Update on Surveillance for Wilms Tumor and Hepatoblastoma in Beckwith–Wiedemann Syndrome and Other Predisposition Syndromes

Jennifer M. Kalish[1,2,3,4], Kerri D. Becktell[5], Gaëlle Bougeard[6], Garrett M. Brodeur[3,4,7], Lisa R. Diller[8], Andrea S. Doria[9], Jordan R. Hansford[10], Steven D. Klein[1], Wendy K. Kohlmann[11], Christian P. Kratz[12], Suzanne P. MacFarland[3,4,7], Kristian W. Pajtler[13,14,15,16], Surya P. Rednam[17], Jaclyn Schienda[8], Lisa J. States[3,18], Anita Villani[19], Rosanna Weksberg[20], Kristin Zelley[4,7], Gail E. Tomlinson[21], and Jack J. Brzezinski[20]

ABSTRACT

Wilms tumors are commonly associated with predisposition syndromes, many but not all of which include overgrowth. Several of these syndromes also include a risk of other embryonal malignancies—particularly hepatoblastoma. Guidelines for surveillance in this population were published in 2017, and recently, members of the American Association for Cancer Research Pediatric Cancer Working Group met to update those guidelines with a review of more recently published evidence and risk estimates. This perspective serves to update pediatric oncologists, geneticists, radiologists, counselors, and other health care professionals on revised diagnostic criteria; review previously published surveillance guidelines; and harmonize updated surveillance recommendations in the North American and Australian contexts for patients with overgrowth syndromes and other syndromes associated with Wilms tumor predisposition.

Introduction

Embryonal tumors such as Wilms tumors and hepatoblastoma are commonly associated with several predisposition syndromes. Although Beckwith–Wiedemann syndrome/spectrum (BWS/BWSp) and *WT1*-related disorders are the most common, there are many other syndromes with a reported increased risk of Wilms tumors. In some syndromes, there is also an increased risk of hepatoblastoma. This article will review the evidence of the risks of Wilms tumors and, where relevant, hepatoblastoma in each syndrome and provide recommendations for surveillance.

This is an update of the 2017 consensus statement from the AACR predisposition syndrome and surveillance guideline working group, with several key changes to the structure of the article. Not all Wilms tumors predisposition syndromes include somatic overgrowth as a feature. Therefore, this article focuses more broadly on all syndromes that have clinical features other than Wilms tumors, which would be detected early in life, allowing for surveillance. Since the last consensus statement, several new genes have been associated with Wilms tumor predisposition (*TRIM28*, *DIS3L2*, *REST*, *CTR9*, *FBXW7*, *NYNRIN*, and *KDM3B*). Variants in these genes either do not have an associated syndrome or that syndrome is not yet defined, and these are characterized in an upcoming publication by the AACR Pediatric Cancer Working Group. Recommendations for surveillance for patients with these variants are discussed in the companion article. Additional data suggest that in BWS, hepatoblastoma risk ends earlier than previously noted.

Although there are existing guidelines for Wilms tumor surveillance from the SIOP-Europe Genome Working Group (1) and for

[1]Division of Human Genetics and the Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. [2]Department of Genetics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania. [3]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania. [4]Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. [5]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin. [6]Department of Genetics, University Rouen Normandie, Inserm U1245, Normandie University, CHU Rouen, Rouen, France. [7]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. [8]Department of Pediatric Oncology, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts. [9]Department of Diagnostic and Interventional Radiology, Hospital for Sick Children, Toronto, Ontario, Canada. [10]Michael Rice Centre for Hematology and Oncology, Women's and Children's Hospital, South Australia Health and Medical Research Institute, South Australia ImmunoGENomics Cancer Institute, University of Adelaide, Adelaide, South Australia, Australia. [11]VA Medical Center, National TeleOncology, Clinical Cancer Genetics Service, Durham VA, University of Utah Huntsman Cancer Institute, Salt Lake City, Utah. [12]Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany. [13]Hopp Children's Cancer Center (KiTZ), Heidelberg, Germany. [14]Heidelberg Faculty of Medicine, Department of Pediatric Oncology, Hematology, and Immunology, Heidelberg University, Heidelberg University Hospital, Heidelberg, Germany. [15]Division of Pediatric Neurooncology, German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany. [16]National Center for Tumor Diseases (NCT), NCT Heidelberg, a partnership between DKFZ and Heidelberg University Hospital, Heidelberg, Germany. [17]Division of Hematology and Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas. [18]Department of Radiology, Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania. [19]Division of Paediatric Haematology and Oncology, Hospital for Sick Children, Toronto, Ontario, Canada. [20]Division of Clinical and Metabolic Genetics, Hospital for Sick Children, Toronto, Ontario, Canada. [21]Division of Hematology-Oncology, Department of Pediatrics, Greehey Children's Cancer Research Institute, University of Texas Health Science Center at San Antonio, San Antonio, Texas.

