NIH Public Access
Author Manuscript
*Eur J Pediatr*. Author manuscript; available in PMC 2011 May 3.

Published in final edited form as:
*Eur J Pediatr*. 2011 March ; 170(3): 285–294. doi:10.1007/s00431-010-1377-2.

# Educational paper:

## Screening in cancer predisposition syndromes: guidelines for the general pediatrician

**Alexis Teplick**,
Division of Oncology, Children's Hospital of Philadelphia, Colket Translational Research Building, Rm 3012, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA

**Megan Kowalski**,
Division of Oncology, Children's Hospital of Philadelphia, Colket Translational Research Building, Rm 3012, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA

**Jaclyn A. Biegel**, and
Departments of Pediatrics, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA, Departments of Pathology, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA

**Kim E. Nichols**
Division of Oncology, Children's Hospital of Philadelphia, Colket Translational Research Building, Rm 3012, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA

Kim E. Nichols: nicholsk@email.chop.edu

## Abstract

Improvements in our understanding of the genetic basis of human disease and increased utilization of genetic testing have identified a variety of heritable disorders associated with the onset of benign or malignant neoplasms during childhood. In many cases, the optimal management of affected children is dependent upon the early detection and treatment of tumors. Surveillance strategies based on the natural history of these lesions are often complex, requiring clinical examinations and radiologic and laboratory studies that evolve over a patient's lifetime. A general pediatrician may be the first to suspect one of these disorders in a patient, or may be faced with questions regarding genetic testing, cancer risk, and cancer screening. The pediatrician may also coordinate and interpret the results of specific surveillance studies. In this review, we present the genetic etiology, presentation, natural history, and surveillance recommendations for four disparate hereditary tumor predisposing syndromes, including Beckwith–Wiedemann syndrome/idiopathic hemihyperplasia, von Hippel–Lindau disease, Li–Fraumeni syndrome, and rhabdoid tumor/schwannomatosis. These examples are meant to offer the clinician practical recommendations as well as a framework upon which to base the understanding and management of other conditions associated with an increased risk to develop tumors in childhood.

### Keywords

Cancer predisposition; Beckwith–Wiedemann syndrome; Genetic testing; Li–Fraumeni syndrome; Rhabdoid tumor; Von Hippel–Lindau

© Springer-Verlag 2011

Correspondence to: Kim E. Nichols, nicholsk@email.chop.edu.

**Conflict of Interest** The authors report no conflicts of interest.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

## Introduction

Cancer is a relatively rare entity in children, affecting approximately 140–150 of every 1,000,000 children less than 20 years of age/year in Europe and the USA [30, 55]. Rarer still are childhood cancers that arise in the context of a genetic predisposition, which are estimated to account for approximately 1% to 10% of all pediatric cancer cases [60]. While some predisposition syndromes such as hereditary retinoblastoma are managed by subspecialists from the outset, many others are not and expectant management falls to the pediatrician. Furthermore, as more cancer-related genes are identified and specific genetic tests become available, pediatricians will be asked about the cancer risks associated with, and optimal management strategies for, various genetic disorders affecting children.

Many of the known cancer predisposing conditions are associated with the development of solid tumors, the management of which relies on surgery, and/or chemo- or radiation therapy. In general, the outcome for patients with solid tumors is related to the stage, or degree of involvement of the body, at the time of diagnosis. Unfortunately, most solid tumors do not cause symptoms until the function of the involved organ is impaired or there is compromise of neighboring or more distant organs. As a result, patients are commonly diagnosed at later stages, when it is more difficult to eradicate the tumors or when cure comes at a cost due to the toxicities of the anti-cancer treatments used.

Cancer screening has evolved as a management strategy to improve the outcomes for those at increased genetic risk to develop solid tumors. While screening is also used to monitor for the development of hematopoietic malignancies, its benefits in this setting are not as clear. The central benefit upon which screening programs are based is the idea that earlier detection may lead to the identification of benign or malignant tumors at a lower stage than otherwise possible. Lower stage lesions are associated with a better overall survival and often need treatment with less extensive surgery as well as less intensive chemo- and/or radiotherapy (Table 1). Screening can also improve the emotional well-being of patients and parents by allowing a sense of expectation and control. However, screening does have disadvantages, most significantly that false-positive results may lead to additional evaluations and potentially unnecessary procedures or surgery [13]. These false-positive results may thus be an emotional drain on affected patients and their families, as well as a financial drain on the already taxed resources of many medical systems. Consequently, it is important to weigh the potential benefits and disadvantages of screening and to establish protocols that address the needs of the population being screened. One must be cognizant of the age-specific cancer risks associated with a given condition and offer screening only when there are effective cancer treatments available (Table 2).

It is recommended that a suspected or confirmed hereditary cancer predisposition syndrome be managed in concert with a pediatric oncologist. Ideally, patients should be seen in a dedicated cancer predisposition clinic where geneticists and pediatric oncologists work in concert to confirm a diagnosis and coordinate genetic testing, and where appropriate, radiologic and laboratory evaluations. Genetic counselors, social workers, and psychologists with experience in pediatric cancer predisposition syndromes can provide invaluable support to patients and families facing one of these diagnoses. For patients who initiate screening, it is imperative that serial radiologic evaluations are performed at a single institution to allow for accurate comparisons to previous imaging studies. When possible, radiologic studies should be reviewed by a pediatric radiologist familiar with the genetic condition and its associated tumor risks. Similarly, serial laboratory evaluations should be performed by a single laboratory, as differences in method and normal ranges may make trends difficult to identify.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

In this review, we discuss cancer screening for four genetic conditions affecting children. Beckwith–Wiedemann syndrome (BWS) and von Hippel–Lindau (VHL) syndrome are two conditions for which effective screening protocols are established, and for which the pediatrician is likely to arrange surveillance and coordinate care. Li–Fraumeni syndrome (LFS) is a disorder in which screening recommendations are not as clearly defined, but which requires that the pediatrician, as the primary caregiver, be alert for the presenting signs of neoplasia. Finally, we review the emerging recommendations in screening for patients with germline *INI1/SMARCB1* mutations, who are predisposed to the development of rhabdoid tumors, as an example where data on surveillance is scarce, but screening may nonetheless prove important for patient management. This review regrettably cannot discuss all the hereditary cancer predisposing syndromes affecting children. Instead, we direct the reader to several excellent recent reviews which discuss the practical issues related to the care of children with other predisposing conditions such as retinoblastoma and the Wilms' tumor (WT)-associated syndromes, the neurofibromatoses, and multiple endocrine neoplasia type 1 [12, 22, 53].

