



Review

# Wilms tumour surveillance in at-risk children: Literature review and recommendations from the SIOP-Europe Host Genome Working Group and SIOP Renal Tumour Study Group



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**Abstract** Since previous consensus-based Wilms tumour (WT) surveillance guidelines were published, novel genes and syndromes associated with WT risk have been identified, and

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diagnostic molecular tests for previously known syndromes have improved. In view of this, the International Society of Pediatric Oncology (SIOP)-Europe Host Genome Working Group and SIOP Renal Tumour Study Group hereby present updated WT surveillance guidelines after an extensive literature review and international consensus meetings. These guidelines are for use by clinical geneticists, pediatricians, pediatric oncologists and radiologists involved in the care of children at risk of WT. Additionally, we emphasise the need to register all patients with a cancer predisposition syndrome in national or international databases, to enable the development of better tumour risk estimates and tumour surveillance programs in the future.

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## 1. Introduction

Wilms tumour (WT) (nephroblastoma) is the most common childhood renal malignancy. Current treatment regimens include a combination of chemotherapy, surgery and, in some cases, radiotherapy, achieving survival rates of 90% [1]. Yet, advanced stage WT is still associated with significant morbidity and mortality. To enable the detection of smaller and lower-stage tumours [2,3], WT surveillance is offered to children with various cancer predisposition syndromes (CPS), with *WT1*-related syndromes and Beckwith-Wiedemann syndrome/spectrum (BWS/BWSp) being the most well-known examples [4–6].

In general, tumour surveillance is recommended if the benefits outweigh the costs and burden. This depends on many factors, including the tumour risk of the screened population and the consequences of early detection for prognosis and management. Worldwide, different countries use different arbitrary thresholds to determine whether WT surveillance is indicated in children with a specific CPS, varying between 1 and 5% estimated childhood WT risk [4,5].

Since previous consensus-based WT surveillance guidelines [4] were published, novel genes and syndromes associated with WT risk have been identified [7–9]. For some previously known syndromes, molecular tests have improved, and/or larger series have been published, enabling better WT risk estimates. More recent surveillance recommendations are limited to BWSp [10] or targeted towards the North American health-care culture [5]. Here, updated WT surveillance guidelines developed by the International Society of Pediatric Oncology (SIOP)-Europe Host Genome Working Group and SIOP Renal Tumour Study Group (RTSG) are presented.

Recommendations and the rationale behind them are discussed based on an extensive literature review and international consensus meetings, addressing all currently known WT predisposition genes and syndromes. Additionally, we discuss imaging modalities and surveillance interval and emphasise the need to prospectively register all patients with a CPS in national or international databases, to enable better risk

estimates in the future. These guidelines are for use by clinical geneticists, pediatricians, pediatric oncologists and radiologists involved in the care of children at risk of WT.

## 2. Methods

The international consensus group was comprised of 16 participants from the United Kingdom, The Netherlands, France, Germany and Japan, including pediatric oncologists, geneticists, a radiologist and an epidemiologist. Discussions occurred via video conferences and email communications. A preliminary meeting was held in June 2020 after which the identified CPS were divided into four groups, discussed in smaller meetings with eight participants each. Various patient/parent representatives were contacted and requested to comment on their experiences regarding the practical and emotional burden, recommended risk threshold and duration and willingness to travel for WT surveillance. Based on the discussions during the meetings and the input from patient/parent representatives, recommendations were developed which were discussed in a final consensus meeting with all participants in November 2020.

A PubMed search was conducted using the keywords “Wilm\*” or “Nephroblastoma\*” or the MeSH term “Wilms Tumour” in combination with synonyms for the various WT predisposition genes and syndromes (Supplemental Table 1). Articles of interest were selected based on title/abstract screening, prioritizing cohort studies, larger series and previous literature reviews with information on WT occurrences for each gene or syndrome. Additionally, the PubMed search was combined with the keywords “Surveillance” or “Screening” to explore the evidence supporting (or against) surveillance.

For the majority of the reviewed genes and syndromes, our literature review identified only a limited number of studies which were mainly case reports or small case series. In order to grade the recommendations that were established during the consensus meetings, we used the following scale which was adapted from the recently published European Reference Network-*PTEN*

cancer surveillance guideline [11]: (i) strong evidence, consistent evidence and new evidence unlikely to change recommendation and expert consensus; (ii) moderate evidence, expert consensus or majority decision but with inconsistent evidence or significant new evidence expected and (iii) weak evidence, inconsistent evidence AND limited expert agreement.

CPS with an estimated childhood WT risk of more than 5% were primarily selected as those where surveillance should be offered [12]. For syndromes with an estimated WT risk between 1 and 5%, additional cancer risks were taken into account when deciding on whether to recommend surveillance. As accurate tumour risk estimates require large, unbiased cohorts with long-term follow-up, we estimated cumulative WT risks by calculating the percentage of reported patients with WT among the total number of reported individuals with a given CPS, acknowledging that such estimates are prone to selection bias. The recommended duration of surveillance was based on the age at which approximately 90–95% of reported WTs have been diagnosed, in accordance with previous guidelines on WT surveillance [4,5] and other CPS [13].