Corresponding Author: Jennifer M. Kalish, Human Genetics, Children's Hospital of Philadelphia, 3501 Civic Center Boulevard, CTRB 3028, Philadelphia, PA 19104. E-mail: kalishj@chop.edu

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BWS from a European-focused international consensus (2), the guidelines presented here are written primarily from the North American perspective. An important distinction between these two approaches is the degree of risk considered to be sufficient for tumor surveillance. In these guidelines, a 1% risk of tumor is the threshold for recommending surveillance (**Table 1**).

Beckwith–Wiedemann Syndrome/ Beckwith–Wiedemann Spectrum

BWS is an overgrowth and cancer predisposition syndrome caused by epigenetic and/or genetic alterations (2). It is classically characterized by pre- and postnatal overgrowth, manifested through features including organomegaly, macroglossia, abdominal wall defects, lateralized overgrowth, and embryonal tumors (2). BWS has been redefined as a spectrum, BWSp, which ranges in severity from the classically described phenotype as above; atypical BWSp with fewer and milder clinical features; and isolated lateralized overgrowth (2). Many cases of BWSp are mosaic, and clinical features vary among patients. Isolated lateralized overgrowth, also referred to as isolated hemihyperplasia, is considered a more subtle presentation of BWSp, leading to a spectrum of features associated with a variety of structural, genetic, or epigenetic abnormalities localized to chromosome 11 (3). The most common tumor types associated with BWS are Wilms tumors and hepatoblastoma; however, other tumors have been reported, including neuroblastoma, rhabdomyosarcoma, pheochromocytoma, and adrenocortical carcinoma (2–4).

Disruption of imprinted growth regulatory genes that are normally expressed in a parent-of-origin–specific manner including *H19*, *IGF2*, and *CDKN1C* on chromosome 11p15 causes BWSp (5). Most cases of BWSp (85%) are not inherited but are instead shown to occur because of epigenetic changes on chromosome 11p15. The most common of these changes is loss of methylation at imprinting control region 2 (*KCNQ1OT1:TSS-DMR*) or gain of methylation at imprinting control region 1 (*H19/IGF2:IG-DMR*; ref. 5). Paternal uniparental isodisomy (UPD) for part or all of chromosome 11 (pUPD11) can also lead to BWSp. In pUPD11, both copies of this region of chromosome 11 are derived from the father. In some cases, the UPD extends to the whole genome (6). These children also need to be evaluated for other imprinting syndromes including Angelman syndrome. Also, rare causes of hereditary BWSp include pathogenic variants (PV) on the maternally derived copy of *CDKN1C*, maternally or paternally inherited deletions or duplications of the 11p15 region, and chromosomal rearrangements.

Tumor risk by molecular subgroup in BWSp

For BWSp, the overall tumor risk typically falls within the range of 8% to 12% (2, 7). Among reported tumors, 47% are Wilms tumors and 25% are hepatoblastoma. Neuroblastomas occur less frequently and are primarily observed in patients with *CDKN1C* PVs. The remaining tumor types are less common and do not meet the risk threshold for cancer surveillance. Individuals with imprinting control region 1 gain of methylation have the highest overall cancer risk, at up to 28%, most commonly Wilms tumors (2, 7). Patients with pUPD11 have a risk range of 16% to 30%, most commonly for Wilms tumors and hepatoblastoma (2, 7). In patients with genome-wide paternal UPD, cancer risk is likely higher than in those with pUPD11, although these cases are too rare to define the actual risk (2, 6); these tumors also seem to occur later in life compared with pUPD11. Individuals with imprinting control region 2 loss of methylation have an overall risk of 2% to 3%, and most tumors reported are hepatoblastoma (2, 7).

Differentiated screening by epigenetic or genetic subtypes in blood has been suggested by some groups (2), whereas others, including the previous AACR guidelines (4), suggest a standardized screening protocol. Recent data have shown that the genetic or epigenetic subtype in blood is not always the same as that found in the tumor or the normal organ tissue from which the tumor arose (7, 8). Furthermore, the level of epigenotype mosaicism in the blood and tissue epigenotypes can vary within one individual (7, 8), which makes relying on the blood epigenotype unreliable for BWSp. We therefore recommend that all patients with BWSp undergo screening for hepatoblastoma and Wilms tumors, except for patients with *CDKN1C* PVs.