## Beckwith–wiedemann syndrome and idiopathic hemihyperplasia

BWS is a phenotypically and genetically diverse disorder characterized by macrosomia, neonatal hypoglycemia, abdominal wall defects, hemihyperplasia, macroglossia, and ear anomalies [69]. BWS is estimated to occur in one in 13,700 live births with 85% of cases being sporadic and 15% familial [59, 69]. Studies indicate that approximately 7.5% to 10% of patients with BWS develop a malignancy, most commonly hepatoblastoma (HB) or WT [6, 63, 69]. Adrenocortical carcinoma, neuroblastoma, and rhabdomyosarcoma are also encountered with a frequency above that in the general population [3, 33, 63]. Other malignancies, such as atypical teratoid/rhabdoid tumor and pheochromocytoma, have been identified in single case reports of patients with BWS, but may be coincidental findings [2, 5, 29]. Isolated hemihyperplasia (IHH) is defined by asymmetric overgrowth of one or more body parts in the absence of other clinical findings. This disorder may represent part of the clinical spectrum of BWS as in many cases it has a similar genetic etiology and profile of cancer predisposition [26].

Multiple genetic and epigenetic abnormalities are observed in patients with BWS or IHH, all of which affect chromosomal locus 11p15.5. Among the genes in this region are the growth promoter *IGF2* (insulin-like growth factor 2) and the tumor suppressor *CDKN1C* (cyclin-dependent kinase inhibitor 1C). These and surrounding genes are "imprinted", or differentially methylated, depending on whether the gene copy is maternal or paternal in origin. As a result, only the maternal or paternal copy is expressed at any given time. The epigenetic aberrations in BWS and IHH lead to aberrant hypomethylation, and thus overexpression, of IGF2, as well as aberrant hypermethylation and repression, of CDKN1C [68]. The combined overexpression of growth promoting genes and inhibition of growth controlling genes may contribute to the overgrowth and tumor predisposition that occur in these conditions.

Fifty-five to 65% of BWS patients have a defect at one of two imprinting control centers that determine methylation of the genes in the region [17, 69]. Paternal uniparental disomy (UPD) at chromosome 11p15.5, in which a child has two copies of the chromosome or chromosomal region from the father, and none from the mother, is the genetic abnormality identified in 20–25% of patients with BWS [17, 69]. About 5% of patients with sporadic BWS harbor germline mutations in *CDKN1C*, whereas approximately 40% of familial cases display this defect [17, 69]. In total, about 75% to 80% of patients with clinical BWS have identifiable molecular abnormalities [69]. The remaining patients may harbor mutations in novel and as yet unidentified BWS-associated genes, or be genetic mosaics for alterations in known genes linked to this condition. In mosaicism, the genetic or epigenetic alteration

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

occurs during embryogenesis with the result that only a subpopulation of cells displays the genetic abnormality. When mosaicism is present, the disease associated genetic abnormality may be difficult to detect if only a small percentage of cells is affected, or if it is isolated to tissues that are not as easily sampled as the blood [6, 17].

There is increasing evidence to suggest that within the spectrum of BWS, distinct molecular abnormalities confer different risks for tumor development. For example, studies indicate that paternal UPD and abnormalities at one of the imprinting control centers have the highest risk of tumor development, whereas mutations of *CDKN1C* may not increase a child's risk for malignancy [17, 19, 67]. However, these genetic findings are complex and have not yet been used to direct decisions in most screening programs. It is likely, however, that future screening programs will be more precisely designed to take into account the particular risks related to the underlying genetic abnormality.

Cancer screening recommendations for patients with BWS or IHH are aimed primarily at detecting HB and WT (Table 3). While the incidence of neuroblastoma is higher in patients with BWS than in the general population, it is not considered high enough to warrant screening. Screening should be used for all patients with a clinical diagnosis of BWS or IHH, even if no underlying molecular abnormality is identified. Apparently unaffected monozygotic twins of children with BWS or IHH should also be screened, as they may have mosaicism that makes the condition difficult to detect [69].

HB presents before 4 years in 95% of cases [63]. Complete surgical resection is the most important element in the treatment of HB, although chemotherapy is often used to shrink tumors prior to surgical resection. Patients whose tumors are completely resected at diagnosis have an event-free survival (EFS) over 90%. In contrast, those whose tumors are initially unresectable have an EFS of less than 70%, and those whose tumors are metastatic have an EFS of 20–30% [31, 48]. Screening for HB begins when the diagnosis of BWS is made or suspected. It is suggested that patients have abdominal ultrasound examinations performed every 3 months, as well as serial evaluation of alpha-fetoprotein (AFP) levels, which are typically increased in patients with HB. Optimally, AFP levels should be evaluated every 6 weeks, or at a minimum every 3 months, when the imaging is performed [14]. AFP levels tend to be higher in patients with BWS, even in the absence of HB. In addition, levels tend to decrease more slowly over time [21]. Therefore, if the initial AFP level is elevated, but there is no abnormality on ultrasound or other imaging, the test may be repeated in 6 weeks. If at that time the levels are falling, they may be rechecked every 6 weeks until they return to normal. If the initial elevation is accompanied by a radiologic abnormality, or if the level fails to fall or continues to increase, the patient should be referred to an oncologist for further evaluation [69]. Screening for HB can be discontinued at the age of 4 years as the majority of these tumors develop before this time.

