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Germline Genetics and Childhood Cancer: Emerging Cancer Predisposition Syndromes and Psychosocial Impacts

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Abstract

Purpose of Review Germline genetic variants contribute to a substantial proportion of cases of cancer in childhood. The purpose of this review is to describe two emerging pediatric cancer predisposition syndromes, including published surveillance protocols, as well as the psychological impacts related to childhood cancer predisposition.

Recent Findings *DICER1* syndrome is pleotropic, predisposing to a variety of tumors and likely phenotypically broader than currently realized. Rhabdoid tumor predisposition syndrome carries a risk for development of aggressive malignancies occurring in nearly any tissue.

Summary New pediatric hereditary cancer syndromes are likely to be identified as genetic evaluation evolves. Advantages and disadvantages of genetic testing and surveillance protocols need to be discussed with patients and families in a team-based approach, with the input of a genetic counselor holding expertise in pediatric cancer predisposition. Finally, literature on psychosocial impacts of hereditary cancer syndromes in pediatric patients is sparse, necessitating further research.

Keywords Cancer predisposition · *DICER1* · Rhabdoid tumor predisposition · *SMARCB1* · *SMARCA4* · Surveillance

Introduction

Fifty years since one of the first descriptions of a familial cancer syndrome by Li and Fraumeni [1], we now know that genetic predisposition contributes to the development of cancer in children at strikingly higher rates than previously appreciated [2••, 3, 4], and that the spectrum of cancer predisposition syndromes is quite broad, with over 100 genes defined as cancer predisposition genes. Furthermore, many of the cancer predisposition syndromes are now more fully characterized with the creation of syndrome-specific patient registries and the description of larger cohorts of patients with these syndromes. The increasing availability and implementation of germline genetic testing create the opportunity to identify children at highest risk for cancer and, moreover, the prospect of early cancer detection and reduced morbidity and mortality [5••, 6]. It also raises questions about the benefits and risks of testing children for mutations in cancer predisposition syndromes, particularly as it relates to the psychosocial well-being of the patient and the family. With this report, we review two of the emerging childhood cancer predisposition syndromes, *DICER1* syndrome and rhabdoid tumor predisposition syndrome, including the clinical phenotype and published surveillance recommendations, as well as what is known about the psychosocial implications of the diagnosis of a cancer predisposition syndrome in a child.

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Cancer Predisposition in Children

Large gene sequencing panels, chromosomal microarrays, and whole-exome sequencing are being used with increased frequency in pediatric medical care. In combination with more routine tumor genomic profiling, a greater number of pediatric patients with cancer predisposition syndromes are being identified. Based on the recent publication by Zhang et al., it is now estimated that germline variants play a role in ~ 8.5–10% of all pediatric cancer diagnoses, a rate mirroring that seen in adult cancer diagnoses, with *TP53*, *APC*, *BRCA2*, *NF1*,

PMS2, *RB1*, and *RUNX1* highlighted as the most commonly identified germline pathogenic mutations in their cohort [2••].

Family history alone is not able to predict the presence or absence of a predisposition syndrome. However, a number of pediatric tumors are highly suggestive of hereditary cancer and warrant referral for additional genetic evaluation including, but not limited to, adrenocortical carcinoma and low hypodiploid acute lymphoblastic leukemia (Li-Fraumeni syndrome), malignant peripheral nerve sheath tumors and optic pathway gliomas (neurofibromatosis), and retinoblastoma (retinoblastoma syndrome) [2••, 7•]. Two additional pediatric tumors often indicative of a pediatric cancer predisposition syndrome, pleuropulmonary blastoma and malignant rhabdoid tumors, will be further discussed below.

Genetic counseling has been defined as the "process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease" [8]. In the setting of hereditary cancer, this includes education about one's cancer risk based on personal and family history, a discussion of testing and management options, including risk-reducing surgeries and surveillance protocols, and "counseling to promote informed choices and adaptation to the risk and/or condition" [8]. Historically, cancer counselors have worked with adults, evaluating for syndromes with well-known cancer risks in adulthood, such as hereditary breast and ovarian cancer (HBOC) or Lynch syndrome. However, a growing number of genetic counselors are now working in the pediatric oncology setting, in which lifetime cancer risks have not been determined and the psychosocial implications of genetic testing, including cancer risk perception and distress levels, have not been thoroughly evaluated. This is particularly true for emerging syndromes such as *DICER1* syndrome and rhabdoid tumor predisposition syndrome.