### 3. Aim and potential benefits of surveillance

WT surveillance aims to improve survival and to reduce treatment-related toxicity for WT patients with a genetic and/or epigenetic predisposition, by enabling the detection of smaller and lower stage tumours. There are no studies directly comparing survival rates or morbidity between screened and unscreened patients. Owing to the generally good prognosis of WT, the effects of WT surveillance on overall survival rates may be small. Diagnosing lower stage tumours can, however, avoid the need for toxic treatment such as anthracyclines or radiotherapy, reducing direct and late side-effects. It has been retrospectively demonstrated that children with BWS or hemihypertrophy undergoing WT surveillance had significantly lower stage WT compared with children not participating in a surveillance program [2,3] and that WTs in patients with Wilms tumour, aniridia, genitourinary anomalies and range of developmental delays (WAGR) syndrome are significantly smaller if they are surveillance-detected than symptomatic tumours [14]. Analysis of a registry-based cohort could provide stronger unbiased evidence in the future.

Diagnosing smaller tumours can also enable nephron-sparing surgery (NSS). The SIOP-RTSG 2016 UMBRELLA protocol recommends NSS for children with a genetic predisposition if feasible depending on the size and location of the tumour [15]. Several studies have demonstrated that NSS can be safely performed in children with a WT predisposition syndrome with unilateral or bilateral WT [16–18]. In patients with WAGR syndrome and WT, mortality was more frequently

caused by end-stage renal disease (ESRD) than the tumour itself [19]. Therefore, NSS is believed to be particularly relevant for patients with a risk of developing renal failure (such as *WT1*-related conditions), where it may prevent or delay the need for dialysis or renal transplantation.

### 4. Costs and burden of surveillance

In 2001, a cost-benefit analysis was performed to estimate the costs per life-year saved for WT and hepatoblastoma surveillance in a hypothetical cohort of children with BWS [20]. The costs were considered to be reasonable in comparison to other population-based cancer surveillance programs at the time [20]. An update of this study is warranted, which would ideally also address additional benefits such as decreased toxicity and the feasibility of NSS.

False-positive or incidental findings detected by surveillance have been reported in children with BWSp. Choyke *et al.* reported two resected renal lesions, which were suspected to be cystic WT, but proved to be infected renal cysts upon histological examination [2]. In one of these patients, a radical nephroureterectomy had been performed. Zarate *et al.* identified renal or liver abnormalities in 25 of 63 (40%) children with BWSp undergoing surveillance [21]. Such findings can trigger unnecessary interventions and investigations, leading to additional costs, and may cause anxiety in patients and their guardians.

The practical and emotional burden associated with cancer surveillance ranges from logistical issues to anxiety around surveillance visits. Based on input from the International WAGR Syndrome Association (IWSA) and the UK BWS Support Group, surveillance visits can be stressful for some parents while reassuring for others, and anxiety similarly varies from child to child. Both groups reported that not undergoing surveillance can also be stressful for parents. Practicalities such as time and transport can be an issue but are less important when surveillance visits can be combined with regular hospital visits for other indications. Overall, both groups emphasised that the benefits of surveillance outweigh the practical and emotional burden, and they would not object to surveillance of longer duration than that being proposed here.

### 5. General recommendations: how to screen

Surveillance should be offered after parents have received counselling about WT risk in their child by a clinical geneticist or genetic counsellor. Renal ultrasonography is the recommended screening modality, which avoids radiation exposure (unlike computed tomography [CT] imaging) and does not require anaesthesia in young children (unlike magnetic resonance

imaging [MRI]). Although CT or MRI may have a higher resolution for discriminating between different tumour types and nephrogenic rests, ultrasonography is believed to be equally effective for initial WT detection based on expert consensus. Guidelines on how to perform renal ultrasound surveillance are provided in Table 1.

Surveillance can be undertaken at a local center but should be performed by someone with experience of pediatric ultrasonography with screen-detected lesions managed at a specialist center. For certain syndromes (specified in Table 1), we recommend replacing renal ultrasonography by full abdominal ultrasonography because of additional abdominal tumour risks.

Previous surveillance guidelines have recommended scans every 3–4 months [4–6,10] as WTs are known to have a high growth rate with the shortest reported estimated doubling time being 11 days [22]. We recommend a surveillance interval of 3 months because in clinical practice, surveillance visits can be delayed, and the consensus group agreed that an interval of  $\geq 4$  months risks higher tumour stage at diagnosis. A recent clinical report demonstrated that growth rate varies between tumours, and this may depend on their molecular characteristics [23]. Whether growth rate also varies between different underlying predisposition syndromes is a relevant research question to address in preclinical models.

