Our understanding of hereditary cancer syndromes in children, adolescents, and young adults continues to grow. In addition, we now recognize the wide variation in tumor spectrum found within each specific cancer predisposition syndrome including the risk for hematologic malignancies. An increased understanding of the genetic mutations, biologic consequences, tumor risk, and clinical management of these syndromes will improve patient outcome. In this article, we illustrate the diversity of molecular mechanisms by which these disorders develop in both children and adults with a focus on Li-Fraumeni syndrome, hereditary paraganglioma syndrome, DICER1 syndrome, and multiple endocrine neoplasia syndrome. This is followed by a detailed discussion of adult-onset tumors that can occur in the pediatric population including basal cell carcinoma, colorectal cancer, medullary thyroid cancer, and adrenal cortical carcinoma, and the underlying hereditary cancer syndromes that these tumors could indicate. Finally, the topic of leukemia predisposition syndromes is explored with a specific focus on the different categories of syndromes associated with leukemia risk (genetic instability/DNA repair syndromes, cell cycle/differentiation, bone marrow failure syndromes, telomere maintenance, immunodeficiency syndromes, and transcription factors/pure familial leukemia syndromes). Throughout this article, special attention is made to clinical recognition of these syndromes, genetic testing, and management with early tumor surveillance and screening.

Several hereditary cancer syndromes are associated with neoplasms throughout childhood into adulthood. Although beyond the scope of this article to describe them all, this section highlights those syndromes that illustrate the diversity of molecular mechanisms by which these disorders develop.

**HEREDITARY CANCER SYNDROMES THAT AFFECT CHILDREN, ADOLESCENTS, AND YOUNG ADULTS**

**Li-Fraumeni Syndrome**

Li-Fraumeni familial cancer syndrome (LFS) is a prototypical familial cancer predisposition syndrome. Classic LFS is defined by a proband with a sarcoma diagnosed younger than 45, who has a first-degree relative diagnosed with cancer younger than 45 and a first- or second-degree relative with a diagnosis of cancer younger than 45 or sarcoma at any age.1 The classic spectrum of tumors includes soft-tissue sarcomas, osteosarcomas, breast cancer, brain tumors, leukemia, and adrenocortical carcinoma (ACC), although other cancers, usually early onset, can be observed. Similar patterns of cancer that do not meet the classic definition have been termed Li-Fraumeni-like syndrome (LFS-L). The Chompret criteria for genetic testing for LFS has an 85% sensitivity and 58% specificity, making it perhaps the most rigorous and relevant definition to justify TP53 mutation analysis.2 Germline (constitutional) alterations of the TP53 tumor suppressor gene are found in more than 75% of LFS cases.3,4 TP53 mutations have been described throughout the coding region (as well some intronic regions), but most are missense mutations in the DNA binding domain that encode a stabilized mutant protein. Carriers are heterozygous for the mutation, and in tumors derived from these individuals, the second (wild-type) allele is frequently deleted or mutated, leading to functional p53 protein inactivation. Several comprehensive databases document germline (and somatic) TP53 mutations and help to evaluate novel mutations as well as phenotype–genotype correlations. Germline TP53 mutations occur at the rate of about 1:5,000 individuals, with the exception of Southeastern Brazil, where a specific germline mutation at codon R337H (c.1010 G>A) within the oligomerization domain, occurs at least 15 times more frequently than any other TP53 mutation associated with LFS. In fact, the carrier rate (1:300) for this mutation is higher than any other known cancer susceptibility mutation of any gene worldwide. Analysis of tumor patterns in R337H carriers and
their families reveals all the common features of LFS/LFS-L, clearly establishing predisposition to a wide spectrum of multiple cancers. In R337H carriers, the penetrance at age 30 is less than 20% (compared with approximately 50% in classical LFS). However, the penetrance over lifetime is approximately 90%, similar to classical LFS.

