Role of Ultrasound in Cancer Predisposition Syndromes

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Cancer predisposition syndromes comprise a multitude of familial cancers, most having an established germline mutation. Most children with a known genetic syndrome undergo routine screening, which includes imaging studies. This chapter describes the use of ultrasound in screening of children with genetic predisposition to solid malignancies. Proper ultrasound protocols, the use of contrast-enhanced ultrasound (CEUS), and imaging recommendations for frequent and rare cancer disposition syndromes are described.

Cancer predisposition syndromes comprise a multitude of familial cancers with a clear mode of inheritance; most have an established germline mutation. Genetic predisposition is thought to account for 5–10% of all pediatric cancers. Most children with a known genetic syndrome undergo routine screening with physical examination, laboratory tests, and imaging examinations to screen for malignancy. The primary goal of screening is to detect disease at an early stage to allow limited therapy with the goals of reducing treatment-associated morbidity and improving outcome and survival [1].

Advances in genetics and molecular biology have improved understanding of the multitude of syndromic conditions and provided an abundance of information for screening and surveillance of patients and their families. Imaging plays a vital role in solid tumor surveillance [2]. It is important to minimize morbidity due to radiation exposure during diagnosis, treatment, and later surveillance. Avoidance of radiation and sedation is particularly relevant in pediatric oncology because children with a predisposition to cancer may undergo innumerable imaging studies during their lifetime. Most recommendations for screening call for imaging modalities that do not entail ionizing radiation, including ultrasound and MRI, even at the cost of sensitivity and specificity [3].

This chapter illustrates the importance of the use of ultrasound in imaging protocols to screen children with cancer predisposition syndromes for solid tumors. Discussion focuses on the benefits and limitations of ultrasound and newer applications of CEUS. The most frequent cancer predisposition syndromes with ultrasound applications are Li-Fraumeni syndrome (LFS), Beckwith-Wiedemann syndrome (BWS) and other overgrowth syndromes, von Hippel–Lindau (VHL) syndrome, and familial adenomatous polyposis (FAP). Rarer syndromes include *DICER1* syndrome, *PTEN* hamartoma tumor syndrome, trisomy 18, and Costello syndrome.

Cancer Screening Models

Cancer screening programs have potential drawbacks and risks that must be acknowledged. The overall societal impact of tumor screening for rare disorders differs from population-based screening programs, such as those for detecting breast cancer. The difference in scale suggests that most cost-benefit analyses likely favor the benefits of screening of children with cancer predisposition syndromes, as in the case of BWS, over the outcomes of not screening [4]. When weighing the risk-to-benefit cost of tumor screening, aside from the financial cost to society, one must also factor in the emotional cost to patients and their families.

There is a paucity of data on the psychosocial impact of testing performed in conjunction with prospective surveillance programs [5, 6]. Testing requires multiple visits to clinics, time off from work or school, distress incurred by undergoing imaging studies and needle sticks, and anxiety awaiting test results. Screening tests also carry the possibility of false-positive findings, adding to the emotional burden. Although most parents believe that tumor screening is associated with a good psychologic outcome, providing security and a sense of control, data have shown an overall increased level of distress and lower quality of life [7, 8]. Screening programs should consist of a multidisciplinary team with the radiologist providing timely and accurate reports.

Ultrasound Imaging

Ultrasound has many advantages in screening for solid tumors in children. It is widely available, portable, and lower in cost than many other imaging modalities and requires neither ionizing radiation nor sedation. Ultrasound is regarded as low risk and has the potential for high yield. It allows dynamic assessment of tumors and may help determine tumor invasion of viscera because it can be used to assess the mobility of structures relative to breathing motion, which may aid in presurgical planning

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[9]. Ultrasound, however, can be limited in children with a large habitus. For very large tumors, the organ of origin can often be difficult to identify, and owing to difficulties with artifacts (such as bowel gas) and attenuation of the beam, the burden of disease can be underestimated with ultrasound. Ultrasound is not a standalone tool for screening and is used in conjunction with genetic testing, physical examination, and biochemical testing [3].

Complete ultrasound protocols should be performed for the given indication. The use of high-frequency linear probes (at least 10–12 MHz) should be used to examine the solid organs to provide greatest detail. Accurate organ measurements must be obtained and compared with those from prior studies when available because organ enlargement is a risk factor for cancer development in cancer predisposition syndromes such as BWS [10]. Color or power Doppler ultrasound should always be used to assist in differentiating solid from cystic lesions. Adjacent vasculature should be examined for tumor invasion and thrombus. Regional lymph nodes should be systematically assessed [9].

Structured reporting provides reproducibility and consistency and allows easy comparison with prior studies. Findings should be made in a clear and concise format with personal communication provided for patients who need additional workup or possibly invasive testing [3]. Limitations of the ultrasound study, such as inability to adequately visualize certain key structures, should be made clear in the report because the clinician may request specific blood tests or imaging modalities to supplement the screening process [9].

Contrast-Enhanced Ultrasound

The role of CEUS is rapidly expanding given recent FDA approval of the contrast agent for use in children. CEUS is increasingly recognized as an important tool in pediatric oncology because it obviates ionizing radiation, sedation, and iodinated or gadolinium-based contrast infusion. The contrast agent can also be safely administered to children with renal impairment. Use of CEUS also allows immediate feedback to the family, alleviating anxiety associated with waiting for a report [11].

Studies have shown the efficacy of CEUS in evaluating lesions in many organ systems, including liver, kidney, testes, and thyroid [11–15]. The bulk of the literature encompasses detection and characterization of liver lesions, showing the superiority of CEUS and affording the opportunity to improve lesion conspicuity and diagnostic confidence. Focused contrast-enhanced studies can be performed to further elucidate findings from gray-scale imaging, tailoring the evaluation to answer a specific diagnostic question.