## 6. General recommendations: when to screen

Surveillance recommendations for all identified CPS associated with an increased risk of WT development are presented in Table 2 and discussed in more detail in the following sections. We recommend initiating

Table 1  
Guidelines for renal/abdominal ultrasonography in children at risk of Wilms tumour, adapted from Scott *et al.*, 2006 [4] and updated.

Equipment	High-frequency probes and pediatric settings. Linear (>10 MHz) in infants, curvilinear (>6 MHz) and linear (>10 MHz) probes in toddlers and children.
Preparation	Fasting and bladder preparation are not required.
Target organ	Kidney only, except for patients with BWS/BWSp, lateralised overgrowth or SGBS, who require a full abdominal ultrasound including adrenal glands and liver to check for other abdominal tumours, including neuroblastoma, hepatoblastoma and adrenocortical carcinoma.
Technique	Appropriate focal point and time gain settings. The whole renal parenchyma should be imaged in longitudinal and transverse planes with the child both supine and prone.
Normal variants	Foetal lobulations, dromedary hump, column of Bertin, duplex or bifid collecting systems.
Suspicious lesions	Solitary or multiple cystic or solid parenchymal lesions with or without sonographic signs of expansile growth. A solid lesion is more likely to represent malignancy than a simple cystic anechoic lesion.

BWS/BWSp, Beckwith-Wiedemann Syndrome/Spectrum; SGBS, Simpson-Golabi-Behmel Syndrome.

surveillance at birth or as soon as a CPS is diagnosed. As molecular confirmation of a CPS can take some months, surveillance can be initiated based on the clinical suspicion of a CPS, while awaiting test results.

If WT surveillance is indicated, we recommend continuing surveillance until a child's 7th birthday regardless of the underlying CPS diagnosis. By the age of 7 years, 90% of sporadic WTs [3], 94% of WTs in children with BWS [3] and >95% of WTs in children with *WT1*-related syndromes [14,19,24] have been diagnosed, and this age has been previously recommended by other groups [5,10]. For other CPS, the number of reported patients with WT was too small to determine this percentage.

Among patients with *WT1*-related syndromes, >90–95% of WTs are diagnosed before the age of 5 years, although patients with nephrogenic rests progressing to (metachronous) tumours after the age of 5 years have been reported [14,25]. Although we have previously suggested screening patients with *WT1*-related syndromes until the age of 5 years [4] and to prolong surveillance only for patients with a prior diagnosis of WT/nephroblastomatosis [14], the consensus group agreed to recommend surveillance until the 7th birthday for all CPS including *WT1*-related syndromes. Factors that influenced this decision were that nephroblastomatosis may not be identified on ultrasound, to maintain consistency with other WT predisposition genes/syndromes and in response to patient/parent representatives' views.

## 7. Considerations for specific WT predisposition genes and syndromes

### 7.1. *WT1* pathogenic variants

WT surveillance is recommended for children with germline pathogenic variants in *WT1*, except for intron 9 mutations. *WT1* was the first known WT predisposition gene [26–28]. Germline *WT1* aberrations are present in an estimated 2–11% of patients with WT [29–33], usually occurring de novo in isolated (non-familial) cases. The exact percentage may vary between different geographic WT cohorts [34]. In addition to an increased risk of WT, *WT1* pathogenic variants are associated with renal disease (glomerulosclerosis) which can lead to renal failure and disorders of sexual development (DSD). There is considerable overlap in the phenotypic spectrum of patients previously referred to as having Denys-Drash syndrome (exon 8 or 9 mutations) or Frasier syndrome (intron 9 mutations) [35], although genotype-phenotype correlations exist [24,36–38]. Notably, WT can also be the first manifestation of a pathogenic *WT1* variant in children with an otherwise unremarkable medical and family history.

Based on data extracted from five studies (Supplemental Table 2), WTs were reported in ~50% of

Table 2

Summary of cancer predisposition genes/syndromes with a reported risk of Wilms tumour (WT) development and surveillance recommendations.