WT is an embryonal tumor of the kidney which typically presents in young children and almost always presents before 10 years of age [4]. Treatment strategies for WT have become very successful, and long-term survival is >90% for localized disease, and >70% for the highest stages of the disease [63]. Screening programs are unlikely to impact these outcomes, and their goal is instead to promote easier surgical management, less intensive chemotherapy, and possible avoidance of radiotherapy. Screening for WT consists of serial ultrasound examinations every 3 months from the time of diagnosis until the age of 8–10 years. In the first 4 years of life, the abdominal ultrasound performed every 3 months to screen for HB is also used to evaluate for renal masses and nephrogenic rests (persistent fetal tissue with a propensity for malignant transformation) that might indicate or portend the development of WT [63]. After the age of 4 years, imaging may be limited to a renal ultrasound, which is faster and less expensive than an abdominal ultrasound, and does not

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

require that the child fast for the exam. For HB and WT screening, ultrasound is favored over MRI or CT as it is widely available, non-invasive, leads to no radiation exposure, only rarely requires sedation, and is generally faster and less expensive.

Data pointing to the benefits of screening in BWS are sparse but encouraging. Choyke et al. reported that patients with BWS or IHH who did not undergo screening had an increased rate of high stage WT (stage III or IV) at diagnosis compared to patients who underwent screening, with 42% of 59 non-screened patients presenting with high-stage disease, versus 0 of 12 screened patients [13]. Unfortunately, three patients in this study had false-positive results, and underwent surgery for what were found to be renal cysts. A report from the National Wilms Tumor Study Group examining 4,669 children enrolled on two Wilms tumor studies, NWTS 3 and NWTS 4, between 1980 and 1995 found that 1.1% of children with Wilms tumor had BWS [50]. The children with BWS were diagnosed at younger ages (mean 28 months) than children without BWS (mean 44 months). Overall, children with BWS presented with lower stage tumors (71.7% versus 55% with stage I or II disease). None of the children with BWS had metastatic disease at presentation, while 12% of the other children did. It is not possible to discern how much these differences in presentation were affected by screening. Nonetheless, it remains feasible that some of them were due to the positive effects of the prospective monitoring for tumors in this at-risk population. Fewer studies exist that evaluate screening for HB in BWS, although case reports have documented pre-symptomatic detection in a small number of patients [48, 70].

## Von Hippel–Lindau

VHL disease is an autosomal dominant disorder associated with the development of multiple benign and malignant lesions. The condition affects approximately 1/36,000 live births [37]. While VHL is most often familial, approximately 20% of cases are sporadic and caused by new mutations. VHL is characterized by development of CNS hemangioblastomas, most frequently in the cerebellum and spinal cord, retinal hemangioblastomas, pheochromocytomas, renal cysts, clear cell renal cell carcinoma (ccRCC), pancreatic cysts and neuroendocrine tumors, cystadenomas of the epididymis and broad ligament, and endolymphatic sac tumors (ELST) [15]. CNS hemangioblastoma is the most common manifestation, occurring in 60–80% of affected individuals, and ccRCC is the most common cause of early mortality [37]. While most of the lesions associated with VHL are benign, their growth can lead to significant complications, including vision loss and neurologic abnormalities, which in many cases can be minimized through routine surveillance and early intervention.

Unlike BWS, VHL is not associated with identifiable morphologic abnormalities in affected individuals. It may therefore escape suspicion until a classic lesion is discovered. The diagnosis should be considered in any individual with a retinal or CNS hemangioblastoma, a pheochromocytoma or paraganglioma at age less than 30 years, or a ccRCC at less than 40 years. Furthermore, the diagnosis should be entertained in individuals with bilateral presentation or a strong family history of any of the classic VHL-related tumors. The diagnosis is confirmed by molecular genetic testing of the *VHL* gene, which can identify the underlying abnormality in nearly 100% of familial cases [57]. In some cases, de novo mutations may demonstrate mosaicism and therefore be difficult to detect. For this reason, clinical diagnosis may be the sole indication for initiation of a screening protocol.

The genetic abnormality responsible for VHL is mutation or deletion of the *VHL* gene, which resides at chromosome band 3p25.3. Patients with VHL syndrome typically harbor a single germline abnormality of the *VHL* gene and sustain an inactivating event on the remaining allele, as in the classic model of a tumor suppressor. Under conditions of normal oxygen tension, the VHL protein (pVHL) forms part of a complex that promotes

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

ubiquitination, and subsequent proteasomal degradation, of hypoxia-inducible factor–α (HIFα). Under hypoxic conditions, HIFα becomes resistant to ubiquitination and heterodimerizes with HIFβ. The HIF αβ heterodimer then acts as a transcription factor to increase the expression of genes that promote angiogenesis, cell growth, and resistance to apoptosis [15, 37]. In the absence of a normally functional pVHL, as is seen in VHL syndrome, HIFα is not degraded in normoxic conditions, leading to increased cell growth, decreased apoptosis, and development of abnormal micro-vasculature. Notably, ccRCC is among the most highly vascular malignancies.

Given the wide variety of tumor types that are associated with VHL, multiple screening modalities are recommended for at-risk individuals (Table 3). Many of the lesions typical of VHL present most frequently in adulthood, but all have been reported to occur occasionally in affected children. Thus, it is recommended that screening for the manifestations of disease begin once the diagnosis is established, or in the case of children born to affected parents, in infancy. As there is limited data to inform screening protocols, most have been developed by clinicians with expertise in the field, with the result that some of the current recommendations remain controversial.

ccRCC and retinal hemangioblastoma are the tumors for which screening recommendations are the strongest. Although ccRCC tends to be less aggressive when it develops in the context of VHL, it is still capable of metastasis, which portends a very poor prognosis [45]. Tumors are usually resected using a nephron-sparing procedure once they reach about 3 cm [16]. When resected in this manner, there is a very low risk of metastasis or later kidney dysfunction [37]. In order to detect lesions at this stage, annual screening with abdominal ultrasound or MRI is recommended, beginning at 8–11 years of age [37, 42]. Retinal hemangioblastomas occur in 60% of patients with half of affected individuals presenting with multifocal or bilateral disease [37]. While the mean age of presentation for these lesions is 25 years, 5% of patients are less than 10 years when they are detected [37]. Retinal hemangioblastomas are not associated with increased mortality and are initially asymptomatic. However, they can result in vision impairment or loss if not treated properly. An initial ophthalmologic exam should be performed soon after birth and repeated annually for children known or suspected to have VHL [49]. Treatment generally involves photocoagulation or cryotherapy and is very effective for preservation of vision.