To optimize the performance of CEUS, the radiologist should first review prior imaging and determine that a CEUS study is indicated. The appropriate ultrasound probe and scanning parameters should be selected. Once the ultrasound contrast agent is injected IV, a timer should be started (equipped with most CEUS software), and recording (≈ 20–40 seconds) should start after the first bubbles are detected. A venous video clip scanning the entire organ should also be recorded. Late-phase (> 5 minutes after injection) imaging should also be performed. If multiple parenchymal lesions are to be evaluated, contrast injections can be repeated according to manufacturer guidelines [11].

Evaluating lesions such as hepatic lesions requires careful evaluation of the vascular enhancement pattern during the arterial, portal venous, and late phases. Initial enhancement of the lesion may be characterized as either central, eccentric, or peripheral with a pattern of uniform, stellate or spoked wheel, haphazard, globular, or peripheral rim enhancement. The portal venous and late phases are important because early lesion washout is usually indicative of malignancy (Fig. 1). Most benign lesions remain isoenhancing or hyperenhancing or continue to fill in the portal venous and late phases [11] (Fig. 2).

Common Cancer Predisposition Syndromes

Developing an appropriate algorithm for both clinical and imaging surveillance depends on the child's cancer predisposition syndrome and in some cases the particular genetic defect. Imaging recommendations for the most frequent cancer predisposition syndromes along with several rare conditions follow.

Li-Fraumeni Syndrome

LFS is among the most aggressive cancer predisposition syndromes. It has high and early-onset cancer risk; the lifetime risk of development of one or more malignancies is almost 100% [16]. This autosomal dominant condition is the result of heterogeneous pathogenic germline TP53 (tumor protein 53) mutations on chromosome 17p13.1. TP53, a tumor suppressor protein, plays a central role in regulating the expression of genes involved in cell cycle arrest, apoptosis, DNA repair, and senescence, particularly in response to DNA damage and other cell stressors. One-half of all female patients will have a malignancy by the age of 30 years, and male patients by the age of 46 years [17]. Core cancers in LFS include osteosarcoma, adrenocortical carcinomas, CNS tumors, soft-tissue sarcomas, leukemia, and premenopausal breast cancer. Soft tissue tumors and osteosarcoma constitute 25–38% of all LFS-related malignancies and are the most common cancers in children. The risk of a second malignancy among children with LFS in whom cancer develops in childhood is 83 times the risk among children in whom cancer does not develop in childhood. Surveillance imaging for these children includes a combination of whole-body MRI, brain MRI, and abdominal and pelvic ultrasound [17].

An expert panel [18] has revised recommendations for screening of children with LFS. Given the high risk of adrenocortical carcinoma in children with LFS, abdominal and pelvic ultrasound every 3–4 months through adulthood is recommended (Fig. 3). In the case of technically unsatisfactory ultrasound, adrenocortical carcinoma–specific blood tests (total testosterone, dehydroepiandrosterone sulfate, and androstenedione) are recommended [18]. Yearly whole-body MRI examinations are recommend, as is yearly dedicated brain MRI. Practical modifications can be made for children to limit the need for gadolinium MRI contrast material and sedatives needed to perform the studies.

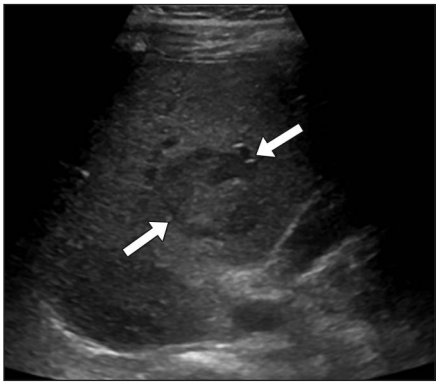
Beckwith-Wiedemann Syndrome

BWS is an overgrowth and tumor predisposition disorder that affects at least 1 in 11,000 children, making it the most

common epigenetic overgrowth cancer predisposition disorder. BWS results from the variable association of overgrowth, abdominal wall defects (omphalocele, umbilical hernia, and diastasis recti), macroglossia, nephrourologic malformations, hemihyperplasia, hyperinsulinemic hypoglycemia, ear anomalies (lobe creases or helical pits), capillary malformations (hemangioma and nevus flammeus at the glabella), and organomegaly [10]. Isolated hemihyperplasia (localized overgrowth of a part of the body) is considered the mild end of the clinical BWS spectrum, but it entails the same implications for cancer development as more severe BWS [19]. Malignancy risk is estimated to be as high as 10% during the first decade of life. The spectrum includes Wilms tumor (43%), hepatoblastoma (20%), adrenal adenoma and carcinoma (7%), and less commonly, neuroblastoma, rhabdomyosarcoma, pancreatoblastoma, and leukemia.

The diagnosis of BWS is clinical, but specific molecular anomalies at chromosome 11p15.5 (11p overgrowth spectrum) are present in 75–70% of patients with BWS [10]. Some genotypes and epigenotypes of BWS lead to elevated risk of malignancy (as high as 28%), whereas other epigenotypes lead to lower risk (as low as 2.8%). Current tumor screening recommendations do not differ on the basis of the genetic cause of BWS. Some clinicians may follow those in higher risk groups more closely or act more urgently on suspected abnormalities [8].