Syndrome/gene		Estimated % of patients with this condition with WT	WT surveillance recommended? If yes: 3-monthly from birth until 7th birthday	Evidence*
<i>WT1</i> mutations	Exonic missense variants	~50%	<b>Yes, renal US</b>	Strong
	Exonic truncating variants	~80%	<b>Yes, renal US</b>	Strong
	Intron 9 variants	~2%	No	Moderate
WAGR syndrome (11p13 deletion encompassing <i>WT1</i> )		~55%	<b>Yes, renal US</b>	Strong
Beckwith-Wiedemann syndrome/ spectrum (BWS/BWSp)	LOM IC2	<1%	No	Moderate
	GOM IC1	~21%	<b>Yes, full abdominal US<sup>A</sup></b>	Strong
	Paternal UPD 11p15	~8%	<b>Yes, full abdominal US<sup>A</sup></b>	Strong
	<i>CDKN1C</i> mutation	~1%	<b>Yes, full abdominal US<sup>A</sup></b>	Moderate
	Classical BWS with negative tests	~5%	<b>Yes, full abdominal US<sup>A</sup></b>	Moderate
Lateralised overgrowth with $\geq 1$ BWS feature		Unknown	<b>Yes, full abdominal US<sup>A</sup></b>	Moderate
Lateralised overgrowth without additional BWS features		Unknown	No	Moderate
Perlman syndrome ( <i>DIS3L2</i> ) (recessive)		~64%	<b>Yes, renal US</b>	Strong
<i>PIK3CA</i> -related overgrowth ( <i>PIK3CA</i> ) (somatic mosaic)		1–5%	No	Moderate
Simpson-Golabi Behmel syndrome ( <i>GPC3/GPC4</i> )		~3%	<b>Yes, full abdominal US<sup>A</sup></b>	Moderate
<i>TRIM28</i> mutations		>50% penetrance	<b>Yes, renal US</b>	Moderate
<i>REST</i> mutations		>50% penetrance	<b>Yes, renal US</b>	Moderate
<i>CTR9</i> mutations	Truncating/splicing variants	Appears high	<b>Yes, renal US</b>	Moderate
	Missense variants	WT not reported	No	Moderate
<i>HACE1</i> mutations		Unknown	No	Moderate
<i>KDM3B</i> mutations		Appears low	No	Moderate
<i>FBXW7</i> mutations		Unknown	No	Moderate
<i>NYNRIN</i> mutations (recessive)		Unknown	No <sup>B</sup>	Moderate
Fanconi anaemia	FANC-D1 ( <i>BRCA2</i> ) (recessive)	~20%	<b>Yes, renal US</b>	Strong
	FANC-N ( <i>PALB2</i> ) (recessive)	~40%	<b>Yes, renal US</b>	Strong
	Other subtypes	WT not reported	No	Moderate
Mulibrey nanism ( <i>TRIM37</i> ) (recessive)		~6–8%	<b>Yes, renal US</b>	Moderate
Mosaic variegated aneuploidy (MVA)	<i>BUB1B</i> variants (recessive)	~50%	<b>Yes, renal US</b>	Moderate
	<i>TRIP13</i> variants (recessive)	~20%	<b>Yes, renal US</b>	Moderate
	<i>CEP57</i> variants (recessive)	WT not reported	<b>Yes, renal US</b>	Moderate
	MVA with unknown cause	WT not reported	<b>Yes, renal US</b>	Moderate
9q22.3 microdeletion syndrome		10–20%	<b>Yes, renal US</b>	Moderate
2p24.3 duplication (encompassing <i>MYCN</i> )		Unknown	No	Moderate
Osteopathia striata with cranial sclerosis ( <i>WTX</i> ) (X-linked)		Unknown, but appears >5%	<b>Yes, renal US</b>	Moderate
2q37 deletion syndrome	Extending to 2q37.1	10–20% (3 cases)	<b>Yes, renal US</b>	Moderate
	More distal deletions	WT not reported	No	Moderate
Bloom syndrome ( <i>BLM</i> ) (recessive)		~3%	No	Moderate
DICER1 syndrome ( <i>DICER1</i> )		<2%	No <sup>C,D</sup>	Moderate
Li Fraumeni syndrome ( <i>TP53</i> )		Low	No <sup>C</sup>	Moderate
Neurofibromatosis type 1 ( <i>NFI</i> )		<1%	No <sup>C</sup>	Moderate
Hyperparathyroidism-jaw tumour syndrome ( <i>CDC73</i> )		<5%	No <sup>C</sup>	Moderate
Constitutional mismatch repair deficiency ( <i>MSH2</i> , <i>MSH6</i> , <i>MLH1</i> , <i>PMS2</i> ) (recessive)		~3%	No <sup>C</sup>	Moderate
Bohring-Opitz syndrome ( <i>ASXL1</i> )		~7%	<b>Yes, renal US</b>	Moderate
Trisomy 13		<1%	No	Moderate
Trisomy 18		~1%	No	Moderate

BWS/BWSp, Beckwith-Wiedemann Syndrome/Spectrum; GOM, gain of methylation; US, ultrasound; WAGR, Wilms tumour, aniridia, genitourinary anomalies and range of developmental delays.

Notes.

A. Additional risk of other abdominal tumours.



B. Surveillance can be considered in a research setting.

C. In these syndromes, cancer surveillance is recommended for other cancer types (beyond the scope of this guideline), but does not include 3-monthly renal or abdominal US.

D. To enable early detection of cystic nephromas, the SIOP-Europe Host Genome Working Group and CanGene-CanVar Clinical Guideline Working Group recommend 6-monthly renal US until the child's 6th birthday (manuscript under review).