DICER1 Syndrome

The *DICER1* syndrome is a rare, autosomal dominant cancer predisposition syndrome with a lifetime risk for a variety of malignant and benign tumors, caused by germline loss-of-function mutations in the tumor suppressor gene, *DICER1*. While the clinical syndrome was described in the mid-1990s, it was not until 2009 that *DICER1* mutations were identified as a genetic link [9, 10]. The *DICER1* gene is a member of the ribonuclease III (RNaseIII) family and is involved in the generation of microRNAs (miRNAs) that modulate post-transcriptional gene expression. It is postulated to act as a haploinsufficient tumor suppressor gene, and typically the wild-type copy is disrupted by a somatic hotspot variant allowing some residual function. Complete loss of *DICER1* is incompatible with life, leading to lethality early in fetal development in mouse models [11–13].

Clinical Phenotype

Pleuropulmonary blastoma, the most common primary lung malignancy in childhood, is often regarded as a sentinel malignancy in *DICER1* carriers. Over 65–70% of patients with PPB are found to have germline loss-of-function mutations in *DICER1* [14]. The malignancy, typically presenting in infants and children before age 7, has been categorized into four pathologic subtypes hypothesized to represent an evolution of the disease. These tumors acquire high-grade and often anaplastic features during progression, from type I PPB (purely cystic) to type II PPB (cystic/solid) to type III PPB (purely solid) [14, 15]. Type Ir PPB, a benign cystic lesion without a primitive cell component, is often considered a type I lesion that did not progress or has regressed, and has been found in *DICER1* carriers of all ages [14, 16]. Treatment and overall survival (OS) for PPB depend greatly on subtype, from an OS of 91% in type I and type Ir to the more aggressive types II and III, with 5-year OS of 71% and 53%, respectively [14, 16].

As noted, the *DICER1* syndrome is pleiotropic, and the International Pleruopulmonary Blastoma / *DICER1* Registry has spearheaded efforts to describe the wide-ranging clinical phenotype. A recent report documented a 5.3% risk for neoplasm by age 10 for the *DICER1* syndrome, and an overall 19.3% risk for neoplasm by age 50 (females 26.5%, males 10.2%) in *DICER1* carriers [17••]. Additional tumor types include cystic nephroma, ovarian Sertoli-Leydig cell tumor, multinodular goiter, and cervical embryonal rhabdomyosarcoma. More rarely, differentiated thyroid carcinoma, Wilms tumor, pituitary blastoma, pineoblastoma, nasal chondromesenchymal hamartoma, juvenile hamartomatous intestinal polyps, and ciliary body medulloepithelioma may develop. Brain tumors, neuroblastoma, T cell–derived Hodgkin lymphoma, and well-differentiated fetal adenocarcinoma of the lung have also been reported [18•, 19, 20]. In their 2019 JCO paper, Stewart et al. published the first quantitative analysis of site-specific neoplasm rates via standardized incidence ratios (SIR) for 102 malignancies observed in a cohort of 207 *DICER1* carriers. The most striking rates were noted in PPB (SIR, 3.2×10^6), gynandroblastoma (SIR, 1.4×10^5), undifferentiated ovarian sarcoma (SIR, 6.8×10^4), and Sertoli-Leydig cell tumors (SIR, 2.2×10^4). Lesser, though significant, rates were documented for spindle cell carcinoma, thymoma, rhabdomyosarcoma, malignant peripheral nerve sheath tumor, teratoma, and thyroid cancer [17••].

Individuals with *DICER1* syndrome may have non-tumor phenotypes, as well. In light of the relationship of cystic nephroma with the *DICER1* syndrome, Khan et al. carried out a family-based study to further evaluate for associated structural renal abnormalities. They identified a significantly increased percentage of affected individuals with ultrasound-detected collecting system anomalies, nephrolithiasis, and/or nephrocalcinosis (8/89; $p = 0.02$) [21]. While Wilms tumor

has been described in *DICER1* patients previously, this group found no *DICER1*-associated genitourinary malignancies in their cohort. Huryn et al. recently published a study on the ocular phenotype of *DICER1* syndrome, identifying 22% of *DICER1* carriers as affected by ocular abnormalities and two patients with a ciliary body medulloepithelioma during the routine ophthalmologic exam [22].

