Wilms tumour

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Abstract | Wilms tumour (WT) is a childhood embryonal tumour that is paradigmatic of the intersection between disrupted organogenesis and tumorigenesis. Many WT genes play a critical (non-redundant) role in early nephrogenesis. Improving patient outcomes requires advances in understanding and targeting of the multiple genes and cellular control pathways now identified as active in WT development. Decades of clinical and basic research have helped to gradually optimize clinical care. Curative therapy is achievable in 90% of affected children, even those with disseminated disease, yet survival disparities within and between countries exist and deserve commitment to change. Updated epidemiological studies have also provided novel insights into global incidence variations. Introduction of biology-driven approaches to risk stratification and new drug development has been slower in WT than in other childhood tumours. Current prognostic classification for children with WT is grounded in clinical and pathological findings and in dedicated protocols on molecular alterations. Treatment includes conventional cytotoxic chemotherapy and surgery, and radiation therapy in some cases. Advanced imaging to capture tumour composition, optimizing irradiation techniques to reduce target volumes, and evaluation of newer surgical procedures are key areas for future research.

Nephron-sparing surgery
An operation to remove a kidney tumour by removing only part of the surrounding normal renal parenchyma.

Wilms tumour (WT) is the most common renal tumour of infants and young children^{1,2}. WT is intimately linked to early nephrogenesis, which it resembles morphologically³ and transcriptionally^{4,5}. WT may occur sporadically or in the context of bilateral tumours, multifocal disease and specified genetic predisposition syndromes that frequently include either genitourinary malformation or overgrowth³. Beyond genetic predisposition, external causative factors for WT are not yet defined. The molecular drivers frequently involve blockade of genetic pathways that guide normal embryogenesis of the genitourinary tract but are not restricted to these. Indeed, the cancer genes that underpin WT are diverse and surprisingly involve ~40 genes.

The implementation of international co-operative group trials and studies across North America, Australia, New Zealand, Europe and Brazil has contributed significantly to improving outcomes^{6–8}. Two international multidisciplinary cooperative consortia — the Children's Oncology Group (COG) Renal Tumour Committee, previously known as the National Wilms Tumour Study Group (NWTSG), and the International Society of Paediatric Oncology (SIOP) Renal Tumour Study Group (RTSG) — have conducted large multi-centre studies since 1969 and 1971, respectively, which have defined the current diagnostic and therapeutic

approach to patients with WT (FIG. 1). These groups continue research to optimize disease and patient risk classification and treatment strategies^{9–11}.

In the COG, WTs are treated with primary resection (if possible), followed by risk-adapted adjuvant therapy, whereas in the context of SIOP cooperation, neoadjuvant chemotherapy followed by resection and adjuvant therapy is the preferred treatment approach. Regardless of the initial approach, the overall survival of children with WT is remarkable with rates of >90%. Such satisfying survival rates have been achieved at the same time as fine-tuning treatment by adopting well-studied prognostic factors, leading to a two-drug regimen (vincristine and actinomycin D) prescribed in nearly two-thirds of affected children^{7,10}. Notably, striking survival disparities still exist within countries¹² and between different parts of the world, which remain to be addressed^{13,14}. However, 20% of patients relapse after first-line therapy and up to 25% of survivors report severe late morbidity of treatment^{15,16}. Addressing the long-term effect of radical nephrectomy on renal function and cardiovascular function will probably drive more attention on expanding the role of nephron-sparing surgery (NSS)¹⁷.

Molecular studies are expanding the landscape of cancer genes implicated in WT beyond exclusive roles in nephrogenesis³. The use of next-generation

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<https://doi.org/10.1038/s41572-021-00308-8>

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Nephrogenic rests

Abnormally persistent foci of embryonal cells regarded as precursor lesions of Wilms tumour. Rests are subdivided into two main types: perilobar, confined to the periphery of the renal lobe, and intralobar, found anywhere within the renal lobe.

Overgrowth syndromes

A heterogeneous group of disorders in which the main characteristic is that weight, height or head circumference is two to three standard deviations above the mean for sex and age. The different presentations are dependent on the developmental pathways and organ systems affected.

Aniridia

A rare condition characterized by a partial or complete absence of the iris of the eye.

Nephrotic syndrome

A rare clinical disorder defined by massive proteinuria (>40 mg/m² per hour) responsible for hypoalbuminaemia (<25 g/l), with resulting hyperlipidaemia, oedema, and various complications.

integrative genomic and epigenetic tumour analysis has provided important insights into WT biology. Comparisons of the regulation of progenitor cells in the fetal kidney with the disrupted regulation of their counterparts in WT should provide further insights into tumour formation¹⁸. Targeting WT tumour genes with a non-redundant role in nephrogenesis and targeting the fetal renal transcriptome warrant further therapeutic exploration. Interventions that could prevent the evolution of nephrogenic rests to malignant WT could transform therapy in this setting and could even lead to preventive strategies in children known to be at high risk of developing WT.

This Primer describes our current understanding of WT epidemiology, disease susceptibility and mechanisms, as well as elements of clinical care, including diagnostics and risk-stratified treatment of newly diagnosed disease. In addition, we also outline potential opportunities to further translate new biological insights into improved clinical outcomes. We discuss how the widespread implementation of standardized diagnostics and treatments for as many children as possible, regardless of socioeconomic status or geographical region of origin, may propel further clinical advances.

Epidemiology

Global disease burden

Malignant renal tumours comprise 5% of all cancers occurring before the age of 15 years¹⁹. Every year ~14,000 children (0–14 years of age) are diagnosed worldwide, and 5,000 children die from these diseases, with regional variation in mortality²⁰ (FIG. 2). The incidence of childhood renal tumours is not associated with economic status, but mortality is higher in low-income areas than high-income areas (0.5 per million in high-income areas versus 7.5 per million in low-income areas).

WT is the most common renal tumour in children¹ and studies have found variation in incidence between regions or ethnicities^{2,21} (FIG. 3). The annual incidence of WT in East Asia is lower than in North America or Europe (4.3 per million versus 8–9 per million)². In the USA, children with African-American ancestry have the highest incidence (9.7 per million) whilst those with Asian-Pacific Islander ancestry have the lowest (3.7 per million)². However, owing to the lack of population-based childhood cancer registries in resource-constrained regions, or because of the low quality of the data (that is, not all cancers are reported or not all children are reported), the estimation of global incidence has been difficult^{14,22,23}. In addition, 50% of patients from areas with less resources have metastases at diagnosis²⁴.

Up to 17% of WT occur as part of a recognizable malformation syndrome²⁵, 10% of which are associated with known WT predisposition²⁶ (TABLE 1). Overgrowth syndromes, in particular Beckwith–Wiedemann syndrome, carry ~5% risk of developing WT, ranging from 0.2% to 24% according to the underlying genetic cause^{27–29}. Syndromes involving genitourinary anomalies combined with aniridia and variable intellectual disability, or with nephrotic syndrome, are associated with mutations of the gene *WT1* on chromosome 11p13 and these patients have a greatly increased risk of developing WT^{3,30,31}.

No temporal trends in the incidence of WT were observed within the period 1996–2010 (REF.³), suggesting that environmental factors play a marginal role in WT aetiology. Nevertheless, modifiable risk factors for WT are not well understood.

Influence of sex and age

WT is one of the few childhood cancers that is more common (~10%) in girls than in boys¹⁹. The age-specific incidence of WT peaks at 1 year of age in boys at 17.9 per million person-years. However, in girls, a similar peak remains almost constant at 1, 2 and 3 years of age, with the respective incidences of 17.8, 18.0 and 18.1 per million person-years (FIG. 4).

WT often presents as a solitary lesion, but ~7% are reported to be multifocal and 5–9% bilateral^{1,2,32}. Unilateral tumours occur at a slightly older age than bilateral ones (FIG. 4). The age distribution at diagnosis varies by region and ethnicity, with affected individuals in East Asia being younger at diagnosis than those in the rest of the world, and this observation may be mainly due to earlier onset of the disease^{2,21,33} (FIG. 4). As one possible reason of the variation in age at onset, somatic tumour genetic analysis has shown a lower frequency of tumours with *H19-IGF2* loss of imprinting among Japanese patients with WT than in Caucasian populations³⁴. *H19-IGF2* loss of imprinting-driven WTs are associated with overgrowth syndromes and with perilobar nephrogenic rests; both these features are more common in Caucasian children with older age at diagnosis than in Japanese children (median age at diagnosis was 39 months in UK patients with WT versus 28 months in a similar Japanese patient cohort)^{33–35}. The observation of the incidence peak in infancy and

WAGR syndrome

A rare contiguous gene deletion syndrome (Wilms tumour (WT), aniridia, genitourinary anomalies, and range of developmental delays) associated with a 45–60% risk of developing WT.

Hypospadias

An anatomical congenital malformation of the male external genitalia, characterized by abnormal development of the urethral fold and the ventral foreskin of the penis that causes abnormal positioning of the urethral opening.

Cryptorchidism

The absence of at least one testicle from the scrotum.

Denys–Drash syndrome

A rare condition caused by mutations in the tumour-suppressor gene *WT1*, characterized by a triad of disorders: ambiguous genitalia, nephrotic syndrome leading to end-stage renal disease, and Wilms tumour.

the lower total incidence in East Asian populations is consistent with genetic factors primarily driving WT. Studies with large samples from many countries and different ethnic groups will be needed to validate the likelihood that the genetic heterogeneity of WT explains this variation in clinical features by ethnicity.

Mechanisms/pathophysiology

WT is an embryonal malignancy thought to arise through abortive or disrupted development³⁶. During kidney embryogenesis, intermediate mesoderm differentiates into metanephric mesenchyme, which condenses around the branching ureteric bud structures. This metanephric mesenchyme undergoes a mesenchymal to epithelial transformation to form renal vesicles, which expand and give rise to the majority of cell types of the functional kidney³⁷. In WT, this process can be disrupted at different levels, leading to variable mixtures of blastemal, epithelial and stromal cells that may even exhibit myogenic differentiation. Histology is partly shaped by the underlying genetic defects but may also reflect the timing of divergence from normal nephrogenesis (FIG. 5).