\*Evidence.

(i) strong evidence: consistent evidence and new evidence unlikely to change recommendation and expert consensus.

(ii) moderate evidence: expert consensus or majority decision but with inconsistent evidence or significant new evidence expected.

(iii) weak evidence: inconsistent evidence AND limited expert agreement.

patients with exonic missense mutations, ~80% of patients with exonic truncating mutations and ~2% of patients with intron 9 mutations [36–40]. Patients included in these studies were identified because of the presence of nephrotic syndrome or DSD. A subset of these patients, particularly those with exonic missense variants, had ESRD in infancy and underwent prophylactic bilateral nephrectomies, potentially leading to an underestimate of WT risk in these studies. This is not the case for patients with intron 9 mutations, who typically develop ESRD at older ages [41]. Although patients with intron 9 mutations are frequently diagnosed with DSD, which is associated with a high risk of gonadoblastoma [41], ultrasound or MRI surveillance is not reliable for the early detection of gonadal neoplasms [42]. Therefore, combined with the low risk of WT, renal or abdominal ultrasound surveillance is not recommended for patients with intron 9 mutations.

In series of patients with *WT1* variants and WT, the age at tumour development varied from 0 to 4.5 years, with medians between 9 months and 1.6 years [24,25,29,31,32,36–38,43]. A risk of later-onset metachronous WT has been reported [25].

## 7.2. *WAGR* syndrome

WT surveillance is recommended for all children with *WAGR* syndrome.

*WAGR* syndrome is caused by the contiguous deletion of *WT1* and *PAX6* genes at 11p13. The diagnosis of *WAGR* syndrome is usually established early because of aniridia, frequently accompanied by other ophthalmologic abnormalities, genitourinary anomalies and developmental delay.

Based on data extracted from four published cohorts of patients with *WAGR* syndrome (Supplemental Table 3), WTs were reported in ~55% of all patients [44–47]. Reported ages at WT diagnosis varied from 0.3 to 25 years (median ages: 15–23 months) [14,19,32,45,46,48]. Similar to patients with *WT1* variants, patients with *WAGR* syndrome are at risk of developing metachronous tumours [14] and renal failure [19].

## 7.3. *Beckwith-Wiedemann* spectrum

Surveillance by full abdominal ultrasound is recommended once every 3 months for all molecular subtypes

of BWSp, except for IC2 (*KCNQ1OT1:TSS-DMR*) loss of methylation (IC2 LOM).

BWSp is the most frequently diagnosed WT predisposition syndrome, affecting 1 in 10,500 children in Western populations [49]. BWSp is considered an overgrowth syndrome with a highly variable phenotype which can include (lateralised) overgrowth, macroglossia, abdominal wall defects and hyperinsulinism leading to neonatal hypoglycemia [10].

BWS is molecularly characterised by genetic and/or epigenetic changes at the 11p15.5 imprinted region, which are frequently mosaic. In 2018, the European Cooperation in Science and Technology (COST)-funded European Network for Congenital Imprinting Disorders published a consensus document in which the novel term BWSp was introduced. BWSp includes patients with classical BWS as well as patients with 'atypical BWS' (not meeting the criteria for a clinical diagnosis) or 'isolated lateralised overgrowth' with a BWS-associated molecular (epi)genetic alteration at the 11p15.5 imprinted region [10].

Maternal IC2 LOM, the most prevalent molecular subtype, is associated with an estimated WT risk of only ~0.2%, and therefore, surveillance is not recommended [10,50,51]. Patients with a gain of methylation at the maternal IC1 locus (*H19/IGF2* DMR) comprise only 5% of all patients with BWSp but have an estimated ~21% cumulative risk of WT development [10,50,51]. This risk is estimated to be ~8% in patients with a paternal uniparental disomy of 11p15.5 [10,50,51]. Pooled WT risk estimates and implications for surveillance are described for the major molecular subtypes in Supplemental Table 4, which was adapted from the study by Maas *et al.* and updated to include the more recently published study by Cöktü *et al.* [10,50,51].

## 7.4. *Lateralised overgrowth*

Full abdominal ultrasound is recommended once every 3 months for patients with lateralised overgrowth (LO) and ≥1 additional feature of BWSp. LO, also known as hemihypertrophy or hemihyperplasia, is defined as overgrowth of one side of the body compared with its contralateral side. This may be restricted to (part of) a limb or the face, with a pragmatic definition that it should be apparent 'from the end of the bed' [52]. The incidence is estimated to be 1:13,000 to 1:86,000 live births [53].

If a syndromic diagnosis can be established based on molecular testing or clinical criteria, tumour surveillance should be initiated accordingly. Robust data are lacking for remaining patients (i.e. isolated LO and no detectable molecular finding). Two studies have estimated the overall tumour risk to be around 10%, with WT and neuroblastoma being the most common tumour types [54,55], although it is likely that this includes patients with low-level mosaic BWSp aberrations.