Surveillance Recommendations

In 2016, during the International *DICER1* Symposium, recommendations for genetic testing and surveillance studies were put forth, summarized after group consensus during the 2016 AACR Childhood Cancer Predisposition Workshop [14, 18•]. Surveillance recommendations for patients with the *DICER1* syndrome are based on typical age of onset for the associated disease process as well as risks and benefits of early detection. To date, genotype-phenotype correlations have not been defined, so no altered surveillance recommendations have been made based on specific mutation type. Neonates at risk should have a chest x-ray to screen for pulmonary cysts. For PPB screening in those with germline *DICER1* mutation, consideration should be given to ongoing chest x-rays on an every-6-month schedule until age 8, and then annual chest x-rays from age 8 to age 12. Further, as a more sensitive study for PPB detection, a baseline chest CT should be obtained between 3 and 6 months of age. If normal, a second chest CT at age 2.5 to 3 years is advised. With regard to renal surveillance, abdominal ultrasound is recommended biannually from birth until age 8, and annually thereafter. Pelvic ultrasound should be added to the annual ultrasound evaluation for female *DICER1* carriers starting at age 8 and continue through adulthood. Exact timing for the end of female reproductive tract surveillance is not yet determined, though the oldest known patient with *DICER1*-associated Sertoli-Leydig cell tumor was 61 [14]. Due to the *DICER1*-associated risk for thyroid nodules and malignancy, a baseline thyroid ultrasound is advised at age 8. If normal, repeat ultrasounds every 3 years are sufficient, with adjustment to the schedule based on the development of symptoms or exam findings [18•]. Due to the potential for ciliary body medulloepithelioma, *DICER1* carriers should also undergo annual dilated ophthalmologic exams as part of their disease surveillance [22]. Women whose fetuses are at risk for the inheritance of a pathogenic *DICER1* mutation should have a third trimester ultrasound to evaluate for large lung cysts, which may require early intervention after delivery [14].

In addition to the surveillance imaging studies, concerning signs and symptoms of *DICER1*-associated disease conditions should be reviewed with patients and families, in order to facilitate the timely seeking of medical attention. Family and healthcare provider education is key for early diagnosis and treatment.

Rhabdoid Tumor Predisposition Syndrome

Rhabdoid tumors are rare, aggressive, soft tissue malignancies typically diagnosed in infants and young children, before the age of 3 [23•]. Initially identified as a distinct pathological entity in 1978 and first reported in a large patient case series in 1989, the tumors are named for their "rhabdoid" cells, histologically comprised of eosinophilic cytoplasm and resembling rhabdomyoblasts [24–26]. These tumors occur primarily in the central nervous system (atypical teratoid/rhabdoid tumor [AT/RT]) and kidney (rhabdoid tumor of the kidney [RTK]), though they have been documented in nearly every anatomic location, including but not limited to soft tissue, lung, ovary, and liver (termed extracranial malignant rhabdoid tumors [eMRT]) [27].

Therapy for rhabdoid tumors is multimodal, including chemotherapy, radiation, and surgery. However, despite aggressive treatment, outcomes for patients with rhabdoid tumors are poor, with a 1-year survival estimated at ~31% [27]. Key prognostic factors include stage at diagnosis (4-year OS ~ 42% for stage I and II tumors vs 16% for stage III, IV, and V tumors) as well as age at diagnosis (4-year OS ~9% for infants 0–5 months vs 41% for children > 24 months) [28].

Rhabdoid tumor predisposition syndrome (RTPS), first named as such in 1999, is an autosomal dominant cancer predisposition syndrome characterized by the development of these aggressive rhabdoid malignancies. The syndrome, associated with germline mutations in the *SMARCB1* (also known as INI1) and *SMARCA4* tumor suppressor genes, is now classified into two subsets based on clinical phenotype and genetic link. An estimated 35% of rhabdoid tumor patients will be found to have a germline mutation in one of the two genes. Thus, genetic testing for *SMARCB1* and *SMARCA4* mutations should be considered for any patient presenting with a rhabdoid tumor. It is important to note, and key in genetic counseling, that disease risk has not been classified based on specific mutation [29].

SMARCB1 and *SMARCA4* are components of the chromatin-remodeling SWI/SNF complex. *SMARCB1* stabilizes the complex, enabling SWI/SNF to bind and facilitate enhancer formation and function [30]. *SMARCA4* encodes a SWI/SNF catalytic ATPase subunit. However, the mechanism by which *SMARCA4* loss drives tumorigenesis is still unclear [31].

Rhabdoid tumor predisposition syndrome, type 1 (RTPS1; OMIM No. 609322), caused by loss-of-function germline *SMARCB1* mutations, accounts for the vast majority of familial rhabdoid tumors. Not only do *SMARCB1* carriers develop rhabdoid tumors much earlier than patients with the same malignancy of sporadic nature, they are at risk for developing multiple rhabdoid malignancies. A number of reports of children with RTPS type 1 affected by both AT/RT and eMRT or RTK exist [32, 33]. In more recent years, the clinical spectrum has been expanded to include not only AT/RT and extracranial

rhabdoid tumors but also the rare development of malignant peripheral nerve sheath tumors and multiple, typically benign schwannomas, called schwannomatosis [23•, 34, 35•].

