukuzawa R, Breslow NE, Morison IM, et al. Epigenetic differences between Wilms' tumours in white and East-Asian children. *Lancet*. 2004;363(9407):446-451.
123. Libes JM, Seeley EH, Li M, et al. Race disparities in peptide profiles of North American and Kenyan Wilms tumor specimens. *J Am Coll Surg*. 2014;218(4):707-720.
124. Lovvorn HN, 3rd, Pierce J, Libes J, et al. Genetic and chromosomal alterations in Kenyan Wilms tumor. *Genes Chromosomes Cancer*. 2015;54(11):702-715.
125. Nemes K. In: Adams MP, ed. *GeneReviews. Rhabdoid Tumor Predisposition Syndrome*. University of Washington; 1993.
126. Schultz KAP, Williams GM, Kamihara J, et al. DICER1 and associated conditions: identification of at-risk individuals and recommended surveillance strategies. *Clin Cancer Res*. 2018;24(10):2251-2261.
127. Jongmans MC, Loeffen JL, Waanders E, et al. Recognition of genetic predisposition in pediatric cancer patients: an easy-to-use selection tool. *Eur J Med Genet*. 2016;59(3):116-125.
128. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. *Fam Cancer*. 2014;13(4):637-644.
129. Kauffman EC, Ricketts CJ, Rais-Bahrami S, et al. Molecular genetics and cellular features of TFE3 and TFEB fusion kidney cancers. *Nat Rev Urol*. 2014;11(8):465-475.
130. Maher ER. Hereditary renal cell carcinoma syndromes: diagnosis, surveillance and management. *World J Urol*. 2018;36(12):1891-1898.
131. Pritchard-Jones K, Gatta G. Benchmarking International Survival by Toronto Stage Initiative. University College London; 2022. Accessed June 27, 2022. https://www.ucl.ac.uk/child-health/research/developmental-biology-and-cancer/benchista
132. Madanat-Harjuoja LM, Renfro LA, Klega K, et al. Circulating tumor DNA as a biomarker in patients with stage III and IV Wilms tumor: analysis from a Children's Oncology Group trial, AREN0533. *J Clin Oncol*. 2022;40(26):3047-3056.

How to cite this article: Libes J, Hol J, Neto JCA, et al. Pediatric renal tumor epidemiology: Global perspectives, progress, and challenges. *Pediatr Blood Cancer*. 2023; 70(Suppl. 2):e30343. https://doi.org/10.1002/pbc.30343