Therefore, for all patients with LO, we recommend careful assessment by a clinical geneticist and molecular testing which should include 11p15.5 analysis in germline DNA. Baseline abdominal ultrasonography is advised to assess the presence of organomegaly, which is an additional BWSp feature and therefore an indication for initiating WT surveillance. For significant isolated LO, we advise trying to establish the underlying (epi) genetic cause by testing overgrown tissues and initiating surveillance while awaiting test results. Further research focussing on this group of patients is necessary to clarify WT risks.

### 7.5. Other overgrowth syndromes

WT surveillance is recommended for Perlman syndrome (renal ultrasound) and Simpson-Golabi Behmel syndrome (SGBS) (full abdominal ultrasound). Although WTs are reported in a subset of patients with *PIK3CA*-related overgrowth spectrum (PROS), surveillance is currently not recommended by the consensus group (see paragraph on PROS). In patients with other overgrowth syndromes (e.g. Sotos, Proteus, Malan, Thauvin Robinet Faivre and Weaver syndrome), WTs were only sporadically reported or not at all, and surveillance is therefore not recommended.

Perlman syndrome is an autosomal recessive syndrome associated with a 64% risk of WT development in children surviving the neonatal period, in addition to polyhydramnios, macrosomia, facial dysmorphism, renal dysplasia, multiple congenital anomalies and frequently neurodevelopmental delay [56–58]. More than half of the children with Perlman syndrome die within the first year of life because of respiratory insufficiency, sepsis and/or renal failure [59]. In 2012, biallelic inactivating variants in *DIS3L2* were identified as the cause of Perlman syndrome [60]. *DIS3L2* appears to play a role in normal kidney development, and the mechanism by which Perlman syndrome increases WT risk may be due to increased IGF2 expression as demonstrated in mouse models [61].

SGBS is an X-linked disorder due to pathogenic *GPC3* variants or deletions, which may involve *GPC4*, or a multi-exon duplication of *GPC4* [62,63]. Affected males have pre- and post-natal overgrowth, distinctive facial features, variable levels of intellectual disability and congenital anomalies [64–66]. Older studies reported WT risks between 5 and 15% [67–73], but these

studies did not always include molecular analysis and cases may have been misdiagnosed. A 2019 literature review identified 152 patients with *GPC3* variants and found an overall tumour risk of 8.5%, including 5 WTs (5/152 = 3%), with the most common tumour type being hepatoblastoma [74]. Therefore, full abdominal ultrasonography is recommended once every 3 months for children with SGBS.

PROS covers a range of disorders now known to be caused by somatic mosaic *PIK3CA* mutations, including CLOVES syndrome (congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal anomalies), Klippel-Trenaunay syndrome, megalencephaly-capillary malformation syndrome and fibroadipose hyperplasia [75–77]. Although WT risk estimates vary between different reports, currently available data suggest that the WT risk is less than 5% [76,77]. Other tumour types have not been reported in relation to PROS, and therefore, surveillance is not recommended.

### 7.6. Novel genes

WT surveillance is recommended for all children with germline pathogenic variants in *TRIM28* or *REST*, as well as children with truncating *CTR9* variants.

*TRIM28* was recently identified as a novel WT predisposition gene, with heterozygous germline pathogenic variants currently reported in  $\geq 30$  patients with WT [7,78–81]. Pedigrees from families with *TRIM28* variants suggest a WT penetrance of  $>50\%$  [7,80]. Although the median age at WT diagnosis was young (13 months), only 83% of WTs were diagnosed before the age of 7 years [7,78–81], and further research is needed to determine whether longer surveillance is indicated for this group. Although there is some evidence that WT risk may be preferentially associated with maternally inherited familial *TRIM28* mutations [7], until definitive evidence is available, surveillance should be offered irrespective of the inheritance pattern.

*REST* pathogenic variants were identified in familial WT pedigrees by Mahamdallie *et al.*, in 2015 [82]. Heterozygous germline variants have currently been reported in 19 patients with WT from 14 families [82,83]. Additionally, a *de novo* deletion encompassing *REST* was recently identified in a patient with diffuse hyperplastic perilobar nephroblastomatosis [84]. The *REST* gene encodes the RE1-silencing transcription factor which, similar to *TRIM28*, is thought to play an important role during embryonic development [8]. Pedigrees from families with *REST* variants suggest a disease penetrance of  $>50\%$  [82].

Inactivating heterozygous *CTR9* variants were identified in three WT families by Hanks *et al.* [85] in 2014 and reported in an additional family by Martins *et al.* [86]. These four families included a total of nine patients with WT. In a recently presented conference abstract,

missense *CTR9* variants were reported in 11 patients with neurodevelopmental disorders but no tumours (Meuwissen *et al.*, P08.021.C at the European Society of Human Genetics Virtual Conference 2020.2). This suggests that only truncating variants are associated with an increased risk of WT development.