Recent data have shown that there are no reported cases of Wilms tumors or hepatoblastoma in patients with *CDKN1C* PVs (9). Of the 126 patients reported in this group, 4 had neuroblastoma (3.2%; ref. 9). Other tumor types were observed in <1% of cases. We therefore recommend that the subset of patients with BWSp due to *CDKN1C* PVs be screened for neuroblastoma (these screening guidelines are covered in an upcoming publication by the AACR Pediatric Cancer Working Group; ref. 10) and not for hepatoblastoma and Wilms tumors [which means abdominal ultrasounds for neuroblastoma but no α-fetoprotein (AFP) screening].

WT1-Related Disorders

The *WT1*-related tumor predisposition syndromes are defined as risk of tumors associated with germline PVs in the *WT1* gene and include syndromes also known as Denys–Drash syndrome (11), Frasier syndrome (12), Meacham syndrome, or nephrotic syndrome type 4 (13, 14). Although all these disorders are now considered part of a *WT1*-related tumor predisposition spectrum, eponyms are still commonly used. A number of patients with *WT1*-related syndromes have differences in sexual development (DSD) and are (46,XY) phenotypic females (15). Recommendations for management of individuals with these syndromes should include input from professionals experienced in DSD care. Degenerative renal disease, without evidence of the initial response to steroids, is a hallmark of the *WT1*-related tumor predisposition syndromes and may include proteinuria and mesangial or focal glomerulosclerosis. When these syndromes are initially recognized, often through nephrology evaluation, surveillance should be initiated with abdominal ultrasound every 3 months through 7 years of age as for other predisposition syndromes with risk of Wilms tumors. If renal disease progresses to end-stage renal disease and the child undergoes renal transplant, consideration can be given for nephrectomy of the nonfunctioning kidney as a means of primary prevention.

Risk of gonadal tumors including gonadoblastoma or dysgerminoma is characteristically observed in patients with Frasier syndrome, with splice variants most commonly in exon 9 or 10, whereas those with missense variants in exon 8 or 9 are less likely to develop gonadal tumors but are at risk of developing Wilms tumors. The absolute risk of developing gonadoblastoma is difficult to ascertain as for many patients, the constitutional exon 9/10 splice site variants are found after a gonadal tumor diagnosis. Patients with streak or undescended gonads are at risk for gonadoblastoma—this risk is particularly high in 46,XY females (16). Prophylactic removal of streak ovaries to prevent gonadal tumors could be a consideration in consultation with endocrinologists, urologists, gynecologists, or DSD specialists, but a discussion of this procedure is beyond the scope of these guidelines.

In addition to the *WT1*-related syndromes associated with severe renal disease, *WT1* PVs, usually within the zinc finger

Table 1. Summary of tumor risks and surveillance recommendations.

Syndrome	Molecular variant	Estimated Wilms tumor risk	Other neoplasms	Wilms tumor surveillance?	Other surveillance?	Follows general surveillance protocol?
BWS/BWSp[a]	IC1 GOM	20%	Hepatoblastoma ACC Rhabdomyosarcoma Others	Yes	Hepatoblastoma	Yes
	pUPD 11p15.5	8%	Hepatoblastoma ACC Rhabdomyosarcoma	Yes	Hepatoblastoma	Yes
	IC2 LOM	~1%	Hepatoblastoma	Yes	Hepatoblastoma	Yes
	CDKN1C	<<1%	Neuroblastoma	No	Neuroblastoma	No
	Others	4%–10%	Hepatoblastoma ACC Rhabdomyosarcoma	Yes	Hepatoblastoma	Yes
WAGR	11p13 del	45%–60%	Germ cell tumor	Yes	No	Yes
WT1-related disorders	*WT1*	38%–43%	Germ cell tumor	Yes	No	Yes
SGBS	*GPC3*	5.1%	Hepatoblastoma	Yes	Hepatoblastoma	Yes
Perlman syndrome	*DIS3L2*	70%	No	Yes	No	Yes
BOS	*ASXL1*	>1%	Hepatoblastoma	Yes	Hepatoblastoma	Yes
Trisomy 18	T18	>1%	Hepatoblastoma	Shared decision-making	Hepatoblastoma	Consideration of Wilms tumor surveillance until 12 years of age
OSCS	*AMER1*	>5%	No	Shared decision-making	No	Consideration of surveillance until 12 years of age
Mulibrey nanism	*TRIM37*	8%	RCC Thyroid cancer Thecomas	Yes	No	Yes
PROS	*PIK3CA*	>1% in CLOVES; <1% in others	No	Shared decision-making in CLOVES	No	Yes
2p24 dup/2q37 del	2p24/2q37	Undefined	Neuroblastoma	Shared decision-making	Neuroblastoma in discussion with family	Yes
Sotos syndrome	*NSD1*	<1%	Leukemia Embryonal tumors Pineoblastoma	No	No	No
Weaver syndrome	*EZH2*	<1%	Neuroblastoma	No	Neuroblastoma	No