Our understanding of the genetic causes of WT has long been limited to mutations of *WT1*, *CTNNB1* and *WTX* as well as loss of *H19-IGF2* imprinting, but these alterations only explain a subset of cases³⁸. Additional features such as allele loss on chromosomes 1p and 16q or gain of 1q may underpin aggressive clinical behaviour in some cases, but do not provide mechanistic insights into tumour development or therapeutic targets^{39–41}.

Next-generation sequencing analyses have unveiled many additional drivers, mostly chromatin-modifying and transcription factors as well as microRNA (miRNA) processing genes, many of which are involved in normal renal development^{42–44} (TABLE 2; BOX 1). A surprisingly large fraction of WT (up to 17%) occur in the context of genetic malformation syndromes associated with tumour predisposition²⁵ (TABLE 1). The paradigms are WAGR syndrome and Beckwith–Wiedemann syndrome, which led to the understanding that defects in the tumour suppressor gene *WT1* and loss of *H19-IGF2* imprinting predisposes to WT.

WT1, CTNNB1 and stromal WT

WT1 was originally identified through homozygous deletions in WT^{45,46}. Nevertheless, the functions of this zinc finger protein are more complex — germline inactivation leads to male genitourinary anomalies, such as hypospadias, cryptorchidism, through haploinsufficiency and is associated with an increased risk of developing WT (>50%)⁴⁷. Additionally, dominant-negative mutations, especially of the zinc finger domains that abrogate DNA binding, lead to Denys–Drash syndrome with intersex and renal failure due to diffuse mesangial sclerosis and the risk of developing WT increased >90%⁴⁸. Of note, Frasier syndrome, in which intronic mutations alter the balance of *WT1* splice isoforms rather than altering the WT1 protein amino acid sequence, includes different forms of intersex and renal failure, and carries a risk of gonadoblastoma in streak gonads rather than WT^{49,50}.

Fig. 1 | Timeline of key clinical advances that established the modern clinical management of children with Wilms tumour. 1. The National Wilms Tumour Study group (NWTS), which was supplanted by the Children's Oncology Group (COG) in 2002, and the International Society of Paediatric Oncology (SIOP) initiated organized protocols^{155,227–229}. 2. Researchers started to collect data on the associations between Wilms tumour (WT)-specific therapies and late toxicity in survivors²²⁷. 3. In 1978, anaplastic morphology was shown to correlate with an increased mortality from WT⁹⁸. 4. SIOP progressively recognized that histological subtypes after neoadjuvant chemotherapy were a prognostic factor^{122,160,228,230}. 5. In 1990, SIOP established the Paediatric Oncology in Developing Countries (PODC) committee to promote paediatric oncology in poorly-resourced countries. 6. Researchers showed that lung radiotherapy could be avoided in subgroups of patients with metastases (good responders), setting the new standard²³¹. 7. SIOP-9 trial (1987–1991) showed no benefit from prolonging

pre-nephrectomy chemotherapy to 8 weeks with respect to stage distribution, the 4-week schedule becoming the standard for non-metastatic WT¹⁶⁰. 8. Actinomycin D could be administered in a single dose rather than divided over 5 days, thereby reducing hospital visits for children and health-care delivery costs^{232,233}. 9. Nephrectomy alone in children with very low-risk WT (defined as <24 months of age, with a stage I favourable histology tumour weighing <550 g) was shown to be a valid option, avoiding the risks of central line placement and chemotherapy¹³⁶. 10. Risk stratification of WTs implemented with loss of heterozygosity (LOH) at chromosomes 1p and 16q as adverse prognostic markers³⁹. 11. Current standard treatment for children with stage II and III intermediate-risk histology after preoperative chemotherapy omits doxorubicin (vincristine and actinomycin D)⁷. 12. In 2018, WHO launched the Global Initiative for Childhood Cancer, with the goal of improving outcome in children with cancer around the world, initially focusing on six common cancers including WT¹⁷⁴.

Fig. 2 | **The estimated mortality for kidney cancers according to geographical area.** Estimated age-standardized mortality rates in 2020 for kidney cancers in children aged 0–14 years in the world²³⁴. Reprinted from GLOBOCAN 2020, International Agency for Research on Cancer, Estimated age-standardized mortality rates (world) in 2020, kidney, both sexes, ages 0–14, copyright 2020 (REF. ²³⁴).

Mutations in *WT1* are often paired with frequent alterations of *CTNNB1*, which lead to constitutive Wnt signalling⁵¹. In most cases, point mutations or deletions are observed in the phosphodegron motif in exon 3, leading to β -catenin stabilization and nuclear accumulation, where it acts as co-activator with the TCF–LEF transcription factors. These tumours usually exhibit stromal-predominant histology, decreased response to preoperative chemotherapy and represent up to 15% of cases in Caucasian populations⁵². Notably, although the incidence of WT in Japanese children is only 50% of that found in Caucasian children, an increased rate of *WT1* mutations (81%) is observed in bilateral WTs, which points to differences in genetic constitutions⁵³. *WT1*-driven stromal tumours occur at a median age of 22 months and are characterized by the presence of intralobar nephrogenic rests as presumed precursor lesions. *WTX* may likewise facilitate Wnt signalling as it is part of the β -catenin degradation complex. Mutations or loss of expression of *WTX* are observed in up to 30% across histological subtypes, but with intratumoural heterogeneity, suggestive of a late event⁵⁴.

H19–IGF2 imprinting

Chromosome 11p15.5 is frequently altered in WT through copy-neutral loss of heterozygosity with invariance of the maternal allele or loss of imprinting with epigenetic changes on the maternal allele. The net outcome being hypermethylation of the imprinting centre IC1 with elevated expression of the neighbouring growth factor gene *IGF2*, among others. With ~70% incidence

of such alterations, overexpression of *IGF2* is the most frequent change in WT^{43,44,52}. However, tumour initiation may require additional events as loss of imprinting on its own in Beckwith–Wiedemann syndrome only modestly increases WT risk²⁷.

microRNA biogenesis mutations

An unexpected addition to WT driver genes is miRNA processing genes. miRNA biogenesis covers a stepwise maturation process from pri-miRNA via pre-miRNA to mature miRNA. Mutations in WT primarily affect the so-called microprocessor genes *DROSHA* and *DGCR8*, which are involved in pri-miRNA processing^{43,44,55,56}. Heterozygous *DROSHA* mutations tend to inactivate the catalytic core of one of the two RNase III domains that processes pri-miRNA molecules. *DGCR8* mutations affect a single amino acid (E518K) in one of the double-stranded RNA binding domains and the mutations occur homozygously or with monoallelic expression of the mutant. The net result is a reduced and unbalanced miRNA processing. *DGCR8* mutations have been observed predominantly in girls, which remains to be explained.

DICER1, which encodes the second RNase III type enzyme, is rarely mutated in WT, but predisposes to pleuropulmonary blastoma and is implicated in the very rare entity, anaplastic sarcoma of the kidney^{57,58}. The catalytic centre is often mutated on the single functional allele, leading to a partial processing defect with a deficiency in miRNA-5p and largely unaffected miRNA-3p levels.

Studies have found further mutations in *XPO5* (encoding exportin 5), the *DICER1* cofactor *TARBP2*

Frasier syndrome

A rare autosomal recessive disorder that presents with male pseudohermaphroditism with gonadal dysgenesis, renal failure in early adulthood and increased risk of developing gonadoblastoma.

and downstream *let-7* miRNA modulators such as *DIS3L2* or *LIN28B* at a lower frequency in the 1% range but the mechanistic details are as yet unclear. Nevertheless, almost all steps of miRNA biogenesis can be critically altered to drive WT formation and several of these mutations are rather specific to WT. The fact that most mutations do not fully abrogate miRNA production implies that specific miRNA subsets are important to control deviation from regular developmental progression or cell proliferation and survival.

MYCN and transcriptional control

Alterations in *MYCN* may contribute to WT biology in several ways. Elevated expression levels have been described, especially in relapsing and fatal cases. Furthermore, studies have identified specific P44L point mutations or copy number gains with one or a few additional copies^{44,55,59}. Proline 44 is located immediately upstream of the conserved MYC box I that interacts with AURKB, FBXW7 (REF.⁶⁰) and GSK3 to control N-Myc stability. Stabilization occurs through dephosphorylation at threonine-58 by the phosphatase EYA1, which is recruited to the nucleus by the transcription factor SIX2 (REF.⁶¹). This process provides a direct link to the paralogous genes *SIX1* and *SIX2* that control early kidney development. *SIX1* and *SIX2* can be found as drivers of blastemal-predominant WT if their DNA binding domain becomes subtly altered by stereotypic Q177R mutations⁴⁴.

Intriguingly, several MYC-interacting protein complexes can be targets of mutations in WT. The obligate heterodimerization partner MAX can exhibit R60Q

mutations in the helix-loop-helix domain to alter its transcriptional potency. N-Myc exerts its effects on transcriptional control through a multitude of interactions with the core transcriptional machinery to regulate polymerase pausing. The PAF1 transcription complex is one of the critical interactors in this respect and several of its components such as *CDC73*, *MLLT1-ENL* and *CTR9* have been shown to be mutated in familial and sporadic cases of WT⁶². Collectively, these data indicate that *MYCN* hyperactivity through various means can contribute to WT through a multitude of mechanisms.

Epigenetic modifiers

A striking genotype–phenotype correlation is observed in epithelial-predominant WT, which is often driven by inactivating *TRIM28* mutations (REFS^{63–66}). Gene expression analyses have identified these tumours as more mature, post-induction tumours with excellent prognosis. *TRIM28* is part of a chromatin silencing complex that has an important function in the repression of endogenous retroviral transcript in embryonic cells. Indeed, these tumours show strong induction of transcripts from repetitive elements, but the mechanistic links to oncogenic transformation in these tumours with otherwise few mutations remains to be established.

Besides *TRIM28*, studies have shown that a whole array of epigenetic regulators are potential drivers in WT. These regulators include *REST*, *RERE*, *CHD4*, *KDM3B*, *BCOR* and *BCORL1*, which are all components of large protein complexes with diverse enzymatic activities^{42,44}. There is a spectrum of dominant and recessive as well as

Fig. 3 | **The incidence of Wilms tumour according to geographical area and ethnicity.** Age-standardized incidence rates (ASRs) of renal tumours in children 0–14 years of age by world region and ethnicity, 2001–2010 ($N=15,320$). Unspecified, unspecified malignant renal tumours. Adapted from REF.², CC BY 4.0.