Current screening imaging recommendations for BWS include abdominal ultrasound examinations as soon as BWS is diagnosed (or even suspected) and every 3–4 months until the child is 8 years old to screen for solid tumors (Fig. 4). A complete abdominal ultrasound examination should be performed with measurement of abdominal organs, particularly the kidneys, to assess for organomegaly. Measurements should be compared with age-specific nomograms to assess risk of Wilms tumor. In addition to assessment



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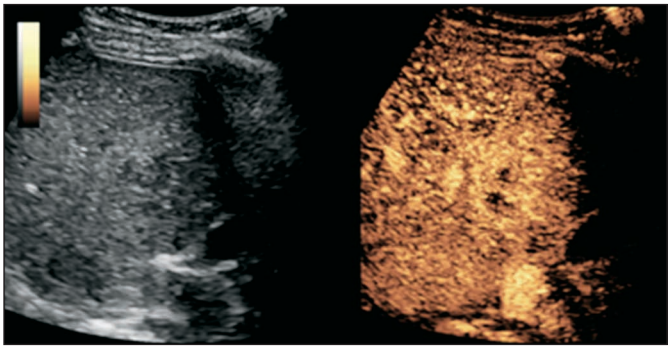

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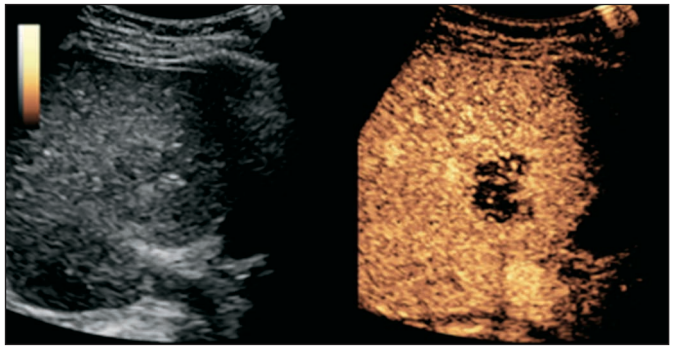

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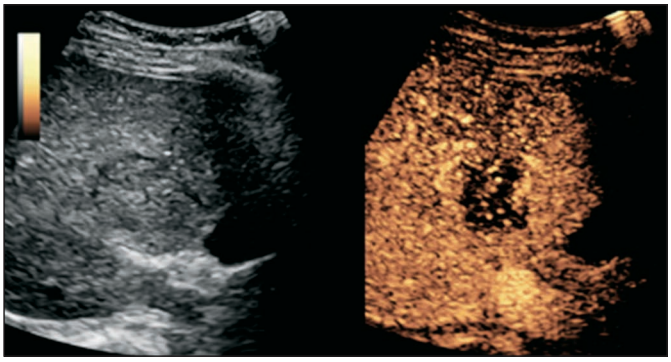

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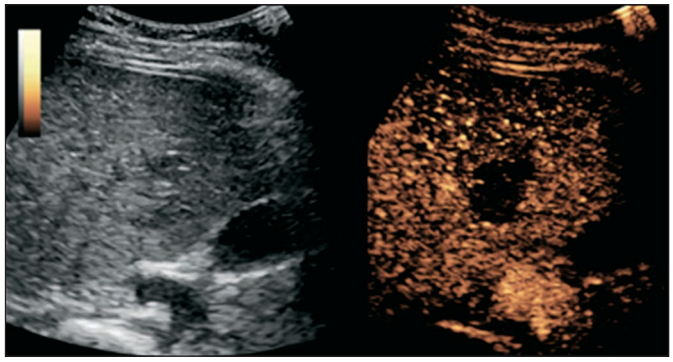

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Fig. 1—17–year old girl with history of Ewing sarcoma of left iliac wing and liver lesion detected at follow-up spinal MRI (not shown).
A, Transverse gray-scale ultrasound image shows heterogeneous solid lesion (*arrows*) within segment II of liver.
B–E, Transverse contrast-enhanced (*right*) and corresponding gray-scale (*left*) ultrasound images obtained 13 (**B**), 33 (**C**), and 59 (**D**) seconds and 3 minutes (**E**) after IV administration of ultrasound contrast agent show early arterial enhancement with rapid washout of lesion. Scant flow within lesion is evident at 1 minute. No substantial residual contrast agent is evident within lesion at 3 minutes. Early enhancement and rapid washout are characteristic of malignant lesion. Biopsy result was metastatic Ewing sarcoma.

solid viscera, sweeps of the four quadrants should be performed to assess for additional abdominal masses [10]. This screening schedule allows diagnosis of the tumor at an earlier stage than it would be among patients who are not screened, allowing more preservative treatment (i.e., nephron-sparing strategy). This is of paramount importance in BWS given the increased risk of recurrent, bilateral, or metachronous Wilms tumor and the overall increased incidence of nonmalignant renal diseases later in childhood and adulthood that may decrease renal function.

The mean age at diagnosis of Wilms tumor is 38 months, and 75% of all Wilms tumors occur before the age of 5 years [20]. Even after a tumor is diagnosed and treated, screening persists because of the risk of concomitant tumor development. In addition to imaging, most centers evaluate α-fetoprotein levels every 3 months until the age of 4 years to screen for hepatoblastoma. Patients with who have *CDKN1C* mutations are screened for neuroblastoma by means of urine homovanillic acid and vanillylmandelic acid testing [8].

Other rare genetic syndromes with predisposition to development of Wilms tumor (with or without hepatoblastoma) include Bohring-Opitz, Mulibrey, Perlman, Simpson-Golabi Behmel, WAGR (Wilms tumor, aniridia, genitourinary abnormalities, and intellectual disability), Denys-Drash, Frasier, Sotos, and Weaver syndromes. These syndromes evaluated with the same ultrasound screening approach as for BWS. Denys-Drash syndrome carries the highest risk of malignancy, Wilms tumor developing in more than 90% of patients. Notably, over 75% of patients with