Abbreviations: ACC, adrenocortical carcinoma; GOM, gain of methylation; IC1, imprinting control region 1; IC2, imprinting control region 2; LOM, loss of methylation; RCC, renal cell carcinoma.
[a]Acceptable risk is 1% in North America and 5% in most of Europe. This leads to different risk thresholds for tumor screening guidelines. These guidelines are based on the North American risk threshold of 1%.

regions, are observed in few cases of apparently sporadic Wilms tumors (17). These patients may have minor genitourinary abnormalities including cryptorchidism or hypospadias.

The *WT1*-related tumor predisposition syndromes, however, are distinct from Wilms tumor, aniridia, genitourinary tract abnormalities, range of developmental delay (WAGR) syndrome, which involves a large germline deletion spanning a larger section of the chromosomal region and includes both *WT1* and *PAX6*, the latter causing pan-ocular disease including aniridia. The risk for Wilms tumors in WAGR syndrome is high (45%–60%), but it occurs in the same timeframe as in other Wilms tumor predisposition syndromes, and therefore tumor surveillance recommendations are the same as for other Wilms tumor predispositions. Additional screening interventions to evaluate kidney health should extend into adolescence and beyond as these patients are at risk for chronic kidney disease, as observed in up to 51% of patients with WAGR syndrome (18).

Simpson–Golabi–Behmel Syndrome

Simpson–Golabi–Behmel syndrome (SGBS) is an overgrowth syndrome characterized by hypertelorism, frontal bossing, macroglossia, macrosomia, overgrowth, kidney abnormalities, thick lips, supernumerary nipples, prognathism, developmental delay, organomegaly, and embryonal tumors (19). SGBS is caused by PVs or deletions of *GPC3*, which maps to the X-chromosome. Most reported cases are males; however, females with skewed X-inactivation have been reported (20).

To date, 189 cases of SGBS have been reported (21). The most frequently observed tumor types were hepatoblastoma (5.1%) and Wilms tumors (5.1%; ref. 21). Other tumor types were observed in <1% of cases (21). The mean age at which Wilms tumors was diagnosed was 28 months, ranging from 0 to 84 months. The mean age at which hepatoblastoma was diagnosed was 17 months, ranging from 9 to 36 months. We recommend screening patients with SGBS with the same approach as BWSp. Currently, there are not enough data for a formal screening guideline for females with SGBS; however, screening should be considered for features of SGBS and based on discussion with the family.

Perlman Syndrome

Perlman syndrome is a rare autosomal recessive overgrowth disorder caused by PVs in the *DIS3L2* gene that encodes a protein involved in mRNA and miRNA processing (22). Aside from overgrowth, children with Perlman syndrome have multiple significant syndromic features, including characteristic facies, fetal hydrops, ascites, hydronephrosis, hypotonia, and developmental delay (23). Based on collections of case series and reports, ~70% of survivors of the neonatal period will develop Wilms tumors (23, 24). Despite prevalent comorbidities, survival after appropriate multimodal therapy has been reported in the literature for children with Perlman syndrome whose tumors have been detected on surveillance (25, 26). Therefore, surveillance is recommended for children with this condition to facilitate earlier diagnosis and less invasive management.

Bohring–Optiz Syndrome

Bohring–Opitz syndrome (BOS) is a condition defined by PVs in *ASXL1* and characterized by a distinctive clinical presentation. Patients with BOS have a combination of atypical facial features, microcephaly, growth issues, developmental delays, upper extremity deformities, and seizures (27, 28). Despite the small number of patients with BOS identified to date, there is concern about the increased risk for malignancies in patients with BOS as *ASXL1* has been identified as a tumor suppressor gene (29). Three patients with BOS have been diagnosed with Wilms tumors: two diagnosed with bilateral Wilms tumors (ages 1.5 and 5 years) and one diagnosed with unilateral Wilms tumors (age 4 years; refs. 30, 31). One additional patient was diagnosed with nephroblastomatosis at 5 months of age on autopsy (32). Based on available data, the risk for Wilms tumors is estimated to be >1% (30, 31). Recently, the number of cases of hepatoblastoma reported in patients with BOS has increased to 3, suggesting an overall risk >1% as the overall number of reported patients with BOS is <300. The cases were diagnosed at the ages of 15 months, 18 months, and 2 years (33). Given this estimated increased risk, the recommendation is to pursue Wilms tumor and hepatoblastoma screening for patients with BOS. No other tumor screening is currently recommended based on available literature.