Table 1 | Heritable syndromes associated with an increased risk of Wilms tumour

Syndrome	Locus	Genetic lesion	Phenotype	Estimated risk of WT (%)	Refs
WAGR	11p13	11p13 deletion encompassing <i>WT1</i>	Aniridia, genitourinary anomalies, delayed-onset renal failure	~50	209
Denys–Drash	11p13	Point mutation zinc-finger region of <i>WT1</i>	Early-onset nephrotic syndrome (diffuse mesangial sclerosis), ambiguous genitalia	~75	210
Frasier	11p13	Point mutation in <i>WT1</i> intron 9 donor splice site	Ambiguous genitalia, streak gonads, focal segmental glomerulosclerosis, diffuse mesangial sclerosis	Case reports	72
Beckwith–Wiedemann	11p15	Dysregulation of imprinted genes including <i>IGF2</i> and <i>H19</i>	Overgrowth syndrome. Organomegaly, large birthweight, macroglossia, omphalocele, hemihypertrophy, ear pits and creases, neonatal hypoglycaemia	0.2–24	28,211
Simpson–Golabi–Behmel	Xq26.2	<i>GPC3</i> mutations/deletions	Overgrowth syndrome. Prenatal and postnatal overgrowth, visceral and skeletal abnormalities (course facies), congenital heart defects, a variable degree of psychomotor impairment	~3	211
Li–Fraumeni	17p13	Heterozygous <i>TP53</i> mutations. Genome instability disease	Familial predisposition to cancer	Low, but several cases reported	212
Mosaic variegated aneuploidy	15q15	Biallelic <i>BUB1B</i> or <i>TRIP13</i> mutations. Genome instability disease	Microcephaly, intellectual disabilities, cataracts, heart defects	>70	213,214
Fanconi anaemia D1	13q12	Biallelic <i>BRCA2/FANCD1</i> mutations. Genome instability disease	Short stature, radial ray defects, bone marrow failure, but heterogeneous clinical presentation (one-third of individuals with Fanconi anaemia have a normal appearance)	20–40	215,216
Hyperparathyroid-jaw tumour	1q25–q31	Heterozygous <i>HRPT2</i> mutations	Fibro-osseous lesions of jaw, parathyroid tumours	Low, but several cases reported	217,218
Bloom	15q26	Biallelic <i>BLM</i> mutations. Genome instability disease	Short stature, photosensitivity, microcephaly, insulin resistance, immunodeficiency	3	219
Perlman	2q37	Biallelic inactivating variants in <i>DIS3L2</i>	Prenatal overgrowth, facial dysmorphism, developmental delay, cryptorchidism, renal dysplasia	~64	220
Trisomy 18 (Edward)	18q11.2–q23	Complete trisomy 18 (95%); mosaic trisomy 18 (5%)	Congenital cardiac anomalies; dysmorphic facial features, clenched hands, and rocker-bottom feet	Case reports	221
Mulibrey nanism	17q22–q23	Biallelic <i>TRIM37</i> mutations	Growth deficiencies, cardiomyopathies, characteristic facies, a predisposition towards developing metabolic disorders (type II diabetes mellitus) (Finnish population)	~6–8	222,223

WT, Wilms tumour.

Chromothripsis

A catastrophic chromosomal shattering event associated with random rejoining.

Li–Fraumeni syndrome

An inherited autosomal dominant cancer predisposition disorder that is usually associated with abnormalities in *TP53* located on chromosome 17p13.

Anaplasia

Cells with hyperchromatic, pleomorphic nuclei that are three times larger than adjacent cells and have abnormal mitotic figures. Anaplasia is associated with a poor response to chemotherapy.

truncating or missense mutations, some being heritable. Intriguingly, *BCOR* is also the main culprit for driving clear cell sarcoma of the kidney, another childhood renal tumour. In this case the gene is not inactivated as in WT, but harbours small carboxy-terminal tandem duplications corresponding to ~30 amino acids that encompass the binding domains for *PCGF1* and *KDM2B* as part of the polycomb repressive complex (PRC1) that controls, for example, mesodermal differentiation^{67,68}.

***TP53* and anaplasia**

WTs generally have a low mutation load that increases with patient age, and karyotypes tend to be stable^{43,44}. However, the mutation load is different in diffuse anaplastic WT, which frequently harbours oncogenic *TP53* mutations. In most cases, the wild-type allele is lost and the cells are characterized by chromosomal instability including chromothripsis and deregulation of cell cycle and DNA repair genes^{59,69–71}. *TP53*-mutated tumours exhibit strong positive p53 staining owing to the accumulation of the mutant protein, although a smaller

fraction demonstrate negative staining due to null mutations. *TP53* alterations are secondary events in WT progression, in line with WT being reported as a rare feature in Li–Fraumeni syndrome⁷².

Whether *TP53* mutation confers an additional risk independent of the high-risk status of morphological anaplasia is still unknown. Several other genes that fall into the category of genome maintenance and repair, such as *BRCA2*, *PALB2* and *TRIP13*, have been found to be mutated in WT⁷³. Whether such mutations likewise increase mutation load or chromosomal aberrations remains to be determined, and no reports are available on aneuploidy yet.

Nephrogenic rests

The underlying genetic defects also have an impact on the presence of nephrogenic rests in the kidney that occur in 30–40% of patients^{74,75}. These precursor lesions are foci of embryonic renal cells that abnormally persist beyond 36 weeks of gestation. Nephrogenic rests are histologically and anatomically classified as either perilobar

or intralobar⁷⁴. *WT1*-related WT frequently carry few intralobar nephrogenic rests, centrally located within or adjacent to the renal medulla, suggestive of an early developmental lesion. *TRIM28*-associated or Beckwith–Wiedemann syndrome-associated WT tend to harbour perilobar nephrogenic rests in the adjacent kidney tissue rather than intralobar nephrogenic rests. These perilobar nephrogenic rests may even encompass the entire renal cortex in extreme cases. Although few samples have been assayed thus far, nephrogenic rests seem to carry even fewer mutations than their adjacent WT^{5,76,77}.

Bilateral Wilms tumour

Almost one in ten children present with bilateral WT or bilateral disease (WT with nephrogenic rests or nephroblastomatosis visible on imaging in the contralateral kidney), especially in syndromic cases³². *WT1* is the most prominent driver in these cases^{32,52}, together with specific imprinting abnormalities at 11p15 affecting *IGF2*, although neither explain the majority of cases. *TRIM28* inactivation is also frequent in bilateral and familial tumours^{64–66,73}. Importantly, bilateral tumours can be due to early postzygotic founder mutations in somatic cells that emerge before the divergence of left and right kidney primordia⁵. Individual clones may expand to yield mosaic kidneys with molecular evidence of clonal (mosaic) nephrogenesis. Thus, it may be justified to compare bilateral or multifocal tumours with blood and surrounding normal kidney tissue as controls to

differentiate putative germline mutations, postzygotic mosaic events or single tumours with metastatic disease.

Heterogeneity and subclassification

Molecular analysis has unveiled intratumoural heterogeneity of WTs, with either chromosomal copy number alterations or mutations, for example, in *WTX* or *TP53*, being present in only a fraction of cells as evidence of tumour evolution⁷⁸. These differences may become clearer with single-cell or single-nucleus analyses, which already highlighted a great cellular diversity⁴. Even the main driver genes stratify WTs according to the age of the child (for example, *TRIM28*, *WT1* in WT occurring at younger ages (generally <2 years of age), *TP53* (generally >4 years of age) and Beckwith–Wiedemann syndrome occurring at older ages (3–4 years of age)), location of nephrogenic rests (intralobar versus perilobar) or histology (*WT1* in stromal WTs, *TRIM28* in epithelial WTs and *TP53* in anaplastic WTs) (FIG. 5). Nevertheless, the majority of triphasic or blastemal-predominant WTs do not carry defining genetic alterations.

Liquid biopsies

Although WT represents >80% of paediatric renal tumours, other intrarenal tumours exist that are important to differentiate as therapeutic approaches are markedly diverse³¹. These non-Wilms renal tumours are often characterized by rather specific molecular alterations (FIG. 5). These tumours may become amenable to liquid biopsy diagnostics

Fig. 4 | **Age-specific incidence of Wilms tumour according to gender, laterality and geographical area.**

a | Age-specific incidence of Wilms tumour (WT) in children 0–14 years of age, all world regions combined, by sex (N = 13,838) and laterality^a (N = 6,396), 2001–2010. ^aOnly the registries providing information on the laterality for at least 95% of patients with WT are included. **b** | Age-specific incidence of WT in children 0–14 years of age by world region, 2001–2010 (N = 13,838). Adapted from REF.², CC BY 4.0.

looking for diagnostic changes or entity-specific patterns of methylation⁷⁹. In particular, if a neoadjuvant chemotherapy approach is planned and the clinical pattern is unusual, such tests will become helpful to rule out non-WT from the start, or to follow response to treatment during follow-up. The fact that patients with paediatric kidney tumours often have large amounts of circulating tumour DNA makes this approach rather promising⁸⁰.

Tumour models

Modelling WT in the mouse has been difficult with only a few successful scenarios, the first using *Wt1* ablation together with *Igf2* upregulation⁸¹. Other researchers have

successfully employed *Lin28* overexpression or *Dis3l2* mutation^{82,83}. On the other hand, prototypic *Drosha* mutations or *Wtx* deletions did not yield evidence of WT formation but led to either kidney agenesis or aberrant kidney development and functional impairment^{84,85}.

Modelling efforts, including patient-derived xenografts (PDX)⁸⁶, can now be complemented with spheroid and organoid techniques to grow tumour cells in vitro for genetic and histological characterization and for therapeutic compound testing^{87–89}. These models will become an invaluable resource to test novel agents in patients with relapse who respond poorly to conventional regimens, provided a time frame suitable for clinical feedback can be accomplished⁹⁰.