It is not clear whether the lack of detection of TP53 mutations in about 25% of patients with LFS can be explained by other constitutional gene alterations, promoter defects yielding abnormalities of p53 expression, or simply the result of weak phenotype-genotype correlations (i.e., the broad clinical definition encompasses families who do not have LFS). The variability in type of cancer and age of onset within and between LFS families suggests that modifier genes might influence the underlying mutant TP53 genotype. Several modifiers have been described including accelerated age of tumor onset as a result of a single nucleotide polymorphism (SNP) in the MDM2 gene promoter (SNP 309), accelerated telomere attrition, and increased constitutional copy number variations (CNVs), whereas other modifiers such as a 16-bp duplication in TP53 intron 3 (PIN3) delay tumor onset by up to 19 years. Whole genome sequencing of children with sporadic medulloblastoma revealed a subset demonstrating evidence of chromothripsis, defined as a high frequency of tightly localized intrachromosomal rearrangements. The finding of frequent germline TP53 mutations in the subgroup of patients with sonic hedgehog pathway (SHH)-driven medulloblastoma suggests an important role for early TP53 mutations in chromothripsis and provides a possible genetic mechanism for pathogenesis of SHH medulloblastoma (and possibly other tumors) associated with LFS.8 Other genotype-phenotype associations such as apparent overrepresentation of germline TP53 mutations in children with the anaplastic subtype of rhabdomyosarcoma, women with very early onset HER2+ breast cancer, and children with hypodiploid acute lymphoblastic leukemia (ALL) support the notion that tumor subtype and age of onset may be programmed at least in part by mutation subtype and presence of coincident acquired or inherited modifying genetic/genomic events.

The use of surveillance protocols for both adults and children that incorporate total body imaging using rapid sequence whole-body MRI (with or without biochemical marker studies) combined with greater refinement of genetic predictability assays offer hope that molecular testing with early clinical surveillance can improve the natural history of LFS/LFS-L through early detection of biologically less aggressive tumors.

Hereditary Paraganglioma Syndromes
Paragangliomas are benign noncatecholamine secreting tumors that commonly occur in the head and neck region, along the parasympathetic chain. Catecholamine-secreting tumors can develop along the sympathetic chain, in the adrenal medulla (pheochromocytoma), alongside the aortopulmonary vasculature, the organ of Zuckercandl, or even the bladder and vas deferens. Paragangliomas have an estimated population incidence of 1 in 30,000. However, individuals with germline mutations in the succinyl dehydrogenase (SDHx) complex carry an extraordinarily high risk, with disease penetrance perhaps approaching 80%. In addition to paragangliomas and pheochromocytomas, renal cell carcinoma, oncocyto, papillary thyroid cancer, pituitary tumors, gastrointestinal stroma tumors (GIST), and, rarely, neuroblastoma can also be observed. Forty-four percent of adults and 81% of children with metastatic disease carry germline SDHx mutations.

SDH is a component of respiratory Complex II in the mitochondria. SDH is composed of four distinct proteins called SDHA, SDHB, SDHC, and SDHD. A fifth gene, SDHAF2, or SDH Assembly Factor 2, is responsible for assembling all of the individual SDH proteins into a fully functioning enzyme complex. Lack of a functioning SDH complex leads to increased succinate, with subsequent increases in hypoxia inducible factor (HIF) signaling and possible histone deregulation. Germline mutations in other genes such as NF1, VHL, RET, TMEM127, and MAX have also been associated with paragangliomas and pheochromocytomas. Alterations in each SDHx gene lead to different disease phenotypes and clinical presentations, as outlined in Pasini and Stratakis. To facilitate genetic diagnosis, risk assessment, and treatment options, all the SDHx genes can be tested simultaneously.

As in LFS, regular surveillance can detect early tumors in patients with underlying germline SDHx mutations. The importance of detecting smaller, asymptomatic SDH-deficient tumors that can be removed before they transform to malignant, metastatic disease cannot be overemphasized. Annual physical examinations and blood pressure checks (for hypertension caused by increased catecholamines) are helpful, and measurement of serum metabolites, especially fractionated plasma metanephrines are particularly sensitive and specific for detecting secreting paragangliomas and pheochromocytomas. Regular imaging is effective at identifying SDH-related tumors, especially in the setting of negative bio-

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**KEY POINTS**

- Many hereditary cancer syndromes can present in children and adults.
- Understanding the molecular basis of cancer predisposition syndromes will improve understanding of clinical presentation and management.
- Adult-onset tumors rarely present in childhood, but when they do, often represent an underlying genetic risk related to a hereditary cancer syndrome.
- Nearly 60 genes have been associated with different hereditary cancer syndromes that have varying risk for hematologic malignancies.
- Tumor surveillance will diagnose early tumors and improve clinical outcome in children and families recognized to have a hereditary cancer syndrome.
chemical results.16,17 Screening approaches using rapid sequence whole-body MRI (followed by PET/CT imaging to refine the anatomic location of the tumor), in conjunction with urinary and/or fractionated plasma metanephrine levels are considered effective in both adults and children.