Rhabdoid tumor predisposition syndrome, type 2 (RTPS2; OMIM No. 613325) is caused by germline *SMARCA4* mutations. These carriers are at risk for malignant rhabdoid tumors of the ovary, more commonly designated as small-cell carcinoma of the ovary-hypercalcemic type (SCCOHT), a highly lethal tumor occurring in young women (average age 24) [36]. AT/RT development has been observed in these patients, though much less commonly than in RTPS1, and there are only a few reports of extracranial rhabdoid tumors [35•, 37–39].

Surveillance Recommendations

To date, there is little evidence regarding effective surveillance strategies for patients with either RTPS1 or RTPS2. The penetrance of tumors in these syndromes is unknown, and rhabdoid tumors can arise in nearly any tissue. However, due to the aggressive nature of the tumors with significant lethality and young age of onset, particularly in *SMARCB1* carriers with truncating mutations, the following consensus imaging recommendations were recently put forth as a result of the 2016 AACR Childhood Cancer Predisposition Workshop. For *SMARCB1* carriers, a brain MRI every 3 months is recommended from birth (or diagnosis) until age 5. Abdominal ultrasounds are also advised every 3 months. Whole-body MRI until age 5 has been proposed, though the frequency for such imaging is not defined, and additional factors, including the need for sedation, should be discussed with the patient and family [23•]. For *SMARCA4* carriers, routine brain and abdomen imaging is not definitively advised, given the presumed low risk for rhabdoid tumor development in these anatomic sites. Consideration for every-6-month pelvic ultrasound should be entertained for ovarian surveillance; the role for pelvic MRI is not clear [23•].

When SCCOHT does occur, it is typically identified in much younger patients than the more common, though equally as lethal, high-grade serous ovarian malignancies. No cases of SCCOHT have been reported in women over the age of 45 [40]. The NCCN Guidelines for HBOC conclude that there is "insufficient evidence" to make definitive recommendations for a risk-reducing salpingo-oophorectomy for a number of lower-penetrance ovarian cancer susceptibility genes, including *SMARCA4* [41]. However, prophylactic oophorectomy should be discussed for *SMARCA4* carriers and is reasonable for individuals to consider, even before childbearing age has been surpassed. For those patients who are not ready to conceive children, ovarian hyperstimulation and oocyte harvest may be realistic options [40]. Genetic counselors have an essential role in these conversations, due to their expertise in patient education and supportive counseling techniques, as well as evaluation of patients' risk perception, anxiety, and distress levels. These have been shown to be key factors in patients' decision-making process about preventative surgery, as reported in multiple studies in adult women with HBOC [42–44].

Finally, as with *DICER1* syndrome, patient and family education on signs and symptoms of these often–rapidly growing tumors should be discussed, focusing on the seeking of early medical attention.

Psychosocial Impacts

As the number of pediatric patients diagnosed with cancer predisposition syndromes increases, so will psychosocial impacts on these patients and their families. However, these effects have largely been studied in the adult cancer population, specifically as they pertain to patients with more commonly diagnosed hereditary cancer syndromes such as HBOC and hereditary colon cancer (Lynch syndrome and familial adenomatous polyposis). Further, a disproportionately low number of men, as well as racial and ethnic minority patients, have historically been included in such studies.

Testing Impacts

Anxiety regarding genetic testing, positive, negative, or equivocal results as well as personal and family impact, is a common psychosocial theme. Many early studies focused on adults, most often women, and assessed the short-term psychological effect of testing for *BRCA1/2* within the first month post-test. Results indicated that non-carriers experienced reduction in overall anxiety while carriers did not seem to derive psychological benefit [45]. In fact, one study documented significantly higher levels of cancer-specific worry in carriers than in non-carriers at all follow-up intervals, up to a year post-testing [45]. With regard to pediatric patients and testing anxiety, literature is sparse. Questions arise surrounding informed consent and assent for minors undergoing cancer genetic testing, determining the optimal timing of testing for at-risk pediatric patients, and the disclosure of genetic test results after a child has died from cancer. Additionally, concern has been raised regarding potential loss of autonomy for the child, disruption of parent-child or sibling-sibling relationships, and, especially in adolescence, feelings of guilt and self-blame for disease [46].

In a recent study interviewing adolescents and young adults who had undergone testing for Li-Fraumeni syndrome, all participants believed that genetic testing should be offered to children, identifying the "learning of risk status or genetic predisposition to disease" as an advantage to testing. Half of

participants felt that knowing one's risk status allowed one to prepare, reduced anxiety, and increased one's power in the situation. When asked about testing and how the results affected their general life outlook, all participants indicated either no change or a positive change [47•].