Diagnosis, screening and prevention

Clinical presentation

Most children with WT are asymptomatic at presentation and predominantly have a distended abdomen with a palpable mass⁹¹. Frequently, the parents notice such a mass during dressing or cuddling. Alternatively, WT is identified by the general practitioner or the paediatrician during a regular clinical assessment of a well child or a child with non-specific symptoms. WT usually reveals a non-tender, large flank mass, which does not move with respiration in contrast to splenomegaly. Approximately only one in five children have distinct symptoms; pain, haematuria, fever, hypertension, urinary tract infections, constipation and weight loss are among the most common complaints at presentation^{31,91}. Although rare, symptoms related to metastases, such as dyspnoea (lung), abdominal pain (liver) or tumour thrombus in the renal vein or vena cava or varicocele, may occur⁹². Ultimately, a few children with severe subcapsular haemorrhage may present with rapid abdominal enlargement, anaemia and severe pain. Age at presentation is typically in the range 2–5 years and the incidence of WT in children >10 years is rare. In children with known predisposing syndromes, WT may be captured during routine screening and often at an earlier age or stage, and these children are even more likely to be asymptomatic than children without predisposing syndromes⁹³.

In low-income countries (LICs), interactions between multiple factors usually contribute to a delayed diagnosis compared with diagnosis in high-income regions^{94,95} (BOX 2). These factors include family or relatives' awareness of a possible cancer, contacting and arrival in primary care, health-care staff recognition of cancer and transfer to tertiary care. Furthermore, a much higher number of children in LICs have a distended abdomen due to other conditions, for example, malnutrition, parasitic infections and benign blood diseases than in high-income regions. Hence, identifying, differentiating and prioritizing investigations of the relatively few cases of WT is challenging. Moreover, the latency to diagnosis (patient interval and diagnostic interval) prolongs further, as diagnosis is not only dependent on the recognition by the family, but also by the lack of awareness by the primary care medical personnel and poor referral networks⁹⁶. These factors result in a larger proportion of children presenting with symptoms, a large tumour volume, advanced local stage and

Fig. 5 | Biology of paediatric renal tumours. Cells deriving from intermediate mesoderm form the nephrogenic niche and develop into the various cell types of the normal kidney. Molecular alterations in these cells may result in diverse renal tumours: ~90% being Wilms tumours (WTs) and ~10% other primary renal tumours. In a paradigm of disrupted organ development eventually leading to tumorigenesis, remains of the multipotent nephrogenic zone of the fetal kidney may persist after birth and appear in up to 1% of routine infant autopsies as nephrogenic rests. The natural history and fate of nephrogenic rests is, however, uncertain. These cells may terminate their differentiation, or eventually regress and become sclerotic and obsolescent, whereas others can progress to form hyperplastic nephrogenic rests, with typical genetic changes. Nephrogenic rests are found in >90% of patients with bilateral WTs and in ~30–40% of patients with unilateral sporadic WT. WTs are then characterized by the acquisition of additional genetic and epigenetic changes, some of them being quite specific for histological subtypes. The percentages indicate the frequency of mutation in sporadic cases. It is unclear whether WTs originate directly from nephrogenic blastema without progression through nephrogenic rest stages. CCSK, clear cell sarcoma of the kidney; CMN, congenital mesoblastic nephroma; LOH, loss of heterozygosity; LOI, loss of imprinting; miRNA, microRNA; RCC, renal cell carcinoma; RTK, rhabdoid tumour of the kidney. ^a*IGF2–H19* LOH/LOI have not been shown in epithelial WTs.

Table 2 | The landscape of cancer genes that are potentially operative in Wilms tumorigenesis

Gene	Role in tumorigenesis	Notes	Reported frequency ⁴²	Potential targeted therapeutic approaches	Refs
TP53	Tumour suppressor gene	Strongly associated with anaplasia; potential driver of disease progression	~5% (50–90% in DA)	p53-specific biological targeting agents	69–71,90
CTNNB1	Oncogene	Stabilizing mutations of the exon 3 phosphodegron or mutations of Arm repeats leading to reduced APC binding; upregulation of Wnt pathway	~15%	β-catenin/transducin β-like protein 1 inhibitor (tegavivint, COG trial)	38,42,51, 203,224
WT1	Tumour suppressor gene	Germline mutations are associated with genitourinary anomalies or intersex; stromal-predominant tumours; association with ILNR	~10–20%	Immunotherapy	38,45, 46,90
WTX	Tumour suppressor gene	Negatively regulates the Wnt pathway	~10–20%	NA	38,54
SIX1, SIX2	Implicated in renal development	Specificity for blastemal regions; association with PLNR	5–10%	NA	43,44
DROSHA, DGCR8, DICER1 and others	miRNA processing genes	DROSHA: heterozygous mutations of catalytic core; DGCR8: homozygous mutation (E518K) of dsRBD; more frequent in blastemal-predominant tumours; association with PLNR	~15%	Targeting of miRNA processing	43,44, 55,90
MYCN	Oncogene	Copy number gain or specific P44L mutation	~15%	Directly targeting MYCN	59,90,225
H19-IGF2 locus	Epigenetic abnormalities at the imprinted loci on 11p15	LOI or loss of maternal allele (pUPD) at the BWS imprinting centre 1 (IC1) leading to increased IGF2 expression; association with PLNR	~50–80%	Targeting of IGF2; methylation and epigenetic targeting agents	38,43,44, 52,226

Arm, armadillo; BWS, Beckwith–Widemann syndrome; COG, Children's Oncology Group; DA, diffuse anaplasia; dsRBD, double-stranded RNA-binding domain; ILNR, intralobar nephrogenic rest; LOI, loss of imprinting; miRNA, microRNA; NA, not available; PLNR, perilobar nephrogenic rest; pUPD, paternal uniparental disomy.

metastases in low-income regions than in high-income regions^{14,24}.

Diagnosis, classification and staging

Diagnosis of WT can be made reliably on histology, especially WTs in which all three characteristic components — blastemal, epithelial and stromal — are evident. These components may be mixed in any proportion, but WTs showing one or two components are not rare. Epithelial and stromal components may show different lines of differentiation and degrees of differentiation, resulting in a countless number of histological appearances (FIG. 6). WTs composed of only one component may represent a diagnostic challenge and ancillary techniques may be needed to establish the diagnosis⁹⁷. However, no immunohistochemical markers or molecular biology findings are 100% specific for WT. In addition, preoperative chemotherapy, when used, alters the histological appearance of WT, and may result in marked tumour necrosis, or maturation of tumour components. Approximately 7–8% of WTs demonstrate anaplasia, defined as the presence of cells with hyperchromatic, pleomorphic nuclei that are three times larger than adjacent cells and have atypical mitotic figures⁹⁸, and it may occur in any tumour component (blastemal, epithelial or stromal). The definition of anaplasia was further refined to specify whether the anaplasia is diffuse or focal based on the anatomical distribution of anaplastic cells within the tumour⁹⁹. The diagnosis of focal anaplasia is based on the presence of clearly defined one or two foci showing the above-mentioned nuclear criteria with sharp demarcation within the primary intrarenal tumour and without evidence of anaplasia or prominent nuclear atypia

(defined as nuclear unrest) in other areas. According to SIOP, up to two foci up to 15 mm in size is allowed for the diagnosis of focal anaplasia⁹ whereas according to COG, up to four foci up to 20 mm in size is allowed⁹⁹. Diffuse anaplasia is defined as non-localized anaplasia, which may present in any of these situations: focal anaplasia with marked nuclear unrest in the non-anaplastic tumour; anaplasia beyond the tumour capsule; anaplastic cells in intrarenal or extrarenal vessels, renal sinus or extracapsular sites, in metastases, or in biopsy. Despite well-established criteria, anaplasia represents a diagnostic problem, with ~30–50% discrepancy between institutional pathologists and central pathology review^{100,101}. Anaplasia is very rare in the first 2 years of life, and increases after 4 years of age. Anaplasia is usually neither obliterated nor induced by preoperative chemotherapy.

As SIOP and COG have different treatment initial strategies, relevant differences exist in histological classifications of WTs between the two groups. The COG classification includes anaplastic (focal and diffuse) and non-anaplastic (favourable histology) WTs based on assessment of a chemonaive tumour after up-front surgery. The SIOP classification is based on the assessment of the percentage of preoperative chemotherapy-induced changes and viable tumour components, and includes three major WT risk groups: low-risk tumours (completely necrotic WT), high-risk tumours (blastemal type and diffuse anaplasia), and intermediate-risk tumours (all other types) (TABLE 3). To correctly subclassify the WT, the percentages of chemotherapy-induced changes and viable tumour components are assessed and taken into account⁹. COG has reported histology and outcomes in patients not eligible for up-front surgery using

Box 1 | Wilms tumour predisposition and driver genes

Most genes implicated in Wilms tumorigenesis act in gene expression control and growth factor signalling. Approximately 50% of the genes can be present in mutant form in germline or constitutional DNA conferring increased Wilms tumour (WT) risk⁵¹.

Kidney development

CTNNB1, SIX1, SIX2, WT1^a

Transcriptional machinery

CDC73^a, CREBBP, CTR9^a, FBXW7^a, MAX, MLLT1, MYCN

Chromatin biology or epigenetic modifiers

ARID1A, ASXL1^a, BCOR(L1)^a, BRD7, CHD4, HDAC4, KDM3B^a, RERE, REST^a, TRIM28^a, TRIM37^a

MicroRNA processing and RNA metabolism

DGCR8, DICER1^a, DIS3L2^a, DROSHA, LIN28B, NONO, NYNRIN^a, TARBP, XPO5

Growth factor signalling

ACTB, AMER1, FGFR1, GPC3^a, IGF2 (BWS-IC1)^a, MAP3K4, NF1^a, PIK3CA^a

Genome maintenance

BLM^a, BRCA2^a, BUB1B^a, CHEK2, PALB2^a, TP53^a, TRIP13^a

^aAlso as syndromal or familial WT genes.

the SIOP post-chemotherapy histological classification system but to date has not used this system to guide subsequent treatment in patients with a unilateral tumour¹⁰². The staging criteria between COG and SIOP also differ, making a direct comparison of outcomes stage-by-stage difficult (Supplementary Table 1).