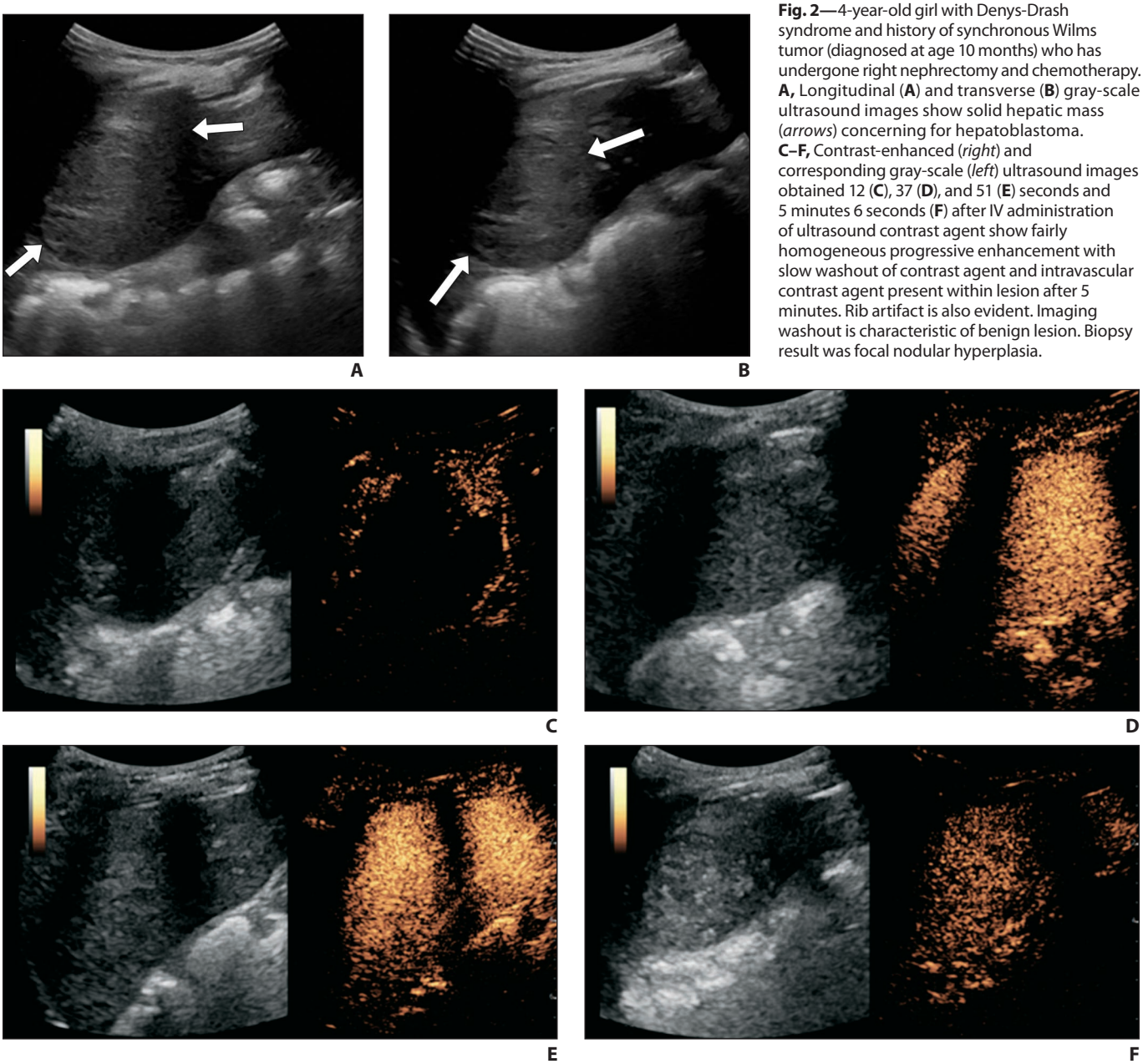


Fig. 2—4-year-old girl with Denys-Drash syndrome and history of synchronous Wilms tumor (diagnosed at age 10 months) who has undergone right nephrectomy and chemotherapy. **A,** Longitudinal (**A**) and transverse (**B**) gray-scale ultrasound images show solid hepatic mass (*arrows*) concerning for hepatoblastoma. **C–F,** Contrast-enhanced (*right*) and corresponding gray-scale (*left*) ultrasound images obtained 12 (**C**), 37 (**D**), and 51 (**E**) seconds and 5 minutes 6 seconds (**F**) after IV administration of ultrasound contrast agent show fairly homogeneous progressive enhancement with slow washout of contrast agent and intravascular contrast agent present within lesion after 5 minutes. Rib artifact is also evident. Imaging washout is characteristic of benign lesion. Biopsy result was focal nodular hyperplasia.

Perlman syndrome have nephroblastomatosis, and those with WAGR syndrome are at 50% risk of development of Wilms tumor [21] (Fig. 5).

Von Hippel–Lindau Syndrome

VHL syndrome is a multisystem autosomal dominant inherited disorder that results from a germline mutation in the *VHL* tumor suppressor gene on chromosome 3p25.3. Functional loss of *VHL* leads to overexpression of proteins that mediate angiogenesis [22]. VHL syndrome is associated with a variety of endocrine and nonendocrine tumors—including hemangioblastoma (CNS and retinal), clear cell renal cell carcinoma (RCC), adrenal pheochromocytoma, pancreatic neuroendocrine tumors, endolymphatic sac tumor, and epididymal and broad ligament cystadenoma—and renal and pancreatic cysts. The prevalence of kidney cancer is as high as 75%, making VHL syndrome the most common cause of hereditary kidney disease. RCCs are frequently bilateral multicentric solid and cystic masses. Although most RCCs present in the 3rd or 4th decade of life, RCC has been reported in patients as young as 3 years [23].