Trisomy 18

Trisomy 18, also known as Edwards syndrome, is a constitutional chromosomal abnormality characterized by an additional copy of chromosome 18. Most often, it is characterized by a full extra copy of chromosome 18 present in all cells, referred to as complete trisomy 18. Less commonly, mosaicism for trisomy 18 or constitutional presence of an additional partial segment of chromosome 18q can occur.

Complete trisomy 18 is characterized by distinctive craniofacial/skeletal findings and a constellation of multisystem conditions, disorders, and defects, including the involvement of cardiovascular, pulmonary, gastrointestinal, genitourinary, and neurologic/central nervous systems. The spectrum of features present in affected children confers a poor prognosis, with demise in neonates/infants being a common occurrence. However, an increasing proportion of children have prolonged survival. Children with mosaicism for trisomy 18 or partial trisomy of chromosome 18q have a variable, often milder, phenotype.

The overall risk of malignancy in children with trisomy 18 is presumed to be at least 1%, with hepatoblastoma and Wilms tumors predominating (4). However, cancer risk estimation is complicated by the high mortality rate in infancy. To date, about 50 cases of hepatoblastoma and 21 cases of Wilms tumors have been reported in children with trisomy 18 (34, 35). Other benign and malignant tumors have rarely been reported (35, 36).

Based on these cancer risks, Wilms tumor and hepatoblastoma surveillance may be warranted for some affected children. However, the decision whether to screen should be considered within the context of a shared decision-making paradigm incorporating the parental goals of care and the parental and medical provider's estimation of potential risks of tumor-directed therapies and interventions (37–39). Depending on the outcome of these longitudinal discussions, surveillance may be initiated, deferred, or discontinued after initiation.

The lack of normal standards for AFP levels in trisomy 18 makes interpretation of levels challenging, and so both the absolute level and the short-term trend should be assessed (35). Due to multiple cases of Wilms tumors occurring in older children with trisomy 18, predominantly female, renal ultrasounds should be performed from every 3 months to 12 years of age.

Osteopathia Striata with Cranial Sclerosis

In 2009, germline loss-of-function variants in *AMER1* were identified as the cause of the very rare condition, namely, X-linked dominant osteopathia striata with cranial sclerosis (OSCS), and were thought to not have an increased risk for cancer (40). PVs in *AMER1* have complete penetrance with variable expressivity for OSCS. Radiographic findings of sclerosis of the skull and long bones are the hallmark characteristics of OSCS (41, 42). Common features include macrocephaly, cleft palate, conductive hearing loss, and longitudinal striations of the long bones. Some individuals have mild learning difficulties and extraskeletal anomalies. Males with somatic mosaic PVs in *AMER1* have features similar to those of females.

There have been multiple case reports and a series on individuals with germline *AMER1* PV and cancer, most commonly Wilms tumors. Thus far, six females have been known to have had Wilms tumors, with the age at diagnosis ranging from 7 months to 12 years (43–46), two of whom had bilateral tumors, and one additional male died neonatally because of bilateral multifocal nephroblastomatosis, found on autopsy (47). Other single cancers have been reported (48, 49). As this is a rare disease with <100 cases, the 7 reported cases imply the risk of Wilms tumors to be significantly higher than 1%, and so surveillance is recommended.

Mulibrey Nanism

Mulibrey (muscle, liver, brain, and eye) nanism is caused by biallelic inheritance of PVs in *TRIM37*, and the most common variant is a Finnish founder variant, c.493-2A>G (50). Associated features include growth deficiency, constrictive pericarditis, characteristic facial features, insulin resistance, vascular liver lesions, infertility (male and female), and a risk for benign and malignant tumors. To date, the largest study with regard to cancer risk comes from a Finnish cohort that reported 210 tumors in 66/89 (74%) affected individuals (50). Since that first publication (which formed the basis of recommendations in the previous guidelines), additional information about renal tumors has been reported. An update of data from the Finnish cohort found that 8/101 (8%) patients developed Wilms tumors (51). A systemic review reported on 14 cases of Wilms tumors in individuals with Mulibrey nanism. The mean age of diagnosis is 1.6 years (0.6–3.7), and all cases achieved remission (52). The frequency of Wilms tumors in this population meets the criteria for screening. Other cancers have predominantly occurred in adulthood, and other than Wilms tumors, each individual cancer type has been reported in ≤2% of affected individuals (50).