Diagnostic imaging. Abdominal ultrasonography is efficient and globally the most available means of investigating suspected WT¹⁰³. Ultrasonography provides information about the organ of origin, extension into the renal and inferior cava veins or urinary collecting system, the contralateral kidney and associated urogenital abnormalities, and may identify liver or lymph node metastases. In resource-limited regions, ultrasonography is sufficient for abdominal staging and can be complemented by chest plain radiography, recognizing that plain radiography may miss smaller pulmonary lesions (typically <1 cm)^{95,104}. In better-resourced settings, cross-sectional imaging is usually undertaken preoperatively with abdominal CT or MRI¹⁰⁵. The main drawback of CT is radiation exposure, but the procedure is rapid, allows continuous imaging of the chest and abdomen, has moderate specificity for detection of preoperative spill, may help distinguish nephrogenic rests from WT and gives excellent pulmonary detail^{106–108}. It is noteworthy that COG and SIOP incorporate centrally reviewed CT identification and response to therapy of lung nodules into current risk stratification treatment algorithms^{10,109}. The main hurdle of abdominal MRI is that moderate to deep sedation is often required in young children but it provides excellent organ details in those with bilateral disease or liver metastases. Abdominal MRI is preferentially recommended for better assessment of potential nephrogenic rests and their distinction from true WT, and by SIOP to attempt to correlate apparent diffusion coefficient mapping with histopathology prediction after preoperative chemotherapy^{105,110}.

Fluorodeoxyglucose (FDG) PET is not routinely used for imaging WT¹⁰⁵. Bone scan or cross-sectional imaging

of other sites is reserved for patients with signs or symptoms suspicious for distant extrapulmonary metastases. Non-pulmonary and non-hepatic metastatic disease is very rare at primary diagnosis of non-anaplastic WT and is more likely observed in anaplastic WT, clear cell sarcoma of the kidney, malignant rhabdoid tumour and renal cell carcinoma, or at WT relapse^{111–113}.

Laboratory testing. Baseline blood work should be performed to confirm adequate renal function, support subsequent chemotherapy and rule out acquired von Willebrand's disorder, which although uncommon may be associated with substantial bleeding risks and can be pre-emptively managed¹¹⁴.

SIOP diagnostic algorithms recommend percutaneous image-guided coaxial core needle biopsy through a retroperitoneal approach in patients 7 years of age or older or in patients with imaging findings unusual for WT (psoas muscle infiltration, numerous calcifications, vessel encasement or massive lymphadenopathy)^{10,115,116}. The currently used cut-off of 7 years to consider a biopsy is under revision, and based on epidemiological data showing the peak incidence of WT versus other non-WTs², a new consensus towards raising the age threshold for biopsy providing there are no other atypical presenting features is forming^{105,115}. COG recommends that primary nephrectomy should be strongly considered in all patients, but if not feasible, open or Tru-Cut needle biopsy should be undertaken with a minimum of 10–12 cores. Notably, needle biopsy cannot reliably distinguish WT from nephrogenic rests, and often misses anaplasia¹¹⁵.

Patients with syndromic features should be referred to medical genetics for counselling and possible testing. Circulating blood or urine tumour DNA is being explored for diagnostic and response or relapse assessment but is not yet standard of care^{80,117,118}.

Prognosis and prognostic features

It is important to recognize that prognostic markers must be interpreted in the context of the accompanying treatment regimen. This principle is relevant to WT as COG advocates for immediate nephrectomy in most patients, whereas SIOP advocates for preoperative chemotherapy¹⁹. Thereafter, prognostic factors used for clinical treatment stratification differ between COG and SIOP^{120,121}. According to both groups, tumour histology and stage are key prognostic indicators, although applied differently and together with other factors in clinical practice. Diffuse anaplasia is regarded as a high-risk tumour by COG and SIOP, whereas focal anaplasia is regarded as an intermediate-risk tumour by SIOP but as a high-risk tumour by COG. A blastemal-type WT after preoperative chemotherapy is also regarded by SIOP as a high-risk tumour and a completely necrotic-type WT as a low-risk tumour¹²² (TABLE 3). Similarly, staging criteria are also different; for example, according to COG, any tumour biopsy results in upstaging to local stage III, whereas according to SIOP, fine-needle aspiration and percutaneous core needle biopsy are ignored for staging purposes³¹, and according to SIOP, the presence of necrotic tumour or chemotherapy-induced changes in

the renal sinus, renal veins and/or the perirenal fat is not a reason for upstaging to stage II⁹ (Supplementary Table 1). Some SIOP criteria have undergone important changes in comparison with the previous SIOP–2001 trial and study criteria. For example, in the current SIOP protocol, the presence of non-viable tumour or chemotherapy-induced changes only at a resection margin is not regarded as stage III⁹.

Other prognostic factors according to SIOP include tumour histological response to preoperative chemotherapy and tumour volume (>500 ml) after chemotherapy for certain WT types. Additional prognostic factors according to COG include age, tumour weight and biomarkers or tumour biology, that is, loss of heterozygosity at chromosomes 1p/16q, loss of heterozygosity at chromosome 11p15, and gain at chromosome 1q¹²¹. For both groups, response of lung metastases to neoadjuvant chemotherapy indicates chemosensitivity and dictates

the intensity of subsequent treatment; for example, if lung lesions are not present at 6 weeks after induction chemotherapy, radiotherapy can be omitted in some patients^{109,123}.

Although the SIOP and COG strategies differ in their upfront treatment approach, they lead to similar overall survival rates of ~90%^{7,39,124}. Patients with stage IV anaplastic WT and/or blastemal type WT have substantially poorer outcomes, with an overall survival rate of <50% despite very intensive therapy^{125,126}.

Despite the good prognosis in most children with WT, ~20% of patients will relapse, predominantly within 2 years of diagnosis^{113,127,128}. The overall survival rate after relapse is ~50% but varies considerably according to the initial treatment received (which in turn reflects initial tumour stage and histology), time to relapse, site of relapse, and patient age^{113,129,130}. Surveillance with abdominal ultrasonography and chest plain radiography are offered, and patients with asymptomatic relapse detected by surveillance seem to have better outcomes¹¹³. Evidence from COG shows a lack of benefit in terms of longer survival after relapse if CT imaging had been used instead of plain radiography and ultrasonography in follow-up surveillance¹²⁸. SIOP data also suggest that surveillance beyond 2 years after completion of therapy has a low yield because of the extremely low relapse rate thereafter¹¹³.

Screening

Genetic testing in children with cancer but also in other (potentially) unhealthy children presenting with certain abnormalities or syndromes is emerging. This testing includes formalized national and regional whole-exome or genome sequencing programmes to detect cancer predisposition in many high-income regions. Accordingly, both novel genes and syndromes associated with WT are revealed and additional children with an increased risk of developing WT are identified, expanding the criteria for screening programmes¹³¹. Regular screening for early diagnosis in children with a known WT predisposition syndrome has been reported to detect smaller and lower-stage tumours but robust evidence is lacking regarding the balanced clinical benefits⁹³. In addition, the benefits should outweigh the costs and burden. The latter is reflected in the different thresholds for performing screening, which typically varies between 1% and 5% for the childhood risk of developing WT²⁹.

Screening is typically offered to children with various cancer predisposition syndromes, such as *WT1*-related syndromes and Beckwith–Wiedemann syndrome or isolated hemihypertrophy (with at least one Beckwith–Wiedemann syndrome feature). Renal ultrasonography is the recommended screening modality, as it avoids radiation and does not require anaesthesia in young children. The screening interval is every 3 months based on the rather rapid growth rate of the tumour and imaging should be performed by an experienced paediatric ultrasonographer⁹³. Screening should start when the WT predisposition is established and should continue, irrespective of the underlying condition, until the child is approximately 7 years old. At this age, the risk of WT development is greatly reduced²⁹.

Box 2 | Challenges and priorities for managing patients with Wilms tumour in low-income and middle-income countries

Challenges

- Highly constrained health-care budgets resulting in insufficient paediatric oncologists, surgeons, anaesthetists and pathologists; shortage of chemotherapeutic agents (which leads to incomplete Wilms tumour (WT) treatment); limited or lacking infrastructure and facilities for imaging and radiation therapy.
- Lack of high-quality specialized paediatric surgical training to perform complex operations (WT with intracaval extension, nephron-sparing surgery).
- Inadequate reporting or data collection within national or hospital registries precludes accurate outcomes assessment.
- Inadequate specialist cancer services.
- Late clinical presentation (delay in diagnosis) owing to family's or relatives' reduced awareness about cancer; contacting and arrival to primary care; health-care staff recognition of cancer (a much higher number of children in low-income countries have a distended abdomen than in high-income countries owing to many other non-malignant conditions; thus it is challenging to differentiate and prioritize investigations for the relatively few children with WT).
- Many patients are diagnosed with already advanced or metastatic tumours.
- Toxicity from surgery and/or chemotherapy can increase mortality and contribute to treatment abandonment.
- Malnutrition is a major concern for higher drug toxicity and treatment-related death.
- Burden of associated comorbidities (infections).
- Patient quality of life largely unrecognized and unprioritized.

Priorities and areas for improvement

- Comprehensive registries are the first step to appropriate resource allocation according to local needs and to the monitoring of improvement.
- Earlier diagnosis through increased education among primary health providers concerning WT diagnosis, and parent education on healthy living and concerning symptoms.
- Adapted treatment regimens to accommodate frail children, to reduce toxicity, and to face specific (temporary or permanent) drug regimen shortages.
- Nutritional programmes, best with locally available calorie-dense foods and fortifiers.
- Implementation of family education programmes may increase compliance with cancer care reducing abandonment.
- Twinning programmes (pairing of hospitals in resource-limited countries with hospitals in developed countries) to improve local medical expertise and education.
- Clinical trials answering locally relevant questions (such as prognostic factors).
- Prioritizing resources to focus on curable clinical situations.
- Palliative care as the main priority for advanced malignancies.