Other genes that have been associated with WT predisposition in the last decade include *HACE1*, *KDM3B*, *FBXW7* and *NYNRIN* [7,87,88]. Based on current evidence, we would not recommend standard surveillance for patients with *HACE1*, *KDM3B* or *FBXW7* variants, given that only few ( $\leq 5$ ) patients have been reported to develop WT and there are no families with multiple affected relatives. *NYNRIN* pathogenic variants seem to predispose to WT development in a recessive manner, with biallelic variants identified in two affected siblings and a third unrelated patient [7]. We suggest that WT surveillance can be considered in a research setting for patients with biallelic (likely) pathogenic *NYNRIN* variants, with the aim to collect more data regarding these patients' WT risk.

### 7.7. Other syndromes

Other syndromes for which WT surveillance is recommended include Fanconi anaemia type D1, Fanconi anaemia type N, Mulibrey nanism, mosaic variegated aneuploidy (MVA), osteopathia striata with cranial sclerosis (OSCS), Bohring-Opitz syndrome (*ASXL1* mutation), 9q22.3 deletions and 2q37.1 deletions (Table 2).

Fanconi anaemia types D1 (biallelic pathogenic *BRCA2* variants) and type N (biallelic pathogenic *PALB2* variants) are associated with estimated WT risks of around 20% and 40%, respectively [89–93]. We did not identify reports of WT in children with Fanconi anaemia because of other molecular causes, although these patients are at risk for a range of other malignancies which are beyond the scope of this guideline [94].

Mulibrey nanism, caused by biallelic pathogenic *TRIM37* variants, has mainly been reported in Finnish patients and is associated with an estimated WT risk of 6–8% [95,96].

MVA can be caused by biallelic *BUB1B*, *TRIP13* or *CEP57* pathogenic variants, while in some patients, the cause remains unknown [97–100]. WTs have been reported in approximately 50% of patients with *BUB1B* variants [101,102], 20% of patients with *TRIP13* variants [99] and, to our current knowledge, none of the reported patients with *CEP57* variants or MVA because of an unknown cause [100,103]. Because of the limited number of reported patients, we recommend WT surveillance for all patients with cytogenetically confirmed MVA.

OSCS is an X-linked condition caused by germline loss-of-function variants affecting the *AMER1* (*WTX*) gene. Currently, WT has been reported in four female heterozygotes [104,105], and bilateral nephrogenic rests were reported at autopsy in a male patient with

OSCS [106]. Although two published OSCS cohorts, including 17 and 22 liveborn patients, respectively, did not report childhood tumours [107,108], we consider WT surveillance to be justifiable based on the well-established role of *AMER1/WTX* in WT development [109].

Bohring-Opitz syndrome is assumed to be genetically heterogeneous, with a subset of patients harbouring germline heterozygous nonsense variants in *ASXL1* [110]. WT or nephroblastomatosis has been reported in 3 of 43 (7%) reported patients with a clinical or molecular diagnosis of Bohring-Opitz syndrome [111,112]. Therefore, WT surveillance is recommended for patients with Bohring-Opitz syndrome.

Among 44 published cases of 9q22.3 microdeletion syndrome, seven patients with WT (16%) were reported [113]. Although these deletions all encompass *PTCH1* and cause a clinical phenotype which overlaps with that of Gorlin syndrome [114], WTs have not been observed in patients with Gorlin syndrome (caused by *PTCH1* or *SUFU* pathogenic variants) [113], and WT surveillance is only recommended for patients with 9q22.3 deletions.

2q37 Deletion syndrome has been reported in around 115 patients [115], with the minimal critical region limited to a single gene (*HDAC4*) on 2q37.3 [116]. WTs were reported in three of these patients, who all had deletions encompassing 2q37.1 (including *DIS3L2*, mutations in which cause Perlman syndrome [discussed previously]) [117]. We suggest that WT surveillance can be considered in cases where the deletion includes 2q37.1.

Constitutional 2p24.3 duplication (involving *MYCN*) has been reported in less than 100 patients overall, with four reported cases of WT or nephroblastomatosis [118–120]. Two WT cases occurred within one family, where an (unknown) additional genetic factor may have played a role [120]. Until more evidence emerges in the future, we would currently not recommend standard WT surveillance.

Until recently, only three patients with WT had been reported in unrelated families with hyperparathyroidism-jaw tumour syndrome (HP-JT), out of a total of >40 reported families (>100 patients) [121,122]. In 2019, Mahamdallie *et al.* identified a germline *CDC73* mutation in a father and his daughter who were both affected with WT but had no additional phenotypic features of HP-JT [7]. We would not currently recommend standard WT surveillance, in line with previously published HP-JT surveillance guidelines [123,124].