Lifetime surveillance is recommended for individuals with *VHL* mutations. In addition to physical examination, blood pressure screening, ophthalmologic and auditory evaluations, and annual measurement of plasma and urine metanephrine levels, imaging plays an important role. Guidelines for visceral manifestations have been revised to place greater emphasis on body MRI than on ultrasound. Rednam et al. [24] have recommended that surveillance for visceral manifestations of VHL syndrome be implemented at 10 years of age, to be followed by annual MRI of the abdomen (for-

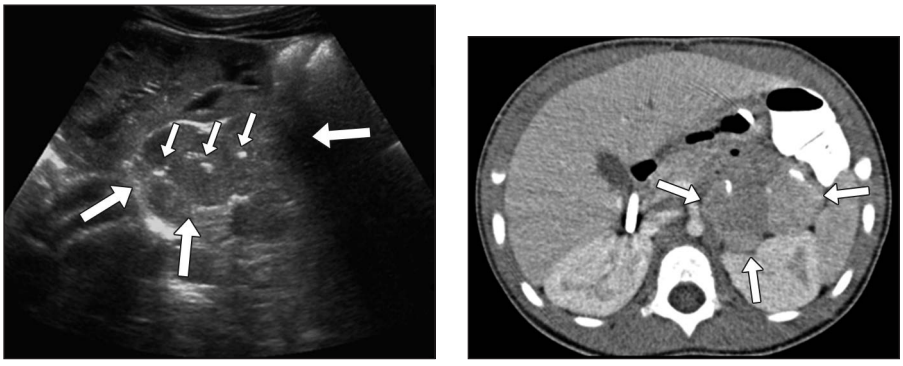


Fig. 3—14-month-old girl with Li-Fraumeni syndrome.
A, Screening gray-scale ultrasound image of left kidney shows abnormal lobulated retroperitoneal mass (*large arrows*) adjacent to kidney hilum and calcifications within mass (*small arrows*). At physical examination, clinicians noted virilization (new from prior examination).
B, Axial contrast-enhanced CT image of abdomen at level of kidneys shows lobulated solid mass with coarse calcifications (*arrows*). Normal left adrenal gland was not identified. Biopsy result was adrenocortical carcinoma.

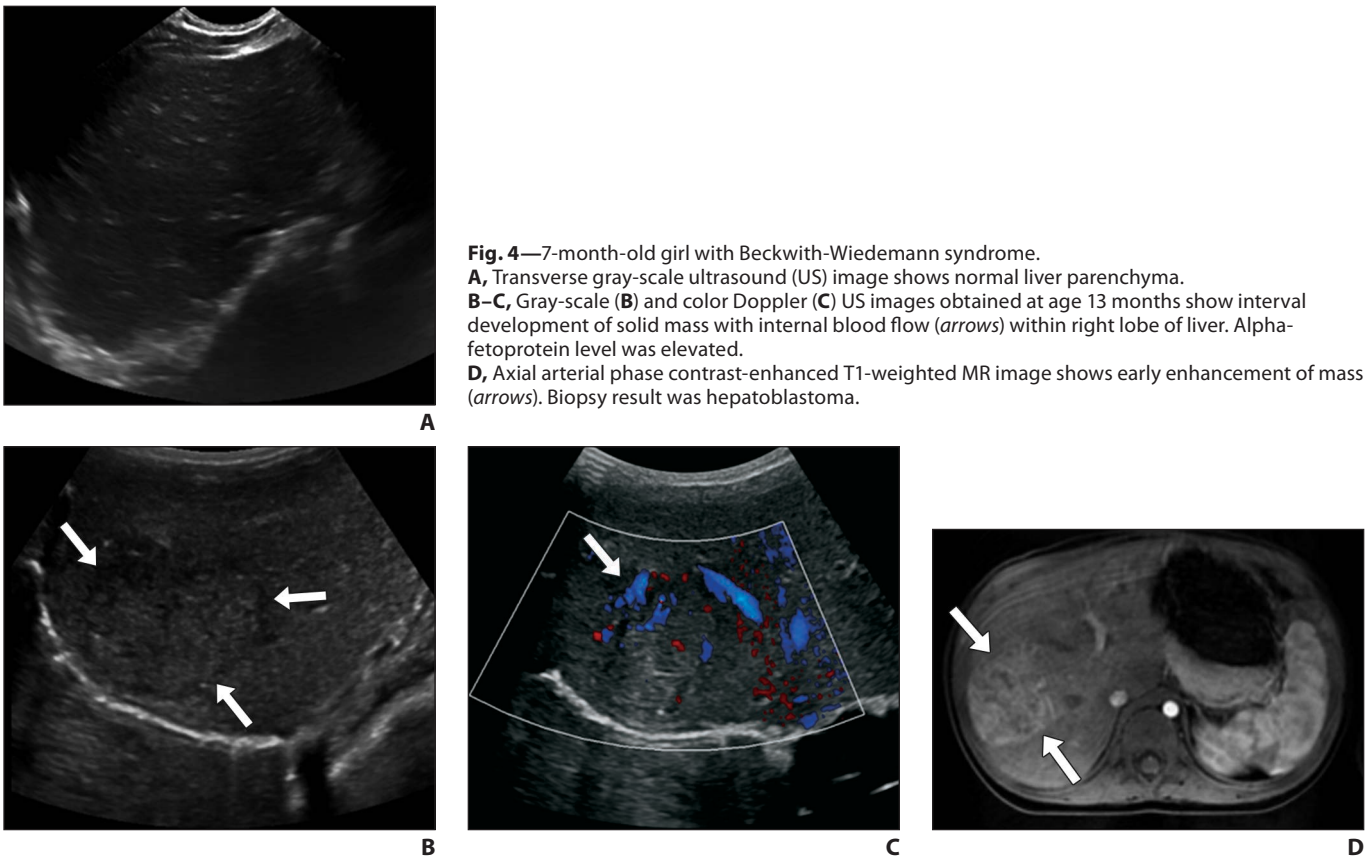


Fig. 4—7-month-old girl with Beckwith-Wiedemann syndrome.
A, Transverse gray-scale ultrasound (US) image shows normal liver parenchyma.
B–C, Gray-scale (**B**) and color Doppler (**C**) US images obtained at age 13 months show interval development of solid mass with internal blood flow (*arrows*) within right lobe of liver. Alpha-fetoprotein level was elevated.
D, Axial arterial phase contrast-enhanced T1-weighted MR image shows early enhancement of mass (*arrows*). Biopsy result was hepatoblastoma.

merly abdominal ultrasound) to maximize the sensitivity and maintain consistency of screening methods for detection of RCC and pancreatic neuroendocrine tumors. Renal mass MRI protocols should be used to ensure optimal tumor detection.