The purpose of WT screening is to enable early NSS, to give less-intensive (that is, less-toxic) chemotherapy, and to avoid radiotherapy. Patients with predisposition syndromes may develop metachronous WT in the contralateral kidney. Hence, the aim is, on balance, to preserve maximal kidney function and ultimately avoid end-stage renal disease whilst still maintaining oncological control. Genetic testing, screening and NSS in LICs are rarely available and consequently, more children progress and succumb to end-stage renal diseases in low-income settings with limited options for dialysis and/or renal transplantation than in high-income regions¹³². High-income regions are researching the potential for (epi)mutation detection in circulating tumour DNA for early diagnosis; however, this detection technique is not yet ready to be used as an alternative to surveillance with ultrasonography in clinical practice^{117,118,133}.

Management

Nephrectomy with adequate lymph node sampling is universally the mainstay of treatment for WT. However, the timing of surgery differs between the SIOP and COG recommendations, and underpins the differences in risk stratification^{134,135}. The SIOP WT studies have centred around pre-nephrectomy therapy since their beginning in 1971. Neoadjuvant chemotherapy allows assessment of *in vivo* histological response to treatment (that is, completely necrotic tumour indicates high responsiveness whilst a predominance of remaining blastemal cells is a marker of chemotherapy resistance), which may be used to guide therapeutic stratification after nephrectomy. According to SIOP protocols, patients are divided into low-risk, intermediate-risk and high-risk groups mainly on the basis of the degree of tumour necrosis and the relative proportion of each of the three cell types (epithelial, stromal or blastemal) remaining in the

Fig. 6 | Different histological patterns of Wilms tumour. a | Mixed type, with the blastemal and epithelial component. **b** | Blastemal type. **c** | Mixed type consisting of the mature epithelial and stromal components. **d** | Epithelial type composed of moderately differentiated tubules. **e** | Stromal type with heterologous elements including cartilage and skeletal muscle. **f** | Anaplasia in Wilms tumour with atypical mitoses, nuclear enlargement and hyperchromasia.

Table 3 | Risk classification according to SIOP Renal Tumour Study Group

Tumour type	For pretreated patients	For patients undergoing primary nephrectomy
Low-risk tumours	Congenital mesoblastic nephroma	Congenital mesoblastic nephroma
	Cystic partially differentiated WT	Cystic partially differentiated WT
	Completely necrotic WT	
Intermediate-risk tumours	WT epithelial type	Non-anaplastic WT and its variants
	WT stromal type	
	WT mixed type	WT focal anaplasia
	WT regressive type	
	WT focal anaplasia	
High-risk tumours	WT blastemal type	WT diffuse anaplasia
	WT diffuse anaplasia	Clear cell sarcoma of the kidney
	Clear cell sarcoma of the kidney	Rhabdoid tumour of the kidney
	Rhabdoid tumour of the kidney	Renal cell carcinoma
	Renal cell carcinoma	

SIOP, International Society of Paediatric Oncology; WT, Wilms tumour. Data from REFS^{9,122}.

viable component of the resected tumour. On the other hand, the COG approach of upfront nephrectomy allows immediate histological diagnosis, molecular analysis of tumour samples unaltered by chemotherapy, and drug-naïve local staging assessment (such as the presence of tumour spill or lymph node involvement). This knowledge can identify a subset of children with very low-risk tumours who may be treated with nephrectomy alone¹³⁶. Each approach has its pros and cons, yet survival rates are similar with an overall survival rate of >90%. According to both groups, the management of WT incorporates risk-based adjuvant chemotherapy and radiotherapy informed by multiple prognostic factors⁶ (Supplementary Table 2).

COG perspective

COG has a recommended strategy of primary nephrectomy for unilateral renal masses in patients without WT predisposition (achievable in >90% of patients) or failing feasibility of nephrectomy, core needle or open biopsy to guide subsequent therapy¹³⁵. Exceptions to upfront biopsy is patients with bilateral disease or patients with a bilaterally predisposed syndrome who should receive neoadjuvant chemotherapy (without biopsy) with the aim of preserving renal units, with surgery at 6–12 weeks after initiation of chemotherapy^{137,138}. The primary surgery using a transabdominal or thoracoabdominal approach allows accurate prechemotherapy staging including assessment of chemotherapy-naïve histology and prognostic molecular testing. Essential surgical tasks in completing a tumour-related nephrectomy include avoidance of tumour spill, ipsilateral hilar and regional lymph node sampling, and assessment and control of extrarenal tumour extension including the renal vein and ureter^{139–142}. Less conventional approaches such as laparoscopic nephrectomy, partial nephrectomy and split renal techniques may be carefully considered in patients with selected small tumours and in expert hands but at this point is confined to a small number of patients^{143–146}.

Chemotherapy is a mainstay of adjuvant therapy except in very low-risk tumours (defined as stage I, favourable histology WT, <550 g with negative lymph nodes and no syndromic features) where observation alone following nephrectomy may be sufficient, especially in the absence of loss of heterozygosity at chromosome 11p15 (REF.¹⁴⁷). Based on COG staging, the bulk of patients with favourable histology WT without certain adverse biomarkers receive regimen EE4A (vincristine and actinomycin D for 18 weeks) for stage I and II, or regimen DD4A (vincristine, doxorubicin and actinomycin D for 24 weeks) for stage III and stage IV favourable histology WTs^{102,109,148–150}. COG recommends the use of CT imaging to identify lung metastases, although it is recognized that up to one-third of lesions <1 cm in diameter may be benign nodules. Biopsy of lung nodules is encouraged if there is any doubt about the nature of the lesion. In addition, round, non-calcified lung nodules not in a fissure visible on chest CT are considered stage IV, regardless of size, unless histologically proven not to be WT¹⁰². The COG study AREN0533 demonstrated that ~40% of patients have complete resolution of pulmonary metastases after 6 weeks of three-drug induction therapy (regimen DD4A) and of these patients, those with tumours without 1q gain can safely have radiation omitted¹⁰⁹. Patients with an incomplete response of lung nodules after 6 weeks of DD4A chemotherapy receive whole-lung irradiation and are escalated to chemotherapy regimen M.

In the setting of loss of heterozygosity at 1p/16q, evidence shows that intensifying therapy to regimen DD4A for stage I and II or to regimen M (DD4A + cyclophosphamide or etoposide) for stage III and IV improves event-free survival outcome^{39,151}. Patients with diffuse anaplastic tumours seem to benefit from a multiagent regimen UH-2 (REF.¹²⁵). This regimen is associated with considerable toxicity and further modifications are currently being tested in COG protocol AREN1921 (NCT04322318) (Supplementary Table 3). A variety of strategies for salvage treatment in patients with relapse are used based on risk. Patients with low-risk relapse are usually managed with stratum B with an expected outcome of ~71% event-free survival rate¹⁵² and patients with higher-risk relapse are typically managed with regimen C¹⁵³ or ICE (ifosfamide, carboplatin and etoposide) with an expected outcome of ~42% event-free survival rate. Some centres use autologous bone marrow transplantation as consolidation therapy in patients with a high-risk tumour but this strategy has never been the subject of a randomized trial to confirm efficacy¹⁵⁴. A detailed summary of the impacts of the first generation of COG studies on WT was published in 2021 and forms the basis of standard management approaches in the COG for those patients not participating in a research study¹⁵⁵.

Newer COG research protocols are testing further refined chemotherapy algorithms incorporating stage, lymph node status, additional somatic molecular biomarkers, cardioprotection with dexrazoxane and new agents^{40,102,125,151}. WT is highly radiosensitive¹⁵⁶ radiation therapy is utilized for the regional management of stage III or IV favourable histology WT, and relapsed and anaplastic WT. COG protocols are incorporating

intensity-modulated radiation therapy¹⁵⁷ with doses ranging from 10.6 to 30.6 Gy depending upon residual tumour and site^{156,158}. National Cancer Cooperative Network¹⁵⁹ guidelines provide further detailed management guidelines and recommend that all children with renal tumours participate in a clinical trial.

SIOP perspective

According to the SIOP strategy, all patients >6 months of age with suspected WT receive either 4 weeks of preoperative chemotherapy with actinomycin D and vincristine (if localized) or 6 weeks of actinomycin D, vincristine and doxorubicin (if metastatic). The SIOP-9 trial showed no advantage on downstaging to more stage I tumours nor on reducing intraoperative tumour rupture by further prolonging the prenephrectomy regimen to 8 weeks¹⁶⁰. The SIOP approach accounts for the risk of misdiagnosis of WT by recommending upfront nephrectomy in infants <6 months of age, and percutaneous core needle biopsy in older children (7 years of age and older) or children with uncertain clinical pictures¹¹⁵.

Radical nephrectomy is regarded as standard in most patients with unilateral WT; however, the systematic use of preoperative chemotherapy may extend NSS opportunities in selected patients with unilateral non-syndromic tumours¹³⁴ to maximize preservation of renal function in patients. Following surgery, patients are stratified into three risk groups according to the histopathological features of the tumour¹²² (TABLE 3); the histological risk group together with tumour stage is used to direct the intensity of adjuvant chemotherapy and the need for radiotherapy (Supplementary Tables 2 and 4).

The regimen used in the experimental arm of the SIOP-2001 trial has been adopted as the new standard regimen for most patients with stage II–III intermediate-risk histology WT^{7,10}. This regimen consists of 27 weeks of postoperative treatment with vincristine and actinomycin D without doxorubicin. This schedule resulted in a non-significant decrease in event-free survival and had no effect on overall survival when randomly compared with the historical standard arm of 27 weeks of these two drugs (vincristine and actinomycin D) plus five doses of doxorubicin at 50 mg/m² (REF.⁷). The use of doxorubicin in patients with intermediate-risk stage II–III tumours is currently recommended only in those with non-stromal or non-epithelial large-volume tumours (that is, ≥500 ml after prenephrectomy chemotherapy), based on a post hoc analysis of patients in the SIOP 2001 trial¹⁰.

Radiotherapy to the flank is administered to patients with stage II WT with diffuse anaplasia or stage III WT (intermediate-risk and all high-risk), and doses range from 14.4 to 25.2 Gy (±10.8 Gy boost only for macroscopic residual disease)^{10,161}. To decrease organ toxicity whilst preserving oncological outcome, the conventional approach of flank irradiation is currently being adapted into a guideline for highly conformal image-guided flank target volume delineation¹⁶².