PIK3CA-Related Disorders/*PIK3CA*-Related Overgrowth Syndromes

PIK3CA is one of the most commonly mutated genes in solid cancers (53). Unlike other PI3K signaling alterations, *PIK3CA*-related overgrowth syndromes (PROS) are generally benign overgrowth disorders caused by postzygotic activating mutations in *PIK3CA*, typically acquired during day 20 to day 56 postgastrulation (54). They are generally found in mesodermal and neuroectodermal derivative tissues and are not typically germline (54). The PROS phenotype is quite variable and includes several disorders previously described as unique and now unified by PVs in a common gene. These include Klippel–Trenaunay syndrome, megalencephaly–capillary malformation syndrome, and congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and scoliosis (CLOVES) syndrome, among others. Several studies have specifically reviewed the risk of the development of cancer. Only a few cases of cancer have been reported in patients with PROS, including Wilms tumors (55–57). Of 483 patients with PROS and a documented *PIK3CA* PV reviewed in a meta-analysis, there were six cases of Wilms tumors and two cases of nephroblastomatosis (1.6%). However, this number may be subjected to ascertainment bias as PROS phenotypes can be subtle and detection of a pathogenic *PIK3CA* variant requires careful selection of tissue for biopsy; additionally, not all of these patients have molecularly confirmed renal findings, suggesting that the denominator could include more unconfirmed cases. It should be noted that of these eight patients, at least seven of them had the CLOVES phenotype. A separate review of patients with megalencephaly–capillary malformation syndrome written before the causative *PIK3CA* variant was described found 2/112 patients had developed a Wilms tumor (58). Four children with PROS were reported to have other tumor types (59). Although the risk of Wilms tumors in PROS could be higher than the 1% surveillance threshold depending on how this literature is interpreted, the risk may be specifically in those with CLOVES syndrome. We therefore recommend a conversation about surveillance in patients with PROS and a CLOVES phenotype, with decisions on surveillance for patients made through shared decision-making with the family.

2p24 Duplication and 2q37 Deletion

Germline 2p24.3 duplication including the *MYCN* and *DDX1* genes has also been reported in some patients with Wilms tumors, including bilateral and familial cases (60–62). In one case, the duplication was inherited from the mother, who had no history of cancer (60). There are also reports of neuroblastoma in patients with partial trisomy 2p (including the 2p24 region), most of which include the *ALK* gene, in addition to *MYCN* (63–69), with one exception (70). Additionally, there have been reports of Wilms tumors in children with 2q37 microdeletions, particularly with breakpoints at or proximal to 2q37.1 (71, 72). Due to the rarity of these chromosomal abnormalities, the tumor risk and spectrum are not well established, and there are no established surveillance guidelines. Surveillance may be considered for the patient and/or close relatives depending on several factors, including the specific genetic abnormality, tumor type, laterality, and age at diagnosis, as well as the family history of tumors and presence or absence of the duplication in family members. If surveillance is agreed upon by the physician and the family, the surveillance recommendations for Wilms tumors and/or neuroblastoma can be used as a guide.

Sotos Syndrome

Sotos syndrome is a disorder of pre- and postnatal somatic overgrowth in which malignancies in childhood have been reported. The most common underlying genetic cause of Sotos syndrome is a PV in *NSD1*, a gene involved in developmental epigenetic regulation (73), although other genes including *NFIX* and *APC2* have been recently implicated with overlapping phenotypes (74).

Physical characteristics of Sotos syndrome include characteristic facies and pre- and postnatal growth with height and weight often exceeding two SDs above the mean (75). Other clinical findings include variable intellectual disabilities, including autism.

Leukemias and multiple types of embryonal and other pediatric solid tumors have been reported in patients with Sotos syndrome; however, these reports are mostly single-case studies or small series. The broad spectrum of tumors observed in Sotos syndrome is described in the previous AACR series (76), to which more recently a pineoblastoma observed in a single patient has been reported (77), as has a complex hamartoma of skin (78). However, despite the broad spectrum of childhood cancer types reported, the overall cancer risk is low, estimated to not exceed 3% to 5%. The risk of any one type of cancer, including Wilms tumors, is likely 1% or less. Because of the relatively low risk, as well as the low number of diverse types of cancers reported, no routine surveillance is recommended. However, the healthcare professional caring for a child with Sotos syndrome should be aware of the reports of cancer with this diagnosis and should promptly evaluate any sign or symptom to suggest a developing cancer diagnosis.

Weaver Syndrome

Weaver syndrome is an overgrowth syndrome initially identified by a clinical presentation of tall stature, variable intellectual disability, and distinct facial features (79), which are associated with underlying pathogenic *EZH2* variants (80). Somatic mutations in *EZH2* have been noted in numerous types of malignancies (81), leading to concern that patients with Weaver syndrome may be at increased risk for tumor development. The most common malignancy reported is neuroblastoma, which has been noted in a total of seven patients (79, 82–87). The largest review notes the risk for development of neuroblastoma to be ~9% (5/56 patients included in cohort). In contrast to other overgrowth conditions, there are no reports of Wilms tumors or hepatoblastoma. Screening for neuroblastoma is warranted in patients with Weaver syndrome, which is addressed in the article by Kamihara and colleagues (10) as part of this series. No additional tumor screening has been recommended based on current data.