Ultrasound may be considered to complement MRI, or it can be used as the primary screening modality if there are contraindications to MRI or gadolinium contrast agents or if MRI is inaccessible to the patient. Given the high sensitivity of biochemical screening for pheochromocytoma, annual metanephric analysis is used beginning at 2 years of age. Biennial brain and spinal MRI with and without contrast administration is recommended at age 8 years. The newer proposed guidelines were largely based on expert opinion. Clinical outcomes among individuals with VHL syndrome screened according to the proposed guidelines must be prospective assessed.

Familial Adenomatous Polyposis

FAP is an autosomal dominant cancer predisposition syndrome caused by pathogenic variants in the *APC* gene, which is most strongly associated with increased risk of colorectal cancer [25]. The birth incidence is 1 in 9000–18,000, and in individuals with classic FAP, polyps typically start developing in late childhood to the teenage years, although polyps have been reported in patients as young as 8 months. Colonic polyps eventually become malignant; the mean age at colorectal cancer diagnosis and therefore elective colectomy is 39 years (range, 34–43 years) [26]. Colorectal cancer occurs most often in adulthood but is occasionally seen in childhood and adolescence and is managed with endoscopy. Children with FAP are at risk of development of hepatoblastoma (0.3–1.6%), most cases occurring before the age of 3 years [27]. As many as 10% of patients with hepatoblastoma have an underlying *APC* mutation and may not have a family history of FAP [22].

There has been substantial controversy regarding hepatoblastoma screening, particularly given the fairly low risk. Many large centers in the United States have incorporated screening practices to include abdominal ultrasound examinations every 3–4 months until age 4 years [27]. The annual lifetime risk of development of papillary thyroid carcinoma is 2–7%. Annual thyroid examinations should begin in the late teen years, and annual thyroid ultrasound examinations can be considered. Additional extracolonic manifestations of FAP include desmoid tumors. These tumors can cause considerable morbidity and mortality, are often provoked by surgery, and have a high rate of recurrence. Screening for desmoid tumors is not generally of benefit unless there is a family history of disease; abdominopelvic MRI may be warranted [27].

DICER1 *Syndrome*

DICER1 syndrome, or pleuropulmonary blastoma (PPB) familial tumor susceptibility syndrome, is a rare autosomal dominant tumor predisposition syndrome caused by mutations in the *DICER1* gene. *DICER1* syndrome includes common conditions, such as multinodular goiter, and several rare but distinct conditions, including PPB, cystic nephroma, ovarian Sertoli-Leydig cell tumor, pituitary blastoma, ciliary body medulloepithelioma, nasal chondromesenchymal hamartoma, and sarcomas of the cervix, kidneys, and cerebrum [28]. The following conditions should warrant investigation for a *DICER1* mutation, even in the absence of a family history: PPB, cystic nephroma, Sertoli-Leydig cell tumor, pituitary blastoma, ciliary body medulloblastoma, embryonal rhabdomyosarcoma of the uterine cervix or ovary, gynandroblastoma, anaplastic sarcoma of the kidney, nasal chondromesenchymal hamartoma, cerebral sarcoma, infant cerebellar embryonal tumor, and pineoblastoma diagnosed before 10 years of age. In addition, those with *DICER1* mutations are at 16–24-fold increased risk of development of differentiated thyroid carcinoma before age 18 years compared with the general population. Multinodular goiter diagnosed before the age of 18 years is also concerning, being the most frequent and least specific phenotype of *DICER1* syndrome. Of these conditions, PPB is the sentinel disease reported in families with early *DICER1* syndrome; approximately 75% of patients with PPB have *DICER1* mutations [29].