Another recent study investigated the use of whole-exome sequencing (WES) of parent-child trios as a tool in identifying cancer predisposition syndromes, specifically evaluating the interest in and acceptance of such comprehensive molecular testing as compared with more targeted testing. Of a total of 94 eligible families over a period of 2 years, 83 (88.3%) agreed to participate in the study. The authors concluded that the overwhelming majority of families were seeking knowledge regarding a possible underlying cancer predisposition syndrome. Many families cited determining a reason for why their child had developed pediatric cancer, an incredibly rare disease, as well as possible risks for recurrence in other children. Further, most parents and children agreed to participate in this comprehensive genetic evaluation almost immediately, supporting the group's notion that families held great enthusiasm for genetic knowledge. On the other hand, reasons for refusal included fear of results (six families, four of these with family history of malignancy), current stress level/mental overload, and cultural objection [48].

Weber et al. recently published their data from seven adolescents with various childhood-onset cancer predisposition syndromes and their experiences with syndrome diagnosis, available support systems, and perceived risks versus benefits surrounding their diagnoses. Based on their study, it was concluded that these adolescents believed knowledge benefit outweighed any associated negative effects and their self-concept could be influenced, but not defined, by diagnosis and related tumor risk [49].

Children's psychological needs change with growth and development [7•]. Thus, developmentally appropriate conversations between children, their parents, and healthcare providers are imperative. As genetic counseling is a longitudinal process, it is recommended to revisit counseling for patients with pathogenic mutations in pre-teen and teenage years, prior to transition from pediatric to adult care, and at the time of family planning [7•].

Surveillance Impacts

"Scanxiety" is a term coined as a reference to cancer-related distress secondary to diagnostic and surveillance imaging, and has been shown to impair quality of life in patients with non-small-cell lung cancer [50]. In his 2011 Time magazine article, Bruce Feiler described it as "a uniquely modern malady…that arises because we're experiencing something entirely new to human beings. For millennia, doctors and patients would have given almost anything to be able to look inside the human body. Now we have an ailment for the fear of what we might find when we do."

Despite this potential effect, the medical and psychological benefits of surveillance have been described for a number of predisposition syndromes. In 2016, Villani et al. published a prospective observational study on individuals with Li-Fraumeni syndrome who chose either to undergo a comprehensive surveillance protocol (involving physical exam; labwork; whole-body, breast, brain MRI; mammography; abdominopelvic ultrasound; colonoscopy) or not. Their results documented a statistically significant higher 5-year overall survival in the surveillance group versus the non-surveillance group (88.8% versus 59.6%; $p = 0.0132$) [5••]. For patients with von Hippel-Lindau syndrome, especially those with truncating mutations who carry the highest risk of renal cell carcinoma and CNS hemangioblastomas, surveillance imaging has been reported as especially beneficial [51]. Gopie et al. determined that surveillance for most hereditary cancers was associated with good psychological outcomes, with a caveat being from individuals with a personal history of cancer or a first degree relative with cancer, some of whom reported increased distress [52]. Additional perceived benefits of surveillance, based on the MD Anderson Cancer Center's Li-Fraumeni Education and Early Detection (LEAD) program, include early malignancy detection, peace of mind due to knowledge regarding current health status, centralized surveillance oversight, and a "knowledge is power" mentality [53].

In relation to pediatric surveillance, literature has focused primarily on parental perspectives. Duffy et al. recently published data on a survey completed by parents of children with Beckwith-Wiedemann syndrome or isolated hemihypertrophy. Screening was determined to decrease parental worry and did not create added burden. Further, the majority of parents agreed that potential of finding their child's tumor early outweighed any stress associated with surveillance [54•]. Parents have also reported improved emotional well-being through a sense of expectation and control along with lower surgical morbidity and less intensive systemic therapy as advantages of tumor screening. Conversely, false positive results leading to additional testing or procedures, increased medical visits, and a lack of proven benefit of screening in many disorders have been highlighted by parents as surveillance disadvantages [55].

Conclusions

In conclusion, as large-scale genetic testing becomes commonplace in pediatric medical care, an increased number of pediatric patients with hereditary cancer syndromes will be identified, and it is likely the spectrum of these syndromes will evolve. Genetic counselors play a key role on the pediatric cancer predisposition team, helping families interpret testing results, understand tumor-related risk, and review options for risk reduction. Surveillance protocols for patients with