Overall Approach to Cancer Screening/Surveillance Protocols

The AACR workshop recommendations are based on North American healthcare culture and may differ from practices in other regions. In North America, screening is advised at a 1% risk threshold, whereas screening in Europe typically uses a 5% threshold. These recommendations aim for a standardized, minimally invasive, universally applicable screening protocol to improve early tumor detection and reduce morbidity and mortality.

It is essential to have comprehensive discussions and informed counseling within the context of a patient's specific syndrome and tumor risk, preferably led by knowledgeable healthcare professionals. One should also acknowledge that these guidelines may result in more frequent and extended screenings for some individuals. However, when surveyed, parents of patients with BWSp indicated that screening provided comfort, as did their knowledge of their child's actual risk (88).

Age brackets for tumor risk may differ between syndromic and sporadic cases. To simplify screening recommendations, our AACR workshop committee suggests a uniform approach for the established cancer predisposition syndromes with a Wilms tumor risk above 1%, with exceptions noted above. Additional screening for hepatoblastoma via monitoring serum AFP measurement levels is advised for BWSp, trisomy 18, SGBS, and BOS. To aid in interpretation of AFP results, AFP norms for BWSp have been developed (89). These recommendations aim to detect tumors early and cover the age range when 95% of tumors typically occur (90, 91). The suggested screening interval is every 3 months to reduce the risk of interval tumor development. As more data accumulate and genetic testing becomes more accessible and understood, future screening recommendations may become more nuanced, considering genetic determinants and syndromic origins of Wilms tumors and hepatoblastoma.

Wilms tumor screening

Wilms tumor screening is influenced by age-related factors. A comprehensive meta-analysis indicates that the mean age for diagnosing Wilms tumors in individuals with BWSp is around 24 months, with the majority of cases occurring before the age of 3 and 95% presenting prior to their seventh birthday (91). Similar age-related incidences have been reported for patients with *WT1*-related disorders. Compared with patients who did not undergo tumor screening, these patients were diagnosed earlier, demonstrating that screening was effective in Wilms tumors (91).

For Wilms tumor screening, we propose initiating screening at birth (or upon diagnosis of the specific syndrome) with renal ultrasound every 3 months up to the child's seventh birthday. In cases in which hepatoblastoma is also a concern, full/complete abdominal ultrasounds are recommended every 3 months until the child's third birthday. After the third birthday, these patients can transition to renal ultrasound screenings every 3 months until their seventh birthday. Given the slightly increased risk for adrenal tumors in patients with BWSp, especially in patients with pUPD11 and genome-wide paternal UPD, the adrenal glands should be imaged as part of these ultrasounds.

Additionally, we advocate for biannual physical examinations conducted by a specialist, such as a geneticist or pediatric oncologist. These evaluations should encompass ongoing education about tumor manifestations, reinforcement of the rationale for screening, and adherence to the screening regimen. They should also address other syndrome-specific manifestations.

Hepatoblastoma screening

Hepatoblastoma screening is strongly advised in the context of syndromes described here with an increased hepatoblastoma risk. The RR is substantially elevated in these children, estimated at 2,280 times that of the general population in BWSp (the most well-described syndrome; ref. 92). The cumulative incidence of hepatoblastoma in patients with BWSp in the literature showed that most patients presented with hepatoblastoma prior to 30 months of age (90). Based on these results, we recommend screening for hepatoblastoma until the third birthday (36 months). We recommend hepatoblastoma screening to include AFP measurements and complete abdominal ultrasounds every 3 months until the third birthday. This represents a shorter hepatoblastoma screening duration than what was recommended in the 2017 guidelines, with screening duration decreased from 48 to 36 months.

Serum AFP screening is highly sensitive for detecting hepatoblastoma, and elevated serum AFP often precedes hepatoblastoma detection via ultrasound. This screening is recommended for patients with BWSp/isolated hemihyperplasia, trisomy 18, SGBS, and BOS. Screening for hepatoblastoma in familial adenomatous polyposis is included in the upcoming work on gastrointestinal polyposis by the AACR Pediatric Cancer Working Group.