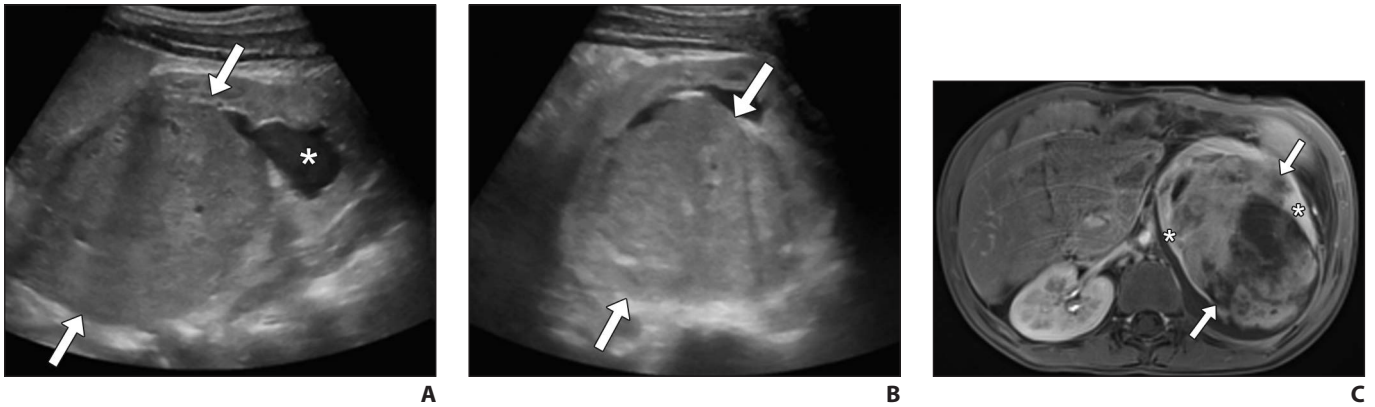


Fig. 5—4-year-old boy with WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, intellectual disability) undergoing routine surveillance.
A and **B,** Sagittal (**A**) and transverse (**B**) gray-scale ultrasound images of left kidney show solid mass (*arrows*) arising from superior pole of kidney. Pelvocaliectasis of lower pole (*asterisk,* **A**) is evident.
C, Axial contrast-enhanced T1-weighted MR image shows large heterogeneously enhancing solid and partially cystic mass (*arrows*) within superior pole of left kidney with resultant mass effect. Claw sign (*asterisks*) with rim of renal parenchyma partially encases mass. Biopsy result was Wilms tumor. Patient was reported to have had normal abdominal ultrasound findings 4 months earlier at outside institution.

Imaging surveillance for *DICER1* syndrome has not been well established given that variants of *DICER1* were described in 2009. The progressive nature of some *DICER1* syndrome–associated tumors suggests the need for effective surveillance to identify lesions at low grades or low stages. A broad approach to screening includes annual history and physical examination, emphasizing thyroid palpation. Imaging protocol recommendations include abdominopelvic ultrasound examinations every 6 months to age 8 then annually until age 40 years [30, 31]. Ultrasound is used to evaluate for renal masses (cystic nephroma, Wilms tumor, anaplastic sarcoma of the kidney) and pelvic masses (ovarian Sertoli-Leydig cell tumors and other sex cord stromal tumors, cervical tumors). Cases of renal cysts progressing to anaplastic sarcoma of the kidney and Wilms tumor have been reported [30].

Consideration should be given to thyroid ultrasound with assessment for regional adenopathy starting at age 8 years. If the findings are normal, repeating every 3 years is justified by the risk of thyroid cancer. If thyroid nodules are visualized, follow-up should be performed according to standard pediatric endocrinology guidelines [31]. Aside from ultrasound screening tests, chest CT and chest radiographic screening protocols are recommended at diagnosis, as are intermittent chest radiography every 6 months to adolescence and annual brain MRI to age 25 years [30, 31]. International consensus surveillance guidelines will likely be refined and tailored as more is learned about this newly described syndrome.

Other Rare Syndromes

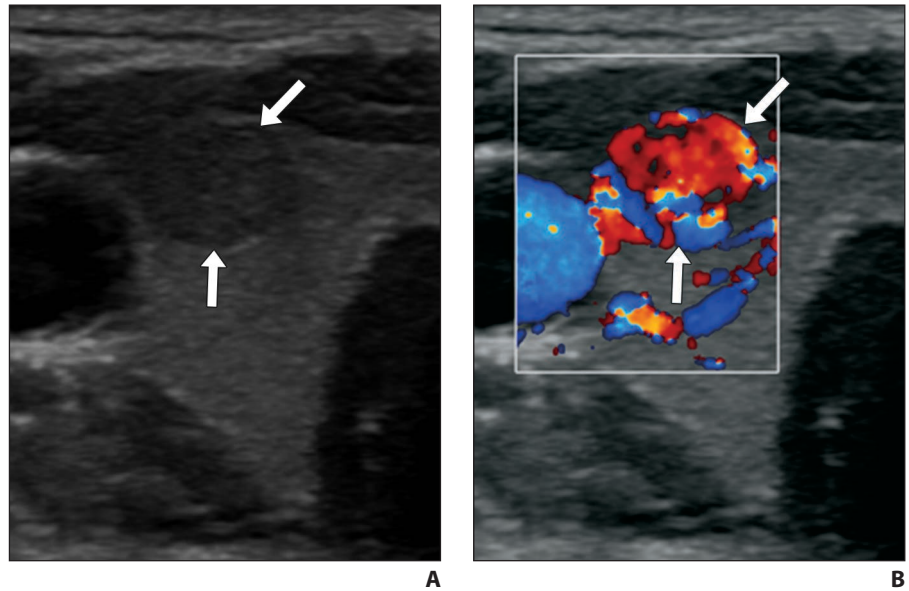
Multiple endocrine neoplasia syndromes—Multiple endocrine neoplasia (MEN) syndromes are autosomal dominant disorders in which both nonendocrine and endocrine tumors develop. The two most common subtypes are MEN1 and MEN2. MEN2 syndrome comprises three subsets: MEN2A, MEN2B, and familial medullary thyroid carcinoma. Individuals with MEN2A are at risk of development of medullary thyroid carcinoma (100% of cases), pheochromocytomas, and parathyroid adenomas and hyperplasia. Individuals with MEN2B are at risk of development of tumors similar to those associated with MEN2A but also may have mucosal neuromas and intestinal ganglioneuromas [22].

Children are stratified by risk to determine their surveillance protocol. Given the assigned risk, either complete thyroidectomy or biannual or annual thyroid ultrasound examinations and measurement of calcitonin levels are recommended [3] (Fig. 6). Individuals with MEN1 subtype may have tumors of the anterior pituitary gland, parathyroid glands, and endocrine pancreas (gastrinomas and insulinomas) and, less frequently, adrenal tumors, carcinoids, schwannomas, and ovarian tumors. These children are followed with MRI of the brain and abdomen. Currently, there is no role for routine ultrasound screening for MEN1 [3].

Trisomy 18—Trisomy 18 (Edwards syndrome) is the second most common constitutional chromosomal abnormality after trisomy 21 and occurs in 1 in 6000–8000 live births. Trisomy 18 is characterized by growth retardation, psychomotor delays, and intellectual disability. There is a high risk of death within the first year of life along with increased risk of development of benign and malignant tumors. Hepatoblastoma and Wilms tumor are the most commonly reported malignancies [21] (Fig. 7). Reports have also described multifocal hepatoblastomas in infants [32]. Cancer screening is controversial given the poor prognosis and tendency to avoid invasive procedures [21].