Abdominal ultrasound or MRI imaging is useful to detect the pancreatic and adrenal lesions of VHL. Pancreatic lesions may be cysts or neuroendocrine tumors, which together occur in 17–56% of patients [37]. Management is surgical, with a typically good prognosis. Pheochromocytoma occurs in 10–20% of patients, and is the only sequela of VHL that is more likely to present in younger patients, with the risk declining after age 30 years [23, 37]. To facilitate the identification of early stage pheochromocytomas, plasma metanephrines should also be evaluated annually starting at age 5 years, particularly for those whose VHL mutations confer a greater risk for developing this tumor. Adrenal cortical sparing surgery may be curative, with a low risk of recurrence or metastasis [1].

CNS hemangioblastomas are the most common consequence of VHL and can cause severe disability or death if allowed to grow unchecked. These tumors have an unpredictable natural history, often remaining at a stable size for years before enlarging. Like many of the other lesions of VHL, they may be multifocal, and continue to develop throughout life. As this clinical picture can result in multiple neurosurgical procedures over a patient's lifetime, observation is generally recommended for asymptomatic lesions [37]. Because intervention is reserved until these hemangioblastomas are symptomatic, screening recommendations are somewhat controversial, but the most common recommendation is to begin screening with gadolinium-enhanced MRI of the brain and spine at puberty (around age 11–15 years), with

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

evaluations repeated every 1 to 2 years. This MRI is also used to evaluate for ELST, which, if detected only once symptomatic, present with nearly universal hearing impairment or loss [32, 40]. As additional evaluation for ESLT, patients should undergo regular audiologic evaluations, especially if there is concern for a hearing deficit. Surgical management maintains pre-operative hearing level, but cannot correct impairments once established.

In addition to the radiology and laboratory studies outlined above, patients with VHL should have annual physical exams, with attention to neurologic function and blood pressure. Many reports exist of patients in whom VHL-related lesions appear to have been detected earlier, and with less associated morbidity, than would have been expected if they had not undergone surveillance [32, 49, 51]. However, systematic investigations into the benefits of screening have not taken place. Historically, life expectancy in patients with VHL has been about 50 years [39]. It seems reasonable that this would increase through the use of standardized comprehensive screening protocols.

## Li–Fraumeni syndrome

LFS is an autosomal dominant disorder associated with the development of soft tissue and bone sarcomas, premenopausal breast cancer, brain tumors, leukemia, and adrenocortical carcinoma [36]. Many other tumor types may also be associated with this disorder [9]. Patients with LFS have a high risk of developing multiple primary tumors, and appear to be particularly sensitive to the carcinogenic potential of radiation exposure [25]. The lifetime risk of cancer development for an individual with LFS is approximately 75% in men and 100% in women [62]. In one study, 10% of affected boys and 18% of girls were diagnosed with cancer before 20 years of age [28]. Although highly penetrant, the expression of disease varies widely and it is often difficult to predict which type(s) of cancer an individual will develop, and at what age(s) the cancers will occur. These issues present a particular challenge for development of a sensible screening protocol for affected individuals.

Various studies have estimated that between 50% and 77% of patients with clinically defined LFS have identifiable germline mutations in the *TP53* tumor suppressor gene [8, 65]. TP53 is a transcription factor that accumulates in response to DNA damage or other cellular stress. It regulates the transcription of many genes which promote temporary cell cycle arrest, senescence, or apoptosis [66]. Abnormalities in the *TP53* gene lead to the production of altered proteins with aberrant transcriptional regulatory capabilities. When the *TP53* gene is unable to produce a normally functioning protein, the cell cycle continues even when the cell has sustained DNA damage, leading to an accumulation of errors. While *TP53* was initially thought to be a typical tumor suppressor in which a second hit is needed to inactivate the remaining normal gene before the cell can progress to malignancy, in many cases this appears not to be true. Rather, mutated TP53 often acts in a dominant fashion, probably by directly interfering with the function of the normal protein product of the unmutated allele [43].

LFS has no phenotypic manifestation other than the increased risk of malignancy, and thus the clinician must suspect the diagnosis on the basis of the family or individual cancer history. The decision of whether to test a pre-symptomatic child for a familial *TP53* mutation is itself a difficult one. As there is not yet a generally accepted screening protocol, and little data to show that screening would alter outcomes, there is concern that knowledge of a mutation would lead only to increased anxiety and psychological distress [34]. However, the few studies conducted have not shown increased psychological distress in individuals once they find that they have a mutation compared to how they felt prior to testing, or in patients with LFS compared to other hereditary cancer syndromes [34, 35]. In one case study, Evans et al. presented two families in which adults were known to have LFS, but the status of children was not known. In both cases, parents self-reported high levels of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

anxiety prior to testing the children for LFS and felt they were bringing their children for medical evaluation in excessive frequency, and for minor ailments. Of these two unrelated children, one was found to have a TP53 mutation, and the other was not. In both cases, the frequency of medical visits decreased and the parents reported decreased anxiety [20]. It appears that in some cases the knowledge of the presence of a mutation is less anxiety provoking than the state of not knowing. The decision of whether or not to test for a mutation is best made on a case by case basis, and a primary pediatrician, with the help of a geneticist or oncologist, is most likely to be able to help a family to make this decision.

Premenopausal breast cancer is among the most common cancers arising in female patients with LFS, and given the excellent surveillance modalities for this tumor type (such as mammography, breast MRI, and breast ultrasound), it is a cancer for which screening is likely to be beneficial [9]. It is important to recognize that age of onset for breast cancer is early in LFS, with some individuals developing cancer in the second or third decade of life [47]. Thus, screening for this cancer should begin at age 18 years with monthly self-breast examination and biannual clinical breast examination. Imaging studies should begin at 20–25 years, or at 5 years earlier than the youngest age at which this cancer was diagnosed in an affected family member, whichever is earlier (Table 3) [44].

No consensus exists as to how to screen patients for the other malignancies associated with LFS. There is general agreement that children with LFS should have a full physical examination at least annually, with a complete blood count and perhaps a urinalysis. Other recommendations include abdominal ultrasound to screen for adrenocortical carcinoma or other intra-abdominal malignancy. It is reasonable to expect that certain malignancies may be more common in one family than another, although there is not necessarily data to support this theory as yet. However, it seems prudent to focus some of the screening toward malignancies that are known to have affected other family members.