For metastatic disease, CT-only nodules are treated as metastases in the current SIOP protocol if they have a transverse diameter of ≥3 mm and imaging appearance suspicious for metastatic nodules after centralized radiological review¹⁰. Following a standard 6-week three-drug

preoperative regimen, 61–67% of patients have complete metastatic response before nephrectomy¹²³. Afterward, current SIOP guideline advise stratifying patients to adjuvant regimens consisting of either vincristine plus increasing cumulative doses of doxorubicin (in the range 150–250 mg/m²) or a four-drug regimen including etoposide, carboplatin, cyclophosphamide and doxorubicin (cumulative dose 300 mg/m²). In patients with remaining lung nodules, metastasectomy and histological confirmation of metastasis is advised. Stratification is based on the local stage of the primary tumour, histology of the primary tumour and the metastatic tumour (if resected), the size of metastases, and their response to preoperative chemotherapy and surgery (Supplementary Tables 2 and 4).

Pulmonary radiotherapy is administered for lung metastases lacking complete response by postoperative week 10. Evidence suggests that the majority of patients achieving a complete response after induction chemotherapy with or without surgery have a satisfactory survival probability even without radiotherapy to the lungs (5-year event-free survival 84%, 5-year overall survival 92%)¹²³. Patients with viable metastases at surgery or high-risk histology of the primary tumour receive radiotherapy to the lungs.

Patients with metastatic and high-risk disease are a rare subgroup with a dismal prognosis, justifying testing of novel and more intensive regimens in first-line therapy¹²⁶. Combinations of vincristine, irinotecan, cyclophosphamide, carboplatin, etoposide and doxorubicin, followed by high-dose melphalan and autologous stem cell rescue, are currently being explored by the SIOP-RTSG^{10,126,130}.

For bilateral tumours, SIOP guidelines aim to limit preoperative chemotherapy to a maximum of 12 weeks, with time intervals for evaluation to 6 weeks, also comparable with the COG approach. In order to maximize the possibility of bilateral NSS, an approach using carboplatin–etoposide in patients with an unsatisfactory response to vincristine–actinomycin D is under evaluation¹⁰. Adjuvant postoperative treatment guidelines generally follow the same principles as for unilateral WT.

Low-income and middle-income regions

Survival in low-income and middle-income countries (LMICs) is much lower than in high-income regions, with overall survival rates ranging from 11% in Sudan to 46% in Malawi^{163–166}. In LMICs factors that reduce the likelihood of a good outcome include delay in diagnosis leading to advanced disease at diagnosis^{94,167}, lack of diagnostic services, insufficient trained personnel, chemotherapy and radiation^{14,95,168,169}, misdiagnosis¹⁶⁷ and abandonment of therapy^{14,169} (BOX 2). Mortality is higher than in high-income regions owing to toxicity from surgery and/or chemotherapy, coupled with malnutrition^{167,170–172}. Addressing these psychosocial issues and malnutrition (chronic and acute) may significantly improve outcomes with time^{95,170,173}. As experience is gained in these countries, there is a need for support for the development of local priorities and for improvement in the availability of curative therapies and palliative care.

Trained physicians, nurses and ancillary personnel are central in providing quality care. The WHO Global Initiative for Childhood Cancer developed the framework of care *CureAll* to provide early diagnosis networks for referral to centres of excellence, to introduce childhood cancer to the Universal Health Coverage schemas and Cancer Control Plans, to introduce cancer and supportive care regimens of care, and to evaluate and monitor schemas to measure progress. These strategic plans are coupled with enabling actions — advocacy, leveraged financing and linked governance¹⁷⁴.

The SIOP approach with prenephrectomy chemotherapy provides the optimum and safest strategy in resource-limited settings. For large abdominal tumours (>500 ml), upfront surgery is associated with a high risk of surgical complications, tumour rupture and infection¹⁷⁵. Patients with severe malnutrition may have decreased clearance of chemotherapy and dose adjustment may be necessary with parallel monitoring of liver function and recovery of myelosuppression^{172,176}. In a preoperative chemotherapy scenario, close attention to the interpretation of pathology according to the SIOP risk classification is key to correct selection of post-operative treatment intensity, but requires specifically trained pathologists^{9,10}.

In LMICs, almost no clinical trials are available, with limited data and information on outcomes¹⁷⁷. Encouraging prospective registration studies and participation in clinical trials has the benefit of building expert clinical capacity, improving facilities and funding treatment and associated costs with the effect of improved survival¹⁷⁷, all according to the local sustainability and capacity building¹⁷⁸.

As an example, the Collaborative WT Africa Project is a multinational prospective clinical study open in seven sub-Saharan countries, which have registered prospective outcomes by implementing the SIOP adapted treatment regimen for WT^{164,179,180}. A minimum requirement of ultrasonography of the abdomen was used for diagnosis. The guidelines recommended preoperative chemotherapy followed by surgery and further chemotherapy, coupled with nutritional rescue. The preoperative treatment included either a 4-week two-drug (vincristine and actinomycin D) or a 6-week three-drug (vincristine, actinomycin D and doxorubicin) regimen depending on the presence of local or metastatic disease, respectively¹⁰⁴. Prolongation of preoperative chemotherapy was an option in patients with a large tumour volume. Patients weighing <12 kg or with severe acute malnutrition were given two-thirds of the calculated dose of the chemotherapy¹⁶⁴. The goal was then to achieve safe nephrectomy with lymph node sampling in patients with improved clinical and nutritional conditions, and tumour shrinking, which are all related to a reduced incidence of intraoperative morbidity. The postoperative chemotherapy aimed to follow the standard SIOP guidelines, but with spacing the administration of vincristine every 3 weeks at a dose of 2 mg/m² as also used for children >1 year of age in specific phases of some COG regimens (capped at 2 mg absolute dose), with the purpose of reducing the burden of frequent travel to hospital¹⁸¹. Acknowledging deficits

in radiotherapy provision (lacking across most of the African network), radiation therapy was used only in Kumasi and Accra, Ghana, for metastatic disease and for stage III abdominal tumour¹⁷⁹.

The lessons learnt from this structured guideline was the need for team members to work according to a shared vision, mission and principles¹⁷⁸. The importance of using local site leaders to set the priorities for a successful clinical trial and keeping processes as simple as possible for data completeness was also appreciated. Good communication, transparency and trust was found to be the cornerstone for successful local implementation of a multinational clinical trial in LMICs.

Just as clinical investigation is the cornerstone for best therapies and practices in high-income regions, research is needed to address the best therapy in different settings (better if tuned to prognostic indicators that have been studied and validated in the local context), best practices, and quality data to further improve outcomes^{164,165}. Multidisciplinary care meetings with mentors improve management and experience of the local and regional groups.

Long-term complications

Despite the greatly improved therapy for WT over time, survivors still report a high frequency (25%) of severe chronic health conditions in adult life^{15,16,182,183}. Patients with WT have a higher risk of death than the general population. In an analysis of children enrolled in the NWTs group between 1969 and 1995, the standardized mortality ratio was 24.3 during the first 5 years after diagnosis, but remained increased for >20 years after diagnosis (standardized mortality ratio 4.3)¹⁸⁴. Although the primary tumour remained the most frequent cause of death >5 years after diagnosis, secondary malignant tumours, cardiac disease and end-stage renal disease were also major causes of mortality.

The hazard ratios for hypertension (8.2), congestive heart failure (23.6) and renal failure (50.7) are all increased among 5-year survivors of WT compared with sibling groups^{15,185,186}. The risk of congestive heart failure increases with the cumulative dose of doxorubicin administered, with a critical threshold of 240 mg/m². Cardiotoxicity is potentiated by the concurrent use of radiotherapy, with girls and infants more susceptible than boys^{15,186}. Similarly, doxorubicin seems to potentiate the adverse effects related to radiotherapy, probably owing to its radiosensitization of cells. These adverse effects include abnormal tissue growth within the target area and secondary malignancies.

The 20-year cumulative incidence of end-stage renal disease is reported to be <1% in patients with unilateral WT and ~10% in patients with bilateral disease^{187–190}. The risk factors associated with end-stage renal disease owing to chronic renal failure are stromal-predominant histology (HR 6.4), intralobar nephrogenic rests (HR 5.9), and age at diagnosis of <24 months or <48 months (HR 1.7 and 2.8, respectively)¹⁹¹. Given the increased risk of cardiovascular morbidity with chronic kidney disease, identifying patients with a high risk of progressive renal impairment early is imperative to preserve the quality of life of long-term survivors. The wider availability

Oophorectomy

A surgical procedure to remove one or both ovaries.

and accuracy of patient genotyping may identify more molecular fingerprints with implications for renal function into adulthood, in order to select a subset of patients with WT without clinical renal impairment at presentation, yet who might benefit from nephron-sparing surgical procedures.

Gonadal dysfunction. Gonadal dysfunction is observed in female WT survivors^{192,193}, and is strongly associated with exposure of the ovaries to radiotherapy (at any dose) and treatment with alkylating drugs^{192,194}. The first-line chemotherapy with two drugs used (that is, vincristine and actinomycin D), in general, does not affect either ovarian reserve or male fertility. Whole-abdomen radiation usually results in primary ovarian failure or premature menopause. Additionally, exposure of patients with WT to treatment including anthracyclines and lung radiation is associated with cardiovascular risks that can affect pregnancy outcomes¹⁹². WT survivors should receive personalized counselling about the type and magnitude of reproductive health risks on the basis of their specific treatment exposure, with older girls with unfavourable histology or high-risk WT being at increased risk. Patients at the highest risk should be offered fertility preservation whenever possible, and after accurate counselling¹⁹⁵. In this view, prior abdominopelvic surgery (done to perform nephrectomy as part of initial cancer treatment) should not be regarded as a barrier to laparoscopic oophorectomy with tissue cryopreservation for fertility preservation.

Quality of life

Parents, charities and survivors of WT have worked closely with researchers and scientists to ensure that research is focused on what is important to families, and to highlight areas of need (BOX 3). The Wilms Tumour Link Group is an example of a parent-led research group

in the UK focused on identifying priorities for future research, and uses a social media group of >600 members from around the world to communicate research updates. Parents of children with WT have participated and presented at international scientific meetings and are considered to be partners in the research process, amplifying the patient voice within childhood cancer research⁹⁰.