cancer predisposition syndromes typically focus on the early identification of tumors, presumably when treatment options are available and with a goal of reducing disease-related morbidity and mortality. In general, these protocols have been well-received by both patients and parents, with perceived benefits including early disease detection, peace of mind related to knowledge of current disease status, and an increased sense of control. Finally, literature is sparse on the psychosocial impacts of pediatric cancer predisposition syndromes, and there is an important need for further study on this topic from both the patient and parent perspectives.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Li FP, Fraumeni JF Jr. Soft-tissue sarcomas, breast cancer, and other neoplasms. A familial syndrome? Ann Intern Med. 1969;71(4): 747–52.
2.•• Zhang J, Walsh MF, Wu G, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med. 2015;373(24):2336–46 **This large-scale sequencing study involving 1120 children and adolescents with cancer identified germline mutations in cancer predisposition genes in 8.5% of patients. Further, family history did not predict an underlying predisposition syndrome for most patients.**
3. Parsons DW, Roy A, Yang Y, et al. 2016 Diagnostic yield of clinical tumor and germline whole-exome sequencing for children with solid tumors. JAMA Oncol. 2016;2(5):616–24.
4. Mody RJ, Wu YM, Lonigro RJ, Cao X, Roychowdhury S, Vats P, et al. Integrative clinical sequencing in the management of refractory or relapsed Cancer in youth. JAMA. 2015;314(9):913–25.
5.•• Villani A, Shore A, Wasserman JD, et al. Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study. Lancet Oncol. 2016;17(9):1295–305 **This prospective, observational study showed feasibility of a long-term comprehensive surveillance protocol for patients with Li-Fraumeni syndrome as well as improved 5-year overall survival for those patients who chose to participate in the surveillance protocol.**
6. Villani A, Tabori U, Schiffman J, Shlien A, Beyene J, Druker H, et al. Biochemical and imaging surveillance in germline *TP53* mutation carriers with Li-Fraumeni syndrome: a prospective observational study. Lancet Oncol. 2011;12(6):559–67.
7.• Druker H, Zelley K, McGee RB, et al. Genetic counselor recommendations for cancer predisposition evaluation and surveillance in the pediatric oncology patient. Clin Cancer Res. 2017;23(13):e91–7 **The 2016 AACR working group recommendations for pediatric cancer predisposition from a genetic counseling perspective are outlined in this article, with a focus on points of entry, the initial and subsequent genetic counseling sessions, testing processes, and the psychologic impact related to surveillance.**
8. Resta RG. Defining and redefining the scope and goals of genetic counseling. Am J Med Genet C Semin Med Genet. 2006;142C(4): 269–75.
9. Priest JR, Watterson J, Strong L, Huff V, Woods WG, Byrd RL, et al. Pleuropulmonary blastoma: a marker for familial disease. J Pediatr. 1996;128(2):220–4.
10. Hill DA, Ivanovich J, Priest JR, Gurnett CA, Dehner LP, Desruisseau D, et al. *DICER1* mutations in familial pleuropulmonary blastoma. Science. 2009;325(5943):965.
11. Rio Frio T, Bahubeshi A, Kanellopoulou C, Hamel N, Niedziela M, Sabbaghian N, et al. *DICER1* mutations in familial multinodular goiter with and without ovarian Sertoli-Leydig cell tumors. JAMA. 2011;305(1):68–77.
12. Bahubeshi A, Bal N, Rio Frio T, Hamel N, Pouchet C, Yilmaz A, et al. Germline *DICER1* mutations and familial cystic nephroma. J Med Genet. 2010;47(12):863–6.
13. Bernstein E, Kim SY, Carmell MA, Murchison EP, Alcorn H, Li MZ, et al. *DICER1* is essential for mouse development. Nat Genet. 2003;35(3):215–7.
14. Schultz KAP, Williams GM, Kamihara J, Stewart DR, Harris AK, Bauer AJ, et al. *DICER1* and associated conditions: identification of at-risk individuals and recommended surveillance strategies. Clin Cancer Res. 2018;24(10):2251–61.
15. Dehner LP, Messinger YH, Schultz KA, et al. Pleuropulmonary blastoma: evolution of an entity as an entry into a familial tumor predisposition syndrome. Pediatr Dev Pathol. 2015;18(6):504–11.
16. Messinger YH, Stewart DR, Priest JR, Williams GM, Harris AK, Schultz KAP, et al. Pleuropulmonary blastoma: a report on 350 central pathology-confirmed pleuropulmonary blastoma cases by the International Pleuropulmonary Blastoma Registry. Cancer. 2015;121(2):276–85.
17.•• Stewart DR, Best AF, Williams GM, et al. 2019 Neoplasm risk among individuals with a pathogenic germline variant in *DICER1*. J Clin Oncol. 2019;37(8):668–76. **This article combines data from three large cohorts and provides the first quantitiate analysis of site-specific neoplasm risk as well as overall malignancy risk in non-proband *DICER1* carriers.**
18.• Schultz KAP, Rednam SP, Kamihara J, et al. *PTEN*, *DICER1*, *FH*, and Their associated tumor susceptibility syndromes: clinical features, genetics, and surveillance recommendations in childhood. Clin Cancer Res. 2017;23(12):e76–82 **The 2016 AACR working group recommendations for pediatric surveillance in *PTEN*, *DICER1*, *FH*, and their associated predisposition syndromes are outlined in this article.**
19. Wu Y, Chen D, Li Y, Bian L, Ma T, Xie M. *DICER1* mutations in a patient with an ovarian Sertoli-Leydig tumor, well-differentiated fetal adenocarcinoma of the lung, and familial multinodular goiter. Eur J Med Genet. 2014;57(11–12):621–5.
20. Kuhlen M, Honscheid A, Schemme J, et al. Hodgkin lymphoma as a novel presentation of familial *DICER1* syndrome. Eur J Pediatr. 2016;175(4):593–7.
21. Khan NE, Ling A, Raske ME, Harney LA, Carr AG, Field A, et al. Structural renal abnormalities in the *DICER1* syndrome: a family-based cohort study. Pediatr Nephrol. 2018;33(12):2281–8.
22. Huryn LA, Turriff A, Harney LA, Carr AG, Chevez-Barrios P, Gombos DS, et al. *DICER1* syndrome: characterization of the ocular phenotype in a family-based cohort study. Ophthalmology. 2019;126(2):296–304.
23.• Foulkes WD, Kamihara J, Evans DGR, et al. Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome.