Costello syndrome—Costello syndrome is caused by germline mutations of *HRAS*. Costello syndrome has features similar to those of Noonan syndrome in addition to mental deficits, poor feeding, hypertrophic cardiomyopathy, tachycardia, typical skin and hair, a coarse face, and high childhood cancer risk, especially for embryonal rhabdomyosarcoma, neuroblastoma, and early-onset bladder cancer. The cumulative incidence of cancer is 15% by age 20 years; thus, abdominal ultrasound examinations are suggested at 3- to 4-month intervals from birth to age 8–10 years [33].

Bloom syndrome—Other syndromes that have predisposition to Wilms tumor, such as Bloom syndrome, follow algorithms for renal ultrasound screening. The classic characteristics of Bloom syndrome include prenatal and postnatal growth deficiency, short stature, sun sensitivity, gastroesophageal reflux, recurrent infections, decreased fertility in men, insulin resistance, and cancer predisposition. Cancers



A **B**

Fig. 6—13-year-old girl with multiple endocrine neoplasia type 2A.
A, Screening gray-scale thyroid ultrasound image shows focal hypoechoic nodule (*arrows*) within right lobe of thyroid gland with hypoechoic halo.
B, Color Doppler ultrasound image shows abundant blood flow within nodule (*arrows*). Biopsy result was medullary thyroid carcinoma. Findings at ultrasound of thyroid 6 months earlier were normal.

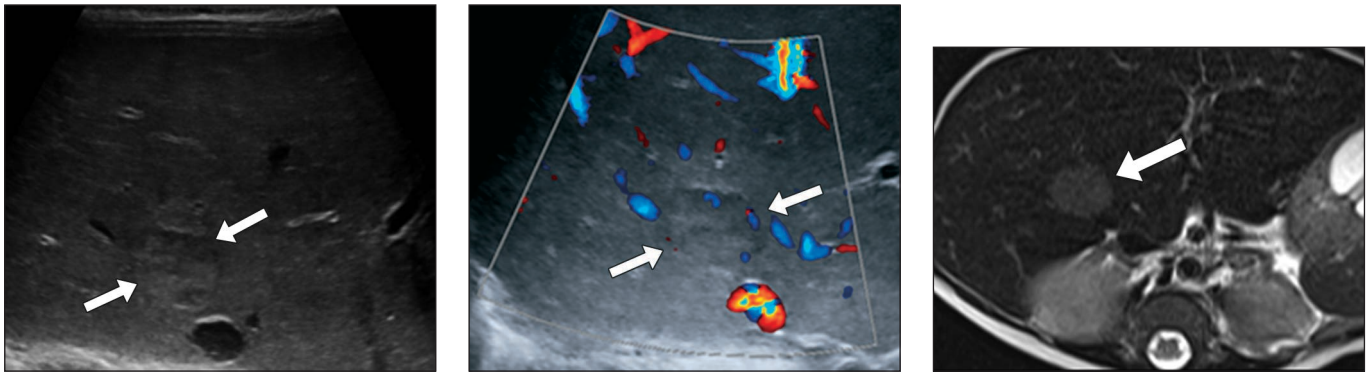


Fig. 7—4-month old boy with trisomy 18 undergoing abdominal ultrasound to evaluate abdominal distention.
A and **B,** Gray-scale (**A**) and color Doppler (**B**) ultrasound images show solid mass (*arrows*) within internal vascularity within right hepatic lobe.
C, Axial T2-weighted MR image shows single hepatic mass (*arrow*) hyperintense to hepatic parenchyma. Mass exhibited early arterial enhancement (not shown) after IV gadolinium administration. Patient had elevated α-fetoprotein level. Biopsy result was hepatoblastoma.

diagnosed during the pediatric period include gastrointestinal, genital, and urinary tract carcinoma, lymphoma, acute lymphoblastic leukemia, acute myeloid leukemia, sarcoma, Wilms tumor, medulloblastoma, and retinoblastoma. Renal ultrasound examinations are performed at diagnosis and every 3–4 months until the age of 8 years [34].

PTEN *hamartoma tumor syndrome*—*PTEN* hamartoma tumor syndrome consists of several autosomal dominant disorders with overlapping and distinctive features. The spectrum includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and *PTEN*-related Proteus-like syndromes. Features shared within the spectrum include macrocephaly, gastrointestinal polyposis, lipomas, vascular malformations, and intellectual disability or autism spectrum disorder. Individuals with this syndrome are at increased lifetime risk of breast, endometrial, and colorectal cancers; RCC; and melanoma. Thyroid cancer is the most predominant risk in childhood, occurring in children as young as 7 years. Revised recommendations for evaluation of children with *PTEN* hamartoma tumor syndrome include initiation of thyroid ultrasound at age 7 years and, if the findings are normal, repeat thyroid ultrasound every 2 years through childhood [31].

Future Directions

Increased application of high-output molecular approaches to diagnosing cancer predisposition syndromes will provide greater insight into the genetic and epigenetic events that drive tumor formation. Future collaborative studies integrating genomic data, clinical (registry) information, and biologic breakthroughs should lead to the use of more patient-tailored surveillance algorithms based on more specific phenotype-genotype mutations [16].

Conclusion

Surveillance of children with cancer predisposition syndromes includes imaging screening. Ultrasound is a valuable radiation-free tool for evaluating for solid organ malignancies. Radiologists are responsible for performing a complete ultrasound assessment, providing accurate and timely reports, and recommending additional testing when necessary. CEUS can serve as an adjunct for more complete imaging assessment.

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