Whole body FDG-PET/CT has recently been examined as a screening modality, given its high sensitivity to many of the typical LFS malignancies [41]. 15 patients with known *TP53* mutations or obligate mutation carrier status underwent whole body and brain FDG-PET/CT evaluation. Of these patients, three were found to have malignancies that were not previously identified through physical examination or routine laboratory testing. All received potentially curative therapy. Although it is impossible to be certain that the outcome for these patients will be better than would have occurred if the lesions had been detected later, it is logically compelling. However, given the possible radiation sensitivity in patients with LFS, the cumulative radiation exposure of routine FDG-PET/CT screening makes it a less attractive option at this time. The study does suggest that there may be benefit to some form of whole body imaging for patients with LFS. MRI is also under evaluation for this purpose, and may be more attractive given the lack of radiation exposure (KE Nichols, unpublished). Annual brain MRI may also be appropriate in certain cases, particularly if there is a family history of brain tumors.

## Rhabdoid tumor and schwannomatosis

Rhabdoid tumors are highly aggressive malignancies that generally present in infancy or early childhood [64]. These tumors are most commonly found in the kidney and CNS (where they are designated as atypical teratoid/rhabdoid tumors, or AT/RT), but may present in nearly any soft tissue site [46]. The survival for patients with these tumors is 15% to 30%, but as expected, varies by stage. In National Wilms Tumor Study Group trials, patients with stage I or II renal rhabdoid tumors had an overall survival of 42% at 4 years, those with stage III, IV, or V disease fared less well with survival of about 16% when evaluated as a group [64]. For those with CNS disease, the prognosis is comparably dismal, with a registry review identifying a median overall survival of 16.75 months [24]. Some of these patients

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

have had prolonged survival, however, with 24% alive 2 years or longer. A large proportion of long-term survivors were treated with radiation therapy, chemotherapy, and stem cell rescue [24]. EFS appears to be better in patients with gross total resection compared to those who had subtotal resections or biopsies of their tumors [24]. These trends are important in the context of screening recommendations, as they suggest that if CNS tumors were detected earlier, they might be more easily resected and associated with improved outcomes for these patients.

The characteristic genetic abnormalities and the primary initiating event for rhabdoid tumors are a mutation and/or deletion of the *INI1/SMARCB1* gene located in chromosome band 22q11.2 [7]. SMARCB1 is part of a chromatin remodeling complex which is involved in regulating gene expression, including genes involved in cell cycle control, DNA repair, and differentiation [54]. Both alleles must be inactivated in order for a tumor to arise, consistent with its function as a tumor suppressor gene. Approximately 35% of patients with rhabdoid tumors have germline *INI1/SMARCB1* alterations [18]. While the majority of germline mutations are de novo, families have been reported in which multiple siblings have been affected. In rare cases, a parent is an unaffected carrier, and can have multiple children with rhabdoid tumor before the condition comes to the attention of a clinical geneticist [11, 52, 58]. Additionally, there have been reports of families in which some members were diagnosed with schwannomatosis, a disorder in which an individual develops two or more benign tumors of the nerve sheath, commonly referred to as schwannomas, while others developed rhabdoid tumors [18, 38, 61]. Most cases of familial schwannomatosis are associated with germline *INI1/SMARCB1* mutations [10, 27]. The penetrance and expressivity of *INI1/SMARCB1* abnormalities are under investigation, and may vary with the specific genetic mutation [18].

Recommendations for surveillance in patients with germline *INI1/SMARCB1* mutations have been developed based on the epidemiology and clinical course of rhabdoid tumors. A group of experts in the field of pediatric cancer genetics including geneticists, oncologists, and radiologists at the February 2009 meeting on “Pediatric Cancer Genetics: From Gene Discovery to Cancer Screening”, (Texas Children’s Cancer Center, Houston, TX) developed the following guidelines, which have not been formally studied (Table 3). From birth to 1 year of age, this working group suggests that patients have thorough physical and neurologic examinations as well as head ultrasounds monthly to assess for the development of a CNS tumor. Furthermore, it is suggested that patients undergo abdominal ultrasound with focus on the kidneys every 2 to 3 months to assess for renal lesions. From 1 year to approximately 4 years, after which the risk of developing a new rhabdoid tumor rapidly declines, brain and spine MRI and abdominal ultrasound should be performed every 6 months [56]. Although there are as yet no studies to confirm the benefit of screening patients with germline *INI1/SMARCB1* mutations, the aggressive natural history of the disease, apparently high penetrance and well-defined age of onset for CNS AT/RT suggest that screening could prove beneficial. Given the potential survival benefit of surgically resectable disease, it is reasonable to postulate that early detection might improve overall survival.

## Conclusion

While hereditary cancer predisposition syndromes are rare, a pediatrician may encounter them at some time in general practice. Often the suspicion for such a syndrome, institution of a screening protocol, and counseling of the family regarding siblings or future pregnancies will fall at least in part to the primary pediatrician. The previous examples are a representative sampling of several syndromes that present in childhood, and hopefully may provide a framework for evaluation and management of other cancer predisposition syndromes for caregivers in the general pediatric setting.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

## Acknowledgments

We gratefully acknowledge the Grundy Vision of Life Fund and the Division of Oncology at the Children's Hospital of Philadelphia, which have supported development of the Pediatric Hereditary Cancer Predisposition Program.