Clin Cancer Res. 2017;23(12):e62–7 **The 2016 AACR working group recommendations for pediatric surveillance in Gorlin and rhabdoid tumor predisposition syndrome are outlined in this article.**
24. Haas JE, Palmer NF, Weinberg AG, Beckwith JB. Ultrastructure of malignant rhabdoid tumor of the kidney. A distinctive renal tumor of children. Hum Pathol. 1981;12(7):646–57.
25. Beckwith JB, Palmer NF. Histopathology and prognosis of Wilms tumors: results from the first National Wilms' Tumor Study. Cancer. 1978;41(5):1937–48.
26. Weeks DA, Beckwith JB, Mierau GW, Luckey DW. Rhabdoid tumor of kidney. A report of 111 cases from the National Wilms' Tumor Study Pathology Center. Am J Surg Pathol. 1989;13(6): 439–58.
27. Brennan B, Stiller C, Bourdeaut F. Extracranial rhabdoid tumours: what we have learned so far and future directions. Lancet Oncol. 2013;14(8):e329–36.
28. Tomlinson GE, Breslow NE, Dome J, Guthrie KA, Norkool P, Li S, 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(30):7641–5.
29. Sredni ST, Tomita T. Rhabdoid tumor predisposition syndrome. Pediatr Dev Pathol. 2015;18(1):49–58.
30. Wang X, Lee RS, Alver BH, Haswell JR, Wang S, Mieczkowski J, et al. *SMARCB1*-mediated SWI/SNF complex function is essential for enhancer regulation. Nat Genet. 2017;49(2):289–95.
31. Xue Y, Meehan B, Macdonald E, Venneti S, Wang XQD, Witkowski L, et al. CDK4/6 inhibitors target *SMARCA4*-determined cyclin D1 deficiency in hypercalcemic small cell carcinoma of the ovary. Nat Commun. 2019;10(1):558.
32. Biegel JA, Fogelgren B, Wainwright LM, Zhou JY, Bevan H, Rorke LB. Germline *INI1* mutation in a patient with a central nervous system atypical teratoid tumor and renal rhabdoid tumor. Genes Chromosomes Cancer. 2000;28(1):31–7.
33. Savla J, Chen TT, Schneider NR, et al. Mutations of the *hSNF5/INI1* gene in renal rhabdoid tumors with second primary brain tumors. J Natl Cancer Inst. 2000;92(8):648–50.
34. Sevenet N, Sheridan E, Amram D, et al. Constitutional mutations of the *hSNF5/INI1* gene predispose to a variety of cancers. Am J Hum Genet. 1999;65(5):1342–8.
35.• Scollon S, Anglin AK, Thomas M, et al. A comprehensive review of pediatric tumors and associated cancer predisposition syndromes. J Genet Couns. 2017;26(3):387–434 **This review highlights various tumor types arising in the pediatric population and cancer predisposition syndromes associated with those tumors, serving as a guide for recognition of these genes and conditions.**
36. Young RH, Oliva E, Scully RE. Small cell carcinoma of the ovary, hypercalcemic type. A clinicopathological analysis of 150 cases. Am J Surg Pathol. 1994;18(11):1102–16.
37. Witkowski L, Carrot-Zhang J, Albrecht S, Fahiminiya S, Hamel N, Tomiak E, et al. Germline and somatic *SMARCA4* mutations characterize small cell carcinoma of the ovary, hypercalcemic type. Nat Genet. 2014;46(5):438–43.
38. Schneppenheim R, Fruhwald MC, Gesk S, et al. Germline nonsense mutation and somatic inactivation of *SMARCA4/BRG1* in a family with rhabdoid tumor predisposition syndrome. Am J Hum Genet. 2010;86(2):279–84.
39. Witkowski L, Lalonde E, Zhang J, Albrecht S, Hamel N, Cavallone L, et al. Familial rhabdoid tumour 'avant la lettre'–from pathology review to exome sequencing and back again. J Pathol. 2013;231(1): 35–43.
40. Berchuck A, Witkowski L, Hasselblatt M, Foulkes WD. Prophylactic oophorectomy for hereditary small cell carcinoma of the ovary, hypercalcemic type. Gynecol Oncol Rep. 2015;12:20–2.