The key for interpretation of AFP measurements is to track the AFP results over time and monitor the normal downward trend, considered in the context of age and clinical status. In addition, AFP norms for BWSp have been developed and can be used to interpret AFP results as AFP values in children with BWSp tend to be elevated during the early months of life compared with standard pediatric values (89). Such an interpretation should ideally be carried out by or in consultation with physicians experienced in monitoring AFP in these syndromes, particularly geneticists and oncologists affiliated with cancer predisposition programs. Small, incremental increases within reference ranges should not trigger additional testing as these can be attributed to various factors such as intercurrent illnesses or developmental milestones like teething. This underscores the importance of gathering a comprehensive medical history when discussing AFP results.

Substantial increases in AFP values (exceeding 50–100 ng/mL) warrant further investigation, including reevaluation of the most recent ultrasound imaging and typically repeating AFP measurements after 6 weeks. Although different intervals for repeat testing have been recommended in isolated cases, it remains uncertain whether repeating the AFP measurement more frequently than every 6 weeks significantly impacts clinical outcomes. If two successive increases occur, further imaging via MRI or contrast-enhanced ultrasound is recommended. In cases of markedly larger increases (exceeding 1,000 ng/mL), repeat testing for validation is advised, and if confirmed, expedited additional imaging becomes imperative.

Radiologic Considerations

Standard ultrasound is recommended for the regular tumor screening with complete abdominal or renal ultrasounds. Fasting is not typically required as imaging the gallbladder is not the focus of these studies. When a concerning finding is noted on regular ultrasound, in some cases, a contrast ultrasound can be used to clarify these findings, in particular to differentiate hemangiomas from hepatoblastoma in the liver. The advantages of contrast ultrasounds in young children are that they do not require sedation for imaging. If contrast-enhanced ultrasound is not available, MRI using a hepatobiliary contrast agent is the test of choice for evaluation of liver masses. If MRI is not available, contrast-enhanced CT can also be used.

Genetic Counseling Considerations

The genetic testing and counseling article in this AACR CPWG series addresses the many nuances and updates to testing children for cancer predisposition (93). As treatment of the cancer and future management may be directly impacted by identifying a cancer predisposition syndrome, we support germline genetic testing for all children diagnosed with Wilms tumors or hepatoblastoma. Specifically, we support recommendations stated in GeneReviews that not only highlight certain populations for germline testing but also allow for further genetic evaluation of all children with Wilms tumors in conversation with the family and in accordance with institutional standards (94). Recommended testing may include 11p15 methylation analysis for BWSp, SNP array for BWSp and chromosomal deletions or duplications such as 2p24 duplication, and single-gene or multigene panel testing. However, the recognition of features associated with syndromes in patients and families can help guide the differential diagnosis. Clinical suspicion for a syndrome that is often or always due to mosaic genetic changes, such as BWSp or PROS, may necessitate genetic testing on multiple tissues.

Identifying a cancer predisposition syndrome in a child with cancer also allows for cascade testing of parents and siblings (93). Siblings who test positive for a cancer predisposition syndrome but do not have cancer should follow the surveillance recommendations put forth in this article. Of note, BWSp is often diagnosed clinically in the setting of negative genetic testing. BWSp occurs sporadically for the most part, but siblings should undergo clinical evaluation if they have any BWSp features. Genetic evaluation should only be performed for siblings when a heritable cause of BWSp is identified in the proband. Many of the other syndromes included in this review, such as BOS and WAGR syndrome, have a high *de novo* rate, but cascade testing should still be considered.

Final Considerations

This article presents an overview of multiple syndromes which include Wilms tumors as a common risk, with some syndromes known to include risks of other tumors. For simplicity, we recommend a standard surveillance strategy using ultrasounds every 3 months in early childhood until the seventh birthday, to cover the reported age range in which 95% of Wilms tumors develop. These ultrasounds should be renal if the syndrome includes only Wilms tumors or complete abdominal ultrasounds until the third birthday, followed by renal ultrasounds until the seventh birthday if the syndrome also includes hepatoblastoma. It is acknowledged that as more is learned about these various syndromes and the consequence of predisposition gene variants on the velocity of tumor development, the age-related windows of tumor susceptibility, degree of observed overgrowth, and possible interactions between the predisposition genes with other gene variants or other factors, more nuanced screening recommendations will be developed. For the rarer syndromes, there may be additional cancer risks beyond Wilms tumors that have not been reported, such that the clinicians caring for these children should remain alert for signs or symptoms of other types of malignancies that would prompt evaluation. Lastly, shared decision-making and other personal and familial factors may influence the degree of surveillance to be undertaken in these and other cancer predisposition syndromes. Levels of parental anxiety versus levels of reassurance associated with cancer screening may be considered. Shared decision-making should be considered in all surveillance plans but has been specifically emphasized in this review for syndromes with a high very early mortality or in syndromes with very low or nonspecific types of tumor risks.

Authors' Disclosures

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