## References

1. Baghai M, Thompson GB, Young WF Jr, et al. Pheochromocytomas and paragangliomas in von Hippel-Lindau disease: a role for laparoscopic and cortical-sparing surgery. Arch Surg. 2002; 137:682–688. [PubMed: 12049539]
2. Baldisserotto M, Peletti AB, Angelo de Araújo M, et al. Beckwith-Wiedemann syndrome and bilateral adrenal pheochromocytoma: sonography and MRI findings. Pediatr Radiol. 2005; 35:1132–1134. [PubMed: 15983774]
3. Barlaskar FM, Hammer GD. The molecular genetics of adrenocortical carcinoma. Rev Endocr Metab Disord. 2007; 8:343–348. [PubMed: 17934868]
4. Beckwith JB. Children at increased risk for Wilms tumor: monitoring issues. J Pediatr. 1998; 132:377–379. [PubMed: 9544882]
5. Bémurat L, Gosse P, Ballanger P, et al. Successful lapaproscopic operation of bilateral pheochromocytoma in a patient with Beckwith-Wiedemann syndrome. J Hum Hypertens. 2002; 16:281–284. [PubMed: 11967723]
6. Bliek J, Gicquel C, Maas S, et al. Epigenotyping as a tool for the prediction of tumor risk and tumor type in patients with Beckwith-Wiedemann syndrome (BWS). J Pediatr. 2004; 145:796–799. [PubMed: 15580204]
7. Biegel JA, Zhou J, Rorke LB, et al. Germ-line and acquired mutations of *INI1* in atypical teratoid rhabdoid tumor. Cancer Res. 1999; 59:74–79. [PubMed: 9892189]
8. Birch JM, Hartley AL, Tricker KJ, et al. Prevalence and diversity of constitutional mutations in the p53 gene among 21 Li–Fraumeni families. Cancer Res. 1994; 54:1298–1304. [PubMed: 8118819]
9. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. Oncogene. 2001; 20:4621–4628. [PubMed: 11498785]
10. Boyd C, Smith MJ, Kluwe L, et al. Alterations in the SMARCB1 (INI1) tumor suppressor gene in familial schwannomatosis. Clin Genet. 2008; 74:358–366. [PubMed: 18647326]
11. Bruggers CS, Bleyl SB, Pysher T, et al. Clincopathologic comparison of familial versus sporadic atypical teratoid/rhabdoid tumors (AT/RT) of the central nervous system. Pediatr Blood Cancer. 201010.1002/pbc.22757
12. Burgess J. How should the patient with multiple endocrine neoplasia type 1 (MEN 1) be followed? Clin Endocrinol Oxf. 2010; 72:13–16. [PubMed: 19552677]
13. Choyke PL, Siegel MJ, Craft AW, et al. Screening for Wilms tumor in children with Beckwith-Wiedemann syndrome or idiopathic hemihypertrophy. Med Pediatr Oncol. 1999; 32:196–200. [PubMed: 10064187]
14. Clericuzio CL, Chen E, McNeil DE, et al. Serum alpha-fetoprotein screening for hepatoblastoma in children with Beckwith-Wiedemann syndrome or isolated hemihyperplasia. J Pediatr. 2003; 143:270–272. [PubMed: 12970646]
15. Clark PE, Cookson MS. The von Hippel-Lindau gene: turning discovery into therapy. Cancer. 2008; 113:1768–1778. [PubMed: 18800388]
16. Coleman JA. Familial and hereditary renal cancer syndromes. Urol Clin North Am. 2008; 35:563–572. [PubMed: 18992610]
17. Cooper WN, Luharia A, Evans GA, et al. Molecular subtypes and phenotypic expression of Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2005; 13:1025–1032. [PubMed: 15999116]
18. Eaton KW, Tooke LS, Wainwright LM, et al. Spectrum of *SMARCB1/INI1* mutations in familial and sporadic rhabdoid tumors. Pediatr Blood Cancer. 2011; 56(1):7–15. [PubMed: 21108436]
19. Engel JR, Smallwood A, Harper A, et al. Epigenotype-phenotype correlations in Beckwith-Wiedemann syndrome. J Med Genet. 2000; 37:921–926. [PubMed: 11106355]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript


20. Evans DG, Lunt P, Clancy T, Eeles R. Childhood predictive genetic testing for Li–Fraumeni syndrome. Fam Cancer. 2010; 9:65–69. [PubMed: 19404774]
21. Everman DB, Shuman C, Dzolganovski B, et al. Serum alpha-fetoprotein levels in Beckwith-Wiedemann syndrome. J Pediatr. 2000; 137:123–127. [PubMed: 10891834]
22. Ferner RE. The neurofibromatoses. Pract Neurol. 2010; 10:82–93. [PubMed: 20308235]
23. Field M, Shanley S, Kirk J. Inherited cancer susceptibility syndromes in paediatric practice. J Paediatr Child Health. 2007; 43:219–229. [PubMed: 17444822]
24. Hilden JM, Meerbaum S, Burger P, et al. Central nervous system atypical teratoid/rhabdoid tumor: results of therapy in children enrolled in a registry. J Clin Oncol. 2004; 22:2877–2884. [PubMed: 15254056]
25. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li–Fraumeni syndrome. J Natl Cancer Inst. 1998; 90:606–611. [PubMed: 9554443]
26. Hoyme HE, Seaver LH, Jones KL, et al. Isolated hemi-hyperplasia (hemihypertrophy): report of a prospective multicenter study of the incidence of neoplasia and review. Am J Med Genet. 1998; 79:274–278. [PubMed: 9781907]
27. Hulsebos TJM, Plomp AS, Woterman RA, et al. Germline mutation of INI1/SMARCB1 in familial schwannomatosis. Am J Hum Genet. 2007; 80:805–810. [PubMed: 17357086]
28. Hwang SJ, Lozano G, Amos CI, Strong LC. Germline p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. Am J Hum Genet. 2003; 72:975–983. [PubMed: 12610779]
29. Jackson EM, Shaikh TH, Zhang F, et al. Atypical teratoid/rhabdoid tumor in a patient with Beckwith-Wiedemann syndrome. Am J Med Genet A. 2007; 143A:1767–1770. [PubMed: 17603804]
30. Kaatsch P, Steliarova-Foucher E, Crocetti E, et al. Time trends of cancer incidence in European children (1978–1997): report from the automated childhood cancer information system project. Eur J Cancer. 2006; 42:1961–1971. [PubMed: 16919764]
31. Katzenstein HM, London WB, Douglass E, et al. Treatment of unresectable and metastatic hepatoblastoma: a pediatric oncology group phase II study. J Clin Oncol. 2002; 20:3438–3444. [PubMed: 12177104]
32. Kim HJ, Butman JA, Brewer C, et al. Tumors of the endolymphatic sac in patients with von Hippel-Lindau disease: implications for their natural history, diagnosis and treatment. J Neurosurg. 2005; 102:503–512. [PubMed: 15796386]
33. Lapunzina P. Risk of tumorigenesis in overgrowth syndromes: a comprehensive review. Am J Med Genet. 2005; 137C:53–71. [PubMed: 16010678]
34. Lammens CRM, Aaronson NK, Wagner A, et al. Genetic testing in Li–Fraumeni Syndrome: uptake and psychosocial consequences. J Clin Oncol. 2010; 28:3008–3014. [PubMed: 20479422]
35. Lammens CRM, Bleiker EMA, Aaronson NK, et al. Regular surveillance for Li–Fraumeni syndrome: advice, adherence and perceived benefits. Fam Cancer. 2010; 9(4):647–654. [PubMed: 20658357]
36. Li FP, Fraumeni JF. Prospective study of a family cancer syndrome. JAMA. 1982; 247:2692–2694. [PubMed: 7077763]
37. Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. Lancet. 2003; 361:2059–2067. [PubMed: 12814730]
38. MacCollin M, Chiocca EA, Evans DG, et al. Diagnostic criteria for schwannomatosis. Neurology. 2005; 64:1838–1845. [PubMed: 15955931]
39. Maher ER, Yates JR, Harries R, et al. Clinical features and natural history of von Hippel-Lindau disease. Q J Med. 1990; 77:1151–1163. [PubMed: 2274658]
40. Manksi TJ, Heffner DK, Glenn GM, et al. Endolymphatic sac tumors: a source of morbid hearing loss in von Hippel-Lindau disease. JAMA. 1997; 277:1461–1466. [PubMed: 9145719]
41. Masciari S, Van den Abbeele AD, Diller LR. F18-fluorodeoxyglucose-positron emission tomography/computed tomography screening in Li–Fraumeni syndrome. JAMA. 2008; 299:1315–1319. [PubMed: 18349092]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript


42. Meister M, Choyke P, Anderson C, Patel U. Radiological evaluation, management and surveillance of renal masses in Von Hippel-Lindau disease. Clin Radiol. 2009; 64:589–600. [PubMed: 19414081]
43. Moule RN, Jhavar SG, Eeles RA. Genotype phenotype correlation in Li–Fraumeni syndrome kindreds and its implications for management. Fam Cancer. 2006; 5:129–133. [PubMed: 16736281]
44. NCCN. The NCCN Clinical Practice Guidelines in Oncology™ Li–Fraumeni syndrome (Version 1.2008). © 2009. National Comprehensive Cancer Network, Inc. ; 2008. www.nccn.orgTo view the most recent and complete version of the NCCN Guidelines, login to http://www.nccn.org
45. Neumann HP, Bender BU, Berger DP, et al. Prevalence, morphology and biology of renal cell carcinoma in von Hippel-Lindau disease compared to sporadic renal cell carcinoma. J Urol. 1998; 160:1248–1254. [PubMed: 9751329]
46. Oda Y, Tsuneyoshi M. Extrarenal rhabdoid tumors of soft tissue: clinicopathological and molecular genetic review and distinction from other soft-tissue sarcomas with rhabdoid features. Pathol Int. 2006; 56:287–295. [PubMed: 16704491]
47. Olivier M, Goldgar DE, Sodha N, et al. Li–Fraumeni and related syndromes: correlation between tumor type, family structure, and TP53 genotype. Cancer Res. 2003; 63:6643–6650. [PubMed: 14583457]
48. Perilongo G, Shafford E, Maibach R. Risk-adapted treatment for childhood hepatoblastoma. Final report of the second study of the International Society of Paediatric Oncology—SIOPEL 2. Eur J Cancer. 2004; 40:411–421. [PubMed: 14746860]
49. Poulsen MLM, Budtz-Jørgensen E, Bisgaard ML. Surveillance in von Hippel-Lindau disease (vHL). Clin Genet. 2010; 77:49–59. [PubMed: 19863552]
50. Porteus MH, Narkool P, Neuberg D, et al. Characteristics and outcome of children with Beckwith-Wiedemann syndrome and Wilms' tumor: a report from the national Wilms tumor study group. J Clin Oncol. 2000; 18:2026–2031. [PubMed: 10811666]
51. Priesemann M, Davies KM, Perry LA, et al. Benefits of screening in von Hippel-Lindau disease—comparison of morbidity associated with initial tumours in affected parents and children. Horm Res. 2006; 66:1–5. [PubMed: 16651847]
52. Proust F, Laquerriere A, Constantin B, et al. Simultaneous presentation of atypical teratoid/rhabdoid tumor in siblings. J Neuroncol. 1999; 43:63–70.
53. Rao A, Rothman J, Nichols KE. Genetic testing and tumor surveillance for children with cancer predisposition syndromes. Curr Opin Pediatr. 2008; 20:1–7. [PubMed: 18197032]
54. Reisman D, Glaros S, Thompson EA. The SWI/SNF complex and cancer. Oncogene. 2009; 28:1653–1668. [PubMed: 19234488]
55. Ries, LAG.; Smith, MA.; Gurney, JG., et al., editors. Cancer incidence and survival among children and adolescents: United States SEER Program 1975–1995. Bethesda (MD): National Cancer Institute; 1999. SEER Program NIH Pub. No. 99–4649
56. Rorke LB, Packer RJ, Biegel JA. Central nervous system atypical teratoid/rhabdoid tumors of infancy and childhood: definition of an entity. J Neurosurg. 1996; 85:56–65. [PubMed: 8683283]
57. Schimke, RN.; Collins, DL.; Stolle, CA. von Hippel-Lindau syndrome. GeneReviews. 2009. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=vhl
58. Sévenet N, Sheridan E, Amram D, et al. Constitutional mutations of the hSNF5/INI1 gene predispose to a variety of cancer. Am J Hum Genet. 1999; 65:1342–1348. [PubMed: 10521299]
59. Slavin TP, Wiesner GL. Developmental defects and childhood cancer. Curr Opin Pediatr. 2009; 21:717–723. [PubMed: 19812499]
60. Strahm B, Malkin D. Hereditary cancer predisposition in children: genetic basis and clinical implications. Int J Cancer. 2006; 119:2001–2006. [PubMed: 16642469]
61. Swensen JJ, Keyser J, Coffin CM, et al. Familial occurrence of schwannomas and malignant rhabdoid tumour associated with a duplication in SMARCB1. J Med Genet. 2009; 46:68–72. [PubMed: 19124645]
62. Tabori U, Malkin D. Risk stratification in cancer predisposition syndromes: lessons learned from novel molecular developments in Li–Fraumeni syndrome. Cancer Res. 2008; 68:2053–2057. [PubMed: 18381406]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript


63. Tan TY, Amor DJ. Tumour surveillance in Beckwith-Wiedemann syndrome and hemihyperplasia: a critical review of the evidence and suggested guidelines for local practice. J Paediatr Child Health. 2006; 42:486–490. [PubMed: 16925531]
64. Tomlinson GE, Breslow NE, Dome J, et al. Rhabdoid tumor of the kidney in the National Wilms' Tumor Study: age at diagnosis as a prognostic factor. J Clin Oncol. 2005; 23:7641–7645. [PubMed: 16234525]
65. Varley JM. Germline TP53 mutations and Li–Fraumeni syndrome. Hum Mutat. 2003; 21:313–320. [PubMed: 12619118]
66. Vousden KH, Prives C. Blinded by the light: The growing complexity of p53. Cell. 2009; 137:413–431. [PubMed: 19410540]
67. Weksberg R, Nishikawa J, Caluseriu O, et al. Tumor development in the Beckwith-Wiedemann syndrome is associated with a variety of constitutional molecular 11p15 alterations including imprinting defects of KCNQ1OT1. Hum Mol Genet. 2001; 10:2989–3000. [PubMed: 11751681]
68. Weksberg R, Shuman C, Smith A. Beckwith-Wiedemann syndrome. Am J Med Genet. 2005; 137C:12–23. [PubMed: 16010676]
69. Weksberg R, Shuman C, Beckwith JB. Beckwith–Wiedemann syndrome. Eur J Hum Genet. 2010; 18:8–14. [PubMed: 19550435]
70. Zarate YA, Mena R, Martin LJ, et al. Experience with hemihyperplasia and Beckwith–Wiedemann syndrome surveillance protocol. Am J Med Genet. 2009; 149A:1691–1697. [PubMed: 19610116]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

**Table 1**

Advantages and disadvantages of tumor screening

| Advantages | Disadvantages |
|---|---|
| Identify small/localized lesions | False-positive results of imaging or laboratory studies may lead to additional testing or unnecessary procedures |
| Lower surgical morbidity | |
| Less intensive chemotherapy | |
| Attenuate/avoid radiotherapy | |
| Improved emotional well-being through sense of expectation and control | Stress and anxiety related to frequent medical and/or laboratory visits |
| Negative results decrease anxiety | False-positive results or results of unclear significance may increase patient concern |
| Decrease tumor-associated mortality | Increased frequency of medical visits |
| Decrease morbidity related to tumors or their treatment | Lack of proven benefit of screening in many disorders |

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

**Table 2**

Considerations in design of surveillance protocols

| Factors to consider when establishing a tumor screening program |
|---|
| Genetic testing should have high sensitivity and specificity |
| Disorder should have high penetrance |
| Age-specific cancer risks should be known |
| Safe, effective, and readily available screening modalities should be used |
| Optimal interval between screening measures should be known |
| Overall duration of screening protocol must be established |
| Effective treatments should be available for tumors if they are detected |

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript



## Table 3

Surveillance recommendations for conditions discussed in this review

| Condition | Associated tumors | Age range of onset (years) | Screening recommendations | Ref |
|---|---|---|---|---|
| BWS/IHH | Wilms' tumor | 0–8 | 0–4 years, abdominal US every 3 months; 4–8 years, renal US every 3 months | [14, 63] |
| | Hepatoblastoma | 0–4 | 0–4 years, abdominal US every 3 months; AFP level every 6–12 weeks | |
| | Neuroblastoma, adrenocortical, carcinoma, rhabdomyosarcoma | | None; however, abdominal US can detect these tumors | |
| VHL | CNS hemangioblastoma | 9–78 (mean, 33) | 11 to 15 years–lifelong, MRI brain and spine every 1–2 y | [1, 37, 42, 49] |
| | Retinal hemangioblastoma | 1–67 (mean, 25) | Birth–lifelong, ophthalmologic exam annually | |
| | Pheochromocytoma | 5–58 (mean, 30) | 5 years–lifelong, plasma metanephrines annually | |
| | Renal cell carcinoma | 16–67 (mean, 39) | 8 to 11 years–lifelong, abdominal US or MRI annually | |
| | Endolymphatic sac tumor | 12–50 (mean, 22) | See CNS hemangioblastoma | |
| | Pancreatic tumor | 5–70 (mean, 36) | See renal cell carcinoma | |
| | Cystadenoma | Unknown | None | |
| LFS | Breast cancer | Median, 33 | 18 years–lifelong, monthly self-breast exam, clinical breast exam every 6 mos | [44] |
| | | | 20 to 25 years (or 5 years earlier than youngest diagnosis in the family)– lifelong, annual breast imaging | |
| | Soft tissue sarcoma | Median, 14 | Lifelong, annual physical exam and complete blood count | |
| | Bone sarcoma | Median, 15 | | |
| | Brain tumor | Median, 16 | | |
| | Leukemia | Median, 27 | | |
| | Adrenocortical carcinoma | Median, 3 | | |
| Rhabdoid tumor | Renal rhabdoid | 0–4 | 0–1 year, abdominal US every 2 to 3 mos; 1–4 years, abdominal US every 6 mos | |
| | CNS AT/RT | 0–4 | 0–1 year, head US monthly; 1–4 years, brain and spine MRI every 6 mos | |

*AFP*, alpha-fetoprotein; *BWS/IHH*, Beckwith–Wiedemann syndrome/idiopathic hemihyperplasia; *CNS*, central nervous system; *LFS*, Li–Fraumeni syndrome; *MRI*, magnetic resonance imaging; *Ref*, References; *US*, ultrasound; *VHL*, von Hippel–Lindau