WTs have also been reported in patients with Bloom syndrome, *DICER1* syndrome, Li Fraumeni syndrome, neurofibromatosis type 1, constitutional mismatch repair deficiency, trisomy 13 and trisomy 18. For these syndromes, the estimated WT risk was considered too low to recommend targeted WT surveillance, although cancer surveillance for other tumour types is warranted in some of these conditions (but outside the scope of this guideline). Considerations and references for these syndromes are listed in Supplemental Table 5.



## 8. Other considerations for children diagnosed with WT/nephroblastomatosis

In children with WT/nephroblastomatosis who have been diagnosed with a CPS, surveillance of the remaining kidney(s) by 3-monthly renal ultrasonography is warranted until the 7th birthday, or longer if indicated by the follow-up guidelines for the treated tumour.

For all patients with bilateral WT/nephroblastomatosis, we recommend surveillance of the remaining kidney(s) by 3-monthly renal ultrasonography until the 7th birthday and genetic testing to exclude germline genetic/epigenetic aberrations. While awaiting test results, siblings may be offered a single ultrasound examination. Recent evidence suggests that bilateral WT may frequently be due to post-zygotic (mosaic) events [125,126]. If germline testing is negative, we therefore recommend that renal tissue from the resected kidney is tested, where possible, to exclude or diagnose a mosaic WT susceptible condition. The consensus opinion was that 3-monthly surveillance for siblings is not recommended if no germline genetic diagnosis is identified in the proband.

## 9. Familial WT

Familial WT is defined as the presence of  $\geq 2$  patients with WT within one family, who are at least third degree relatives of each other (Fig. 1). The WT diagnosis of both patients should be confirmed in their medical records. If the causative gene is not identified after germline genetic testing, WT surveillance until the 7th birthday is recommended for first and second degree relatives of presumed mutation carriers.

## 10. Future perspectives

The development of this guideline has demonstrated an urgent need for more robust data to enable better (Wilms) tumour risk estimates for children with a CPS. We strongly advise clinical geneticists, pediatricians, pediatric oncologists, radiologists and epidemiologists to collaborate in the establishment of national or international CPS registries.

Parent support organizations can play an important role in catalysing the development and/or awareness of such a registry. Several international registries already exist which can be used by clinicians, after local ethical approval and informed consent from parents have been obtained. This includes the DECIPHER database where any patient with a rare genomic variant (single nucleotide variant or copy number variant) can be registered (<https://decipher.sanger.ac.uk/>) [127], or the CPS registry established by the Heidelberg Hopp Childhood Tumor Center and Hannover Medical School, in which patients diagnosed with all types of CPS can be included (<http://www.krebs-praedispotion.de/en/registries/cps-registry/>). This CPS registry includes a self-registration option where (German or English-speaking) parents can register their child's data. Additionally, the IWSA has designed a CoRDS (Coordination of Rare Diseases at Sanford) registry where (parents of) patients with WAGR syndrome can register their data for research purposes (<https://wagr.org/wagr-syndrome-patient-registry/>), and other CPS-specific registries may be realised in the future. Linking such registries to international WT/cancer registries can provide additional insight into tumour risks.

With the rise of genomic sequencing and advances in other molecular techniques in children with cancer, we expect that more children will be diagnosed with a CPS, novel CPS may be identified and known CPS may be further subdivided into molecular subtypes in the future. Therefore, WT surveillance guidelines will require continuous discussion and may be subject to change when new evidence emerges.

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## Conflict of interest statement

The authors have declared no conflicts of interest.

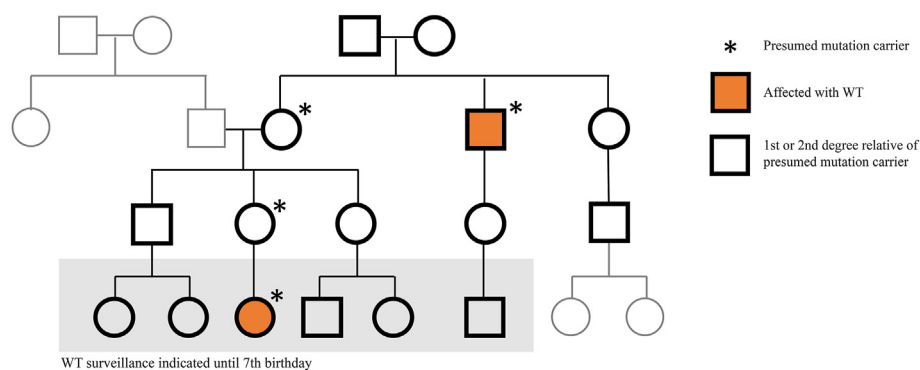


Fig. 1. Example of a familial Wilms tumour (WT) pedigree where the causative gene is not identified.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2021.05.014>.

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