This level of parent and patient involvement in research provides an important opportunity for physicians to work collaboratively. This collaboration facilitates the chance to have a greater impact on what is researched and highlights that not only is cure important but also the child's quality of life and happiness and health after cancer. The active involvement of parents and survivors in research helps translate findings in an equitable and accessible way. Findings are all too often kept within scientific journals that do not allow access to non-academics, so those that are affected by the disease are less informed. Working collaboratively and honestly with families is the key to patient-driven research with real-life translatable outcomes.

As a result of their better quality of life and physical functioning, children surviving renal tumours can hopefully also enjoy an increased involvement in sports. Patient counselling should include explaining any potential contraindication for practising sports carrying a risk of abdominal injuries¹⁹⁶. Practice guidelines, where available, addressing the participation of children and adolescents with a solitary kidney (like most survivors of WT) in high-impact sports do not share a common vision worldwide¹⁹⁷. In Italy, unlike the rest of Europe and the USA¹⁹⁸, having only one kidney automatically disqualifies an individual wishing to participate in any organized competitive contact sport, including basketball and soccer, and sometimes, volleyball (BOX 4).

To instigate positive changes in cancer care through exercise, and to endorse change in patients sensitively, patients, families and health-care teams must be made more aware of current evidence-based information to provide a framework for the harmonization of guidelines for sport participation of renal tumour survivors, to ensure that they can exercise freely yet safely.

Outlook**Basic research**

Increased understanding of the aberrant molecular pathways active in Wilms tumorigenesis has identified many potential targeted therapeutic approaches that could be applied in a clinical setting³⁶. These include miRNA therapeutic modulation^{43,44}, Wnt signalling⁹⁰ and p53-specific biological targeting agents in anaplastic WT^{69,70}. In addition, retinoic acid, although ineffective as a WT therapy in the all-*trans* form¹⁹⁹, may impart a differentiation effect on precancerous nephrotic rests in the 13-*cis* form, potentially mitigating the development of WT in a selected group of patients at risk, particularly those with hyperplastic nephroblastomatosis^{200,201}. Although the options seem intriguing, the main challenges are the relatively few patients in each molecular subgroup, WT intratumoural heterogeneity⁷⁸, few actionable known targets, selection and conduct of

Box 3 | Patient experience

The statement provided has not been edited and the patient's emphases remain in place.

Teenage years, the best ones in everyone's life. I was living unforgettable moments, going out and having parties with my friends. And then, after some medical checks, hell overnight. I had cancer. At first, I started imagining what I would have had to go through, how much I would have suffered. I was lost in doubts, fear and contrasting feelings.

To start chemotherapy shocked me. Eight hours, each impressed in my mind, in which millions of medicine's drops came into my body. I felt exhausted.

As I was left alone for a moment in that hospital room, I abandoned myself to tears at the idea of repeating all of that the next day, and for eight more courses: that thought killed me. I came in that realization in that right moment.

I remember how important it was, for me, to have my friends around and to spend as much time as possible together. I remember they were the only ones who made me laugh, who made me feel normal, like nothing had ever changed. They made me breathe, giving me the oxygen I needed. They reminded me how strong I was, when I was totally worn out. They recalled me what it meant to live, as sometimes I forgot how to do it.

Then, the COVID-19 pandemic situation came, and loneliness. My mum and I, stop. Far away from everyone, from everything. Three months of physical pain for chemo that I kept doing, of discouragement and fear. And, if it wasn't enough, there was also the worry of catching the virus.

Finally, after never-ending months, I came back to my lovely Naples. To my friends, to my family. To the sea, as I saw it, I felt free. Everything finally came to an end, and I couldn't believe it.

-G.B., 16 years old.

Box 4 | International controversies in advice on sporting activities in people with single kidneys

- Most children diagnosed with Wilms tumour (WT) become long-term survivors and living with a surgically solitary kidney.
- Among injuries occurring during sport exposure, the incidence of injuries to the kidneys is very low (sporting kidney injuries are 0.07–0.5% of all sports-related injuries), less frequent than head injuries, and usually without serious sequelae^{235,236}.
- The recommendations for the participation of children and adolescents with a solitary kidney in contact or collision sports have changed over time. The last update from the American Academy of Paediatrics (2001) leans towards player participation without restriction in non-contact sports, and with individual assessment for limited-contact, contact, and collision sports to arrive at an unbiased judgement, which is not based only on the fact of having a solitary kidney¹⁹⁸.
- However, national advice towards permission to participate in high-impact sports varies between countries and over time¹⁹¹.
- Flank protectors have not been rigorously evaluated and an international standard for the protection they may offer is not available¹⁹⁶.
- Individual counselling and decision-making between child, families and oncologist are recommended.

targeted trials and coordination of timely enrolment in the background of competitive trials^{90,202}.

Translational and clinical research

Some novel targets for WT have emerged, mostly based on PDX-dependent drug screens, leading to a few phase I and II trials in WT. Examples include phase II study of IGF1-based inhibition (cixutumumab), anti-VEGF-based therapy (sorafenib, cabozantinib), aurora-A-kinase inhibition (alisertib), and anti-mitotic based therapies either through direct microtubule inhibitory activity (ixabepilone) or via an antibody–drug conjugate linking an antimitotic agent (DM1) to an anti-CD56 antibody (lorvotuzumab) (lorvotuzumab mertansine, IMGN901)²⁰². With the advance of β -catenin targeting, the COG will soon launch the study of tegavivint, a specific β -catenin inhibitor, to include a WT cohort²⁰³.

Advances in refined personalized multilayered biologically derived WT treatment will emerge, in the shorter term, via expanded creation and use of tumour models, ideally sufficient in number to represent the majority of WT biological subtypes^{86,87}. Development of organoids, spheroids and PDX models has progressed from basic investigation to real-time patient-specific drug screening, and application of these approaches is now feasible, with plans evolving to launch an international patient-individualized relapse WT protocol harnessing this opportunity^{90,204}.

Novel imaging investigations also hold promise for advancing WT treatment. For example, diffusion-weighted imaging MRI has been implemented as standard for diagnostic and post-chemotherapy assessment¹⁰⁵. Such techniques may non-invasively quantify tumours and risk-stratify patients with WT prior to surgery, with radiological surrogates (apparent diffusion coefficient mapping) for both necrosis (particularly relevant when tumour size remains stable) and blastemal-type histology²⁰⁵. Radiogenomics holds promise to further expand the utility of imaging in the care of patients with WT, as do artificial learning algorithms, for example,

for the detection and quantification of lung nodules (and disease elsewhere), which dictates intensity of treatment. The import of such technology is magnified by the shift from chest plain radiography to adequate CT scans, which provide detailed information on lung lesions, but also reveal that there is considerable inter-rater and intra-rater variation in interpreting such lesions even by experienced radiologists²⁰⁶.

WT may be amenable to advances in liquid biopsy techniques for diagnostics, monitoring of therapy, and detection of minimal residual disease^{80,118,207}. As an example, COG study AREN1921 (NCT04322318) is collecting serial blood and urine samples in newly diagnosed anaplastic WT and patients with relapsed favourable histology WT to test the potential benefits of liquid biopsy²⁰⁸.

Cooperative group efforts

Both the COG and the SIOP groups have advanced well-organized prospective clinical trials and studies that tightly integrate biological aims and clinical insights, both linked to specific clinical protocols (AREN1921; NCT04322318) or via overarching biobanking and risk-stratification studies (AREN03B2; NCT00898365, SIOP UMBRELLA)¹⁰. Cross-validation (meta-analysis) of data between these groups, especially data from small cohorts of rare patients (such as those with anaplastic tumours, bilateral tumours or relapsing disease) and strategic efforts to synergize intervention trials or observational studies hold promise in continuing to advance diagnostics, risk stratification and therapeutic options. Such ‘harmonization’ between cooperative groups has been formally advanced in the form of the Harmonica Initiative that integrates multidisciplinary dialogue, meetings, consensus building, specific research focus and overall strategies on a trans-continental, inter-cooperative group level^{6,90,127,202}. Likewise, dialogue continues regarding potential trans-Atlantic collaborative trials among the Innovative Therapies for Children with Cancer (ITCC), the Pediatric Early Phase Clinical Trials Network (PEP-CTN), the Pediatric Preclinical Testing Consortium, and parent representatives⁹⁰.

Global efforts

Childhood cancer therapy in LMIC lags behind in diagnosis, therapy and survival, with minimal clinical or biological research. In 2018, WHO launched the Global Initiative for Childhood Cancer. In 2020, WHO published the CureAll Framework technical package WHO Global Initiative for Childhood Cancer, designed to provide guidance to member states for the implementation of childhood cancer services in resource-constrained settings¹⁷⁴. Six tracer cancers, including WT, are targeted to provide guidance for diagnosis, therapy and supportive and survivorship care. With the help of international paediatric cancer partners (academic, regional and global societies and non-governmental organizations), the aim is to establish the necessary training and design of basic, and translational and clinical research¹⁷⁴. Hence, progress in WT survival rates is expected to become more visible in the current decade.

Published online: 14 October 2021

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Acknowledgements

The authors thank both the SIOP Renal Tumour Study Group and the Children's Oncology Group Renal Tumour Committee for their collective expertise. Their work laid the foundations for this Review article. The authors also thank parents and survivors of childhood Wilms tumour for their contribution to setting research priorities.

Author contributions

Introduction (F.S. and K.P.-J.); Epidemiology (F.S., K.P.-J. and K.N.); Mechanisms/pathophysiology (F.S., K.P.-J., M.G., M.M. and S.B.); Diagnosis, screening and prevention (F.S., K.P.-J., C.V.F., J.B., S.L.-F. and G.V.); Management (F.S., C.V.F., K.P.-J., S.L.-F. and V.P.); Quality of life (F.S., K.P.-J. and A.P.); Outlook (F.S., K.P.-J., C.V.F., J.B., M.G., S.L.-F. and J.I.G.); Overview of the Primer (F.S. and K.P.-J.).

Competing interests

All authors declare no competing interests.

Peer reviewer information

Nature Reviews Disease Primers thanks R. Furtwängler, N. Cost, J. Kalapurakal and the other anonymous reviewer(s) for their contribution to the peer review of this work.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Supplementary information

The online version contains supplementary material available at <https://doi.org/10.1038/s41572-021-00308-8>.

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