**DICER1 Syndrome**

DICER1 syndrome is a recently characterized phenotypic association of distinctive dysontogenic, hyperplastic, or overtly malignant tumors.18 The most frequent is the rare childhood lung malignancy pleural-pulmonary blastoma (PPB). Other, primarily endocrine, manifestations include ovarian Sertoli-Leydig cell tumors (SLCT), nodular thyroid hyperplasia, pituitary blastoma, pineoblastoma, papillary and follicular thyroid carcinoma, cervical rhabdomyosarcoma, cystic nephroma, and possibly Wilms tumor.19 Although most of these tumors appear to manifest in childhood, the thyroid tumor and multinodular goiter risk may be pervasive through adulthood. DICER1 germline mutations have been identified in children and young adults affected with one or several of these tumors, and somatic DICER1 mutations have been identified in sporadic component tumors. DICER1 is an endoribonuclease that processes hairpin precursor micro-RNAs (miRNAs) into short, functional miRNAs. Mature 5′ miRNAs as well as other components of the RNA-induced silencing complex (RISC) down-regulate targeted mRNAs.18 Unlike the classic Knudson “two-hit” mechanism that inactivates tumor suppressor genes, the effect of DICER1 loss-of-function appears to result from an initial inactivating mutation that reduces by half the amount of wild-type DICER1 protein, followed by a second hit that specifically eliminates production of 5′ mature miRNAs. Disease penetrance is highly variable. Whereas many manifestations in DICER1-mutation carriers are relatively indolent, the risk in childhood of some potentially lethal tumors such as PPB and pineoblastoma indicates a need for clinical surveillance particularly targeting the lungs, abdomen, and brain. Such surveillance protocols are evolving and are modified in the transition from early childhood to adolescence to adulthood based on the different cancer risks in each age bracket.

**Multiple Endocrine Neoplasia (MEN)**

MEN type 1, MEN type 2A, and MEN type 2B affect different endocrine organs. The most common features of MEN1 are parathyroid adenomas (approximately 90% of cases), pancreatic islet cell tumors (50% to 75% of cases), and pituitary adenomas (25% to 65% of cases).20 One-quarter of MEN1 mutation carriers demonstrate clinical or biochemical evidence of disease by age 15. MEN2A is associated with medullary thyroid carcinoma (MTC), parathyroid adenoma, and pheochromocytoma. The risk of developing MTC in MEN2A mutation carriers is 100%; prophylactic thyroidectomy is recommended before age 5 in all confirmed carriers. MEN2B is a related disorder, but with onset of the tumors in early infancy, ganglioneuroma of the gastrointestinal tract, and skeletal abnormalities.

MEN1 is caused by mutation in the MEN1 tumor-suppressor gene; MEN2A and 2B are caused by mutations in the proto-oncogene RET. Although 100% of RET mutation carriers will develop MTC, up to 1% to 7% of patients with sporadic MTC also harbor germline RET mutations. The pattern of mutations seen in MEN2 families does not follow the “two-hit hypothesis” for tumor suppressor genes—RET is not inactivated, and there is no loss of the second allele in the tumors. Thus, the predisposition to cancer in families with MEN2 is based on the inheritance of an activating mutation in the RET proto-oncogene. This unusual pattern of inheritance is almost unique in the field of hereditary cancer predisposition syndromes. Genetic testing is by direct mutation analysis of the gene. Furthermore, well-established clinical surveillance tools exist for early detection of pheochromocytoma, papillary and medullary thyroid cancer, pancreatic, and pituitary tumors associated with the MEN disorders.

**Summary**

The disorders presented here represent the broad spectrum of hereditary cancer syndromes, the diversity of genetic mechanisms involved in tumorigenesis, and the potential power of gene testing with refined surveillance protocols to guide clinical interventions. Importantly, studies of the constitutional mutations of genes associated with these disorders (and the many other syndromes with increased risk of both childhood and adult cancers) has taught us much about the genetic basis of common sporadic human cancers.

**ADULT-TYPE CANCERS IN CHILDREN: CLUES TO THE PRESENCE OF AN UNDERLYING PREDISPOSITION**

One defining feature of a genetic predisposition to cancer is the development of one or more malignancies at an earlier than expected age. This differs from individuals with sporadic (i.e., nonheritable) cancers who do