41. The NCCN Clinical practice guidelines in oncology genetic/familial high-risk assessment: breast and ovarian (version 3.2019).
42. Cabrera E, Blanco I, Yague C, et al. The impact of genetic counseling on knowledge and emotional responses in Spanish population with family history of breast cancer. Patient Educ Couns. 2010;78(3):382–8.
43. Rantala J, Platten U, Lindgren G, Nilsson B, Arver B, Lindblom A, et al. Risk perception after genetic counseling in patients with increased risk of cancer. Hered Cancer Clin Pract. 2009;7(1):15.
44. Tong A, Kelly S, Nusbaum R, Graves K, Peshkin BN, Valdimarsdottir HB, et al. Intentions for risk-reducing surgery among high-risk women referred for *BRCA1/BRCA2* genetic counseling. Psychooncology. 2015;24(1):33–9.
45. Watson M, Foster C, Eeles R, et al. Psychosocial impact of breast/ovarian (*BRCA1/2*) cancer-predictive genetic testing in a UK multicentre clinical cohort. Br J Cancer. 2004;91(10):1787–94.
46. MacDonald DJ, Lessick M. Hereditary cancers in children and ethical and psychosocial implications. J Pediatr Nurs. 2000;15(4):217–25.
47.• Alderfer MA, Lindell RB, Viadro CI, et al. Should genetic testing be offered for children? The perspectives of adolescents and emerging adults in families with Li-Fraumeni syndrome. J Genet Couns. 2017;26(5):1106–15 **This article documents genetic testing perspectives of adolescents and young adults in families with Li-Fraumeni syndrome. In general, all believed testing should be offered to children and was viewed as a way to learn about risk status, allow for disease prevention efforts, and reduce both uncertainty and anxiety.**
48. Brozou T, Taeubner J, Velleuer E, Dugas M, Wieczorek D, Borkhardt A, et al. Genetic predisposition in children with cancer - affected families' acceptance of Trio-WES. Eur J Pediatr. 2018;177(1):53–60.
49. Weber E, Shuman C, Wasserman JD, et al. "A change in perspective": exploring the experiences of adolescents with hereditary tumor predisposition. Pediatr Blood Cancer. 2019;66(1):e27445.
50. Bauml JM, Troxel A, Epperson CN, Cohen RB, Schmitz K, Stricker C, et al. Scan-associated distress in lung cancer: quantifying the impact of "scanxiety". Lung Cancer. 2016;100:110–3.
51. Binderup ML, Jensen AM, Budtz-Jorgensen E, et al. Survival and causes of death in patients with von Hippel-Lindau disease. J Med Genet. 2017;54(1):11–8.
52. Gopie JP, Vasen HF, Tibben A. Surveillance for hereditary cancer: does the benefit outweigh the psychological burden?–a systematic review. Crit Rev Oncol Hematol. 2012;83(3):329–40.
53. Ross J, Bojadzieva J, Peterson S, Noblin SJ, Yzquierdo R, Askins M, et al. The psychosocial effects of the Li-Fraumeni Education and Early Detection (LEAD) program on individuals with Li-Fraumeni syndrome. Genet Med. 2017;19(9):1064–70.
54.• Duffy KA, Grand KL, Zelley K, et al. Tumor screening in Beckwith-Wiedemann syndrome: parental perspectives. J Genet Couns. 2018;27(4):844–53 **This article is the first to describe parental perspectives on tumor surveillance for children with Beckwith-Wiedemann syndrome and isolated hemihypertrophy. Parents reported overall decreased worry associated with screening and noted that screening did not increase either worry or create a burden. This highlights a need for educating families about tumor risk to facilitate informed decisions regarding tumor surveillance.**
55. Teplick A, Kowalski M, Biegel JA, Nichols KE. Educational paper: screening in cancer predisposition syndromes: guidelines for the general pediatrician. Eur J Pediatr. 2011;170(3):285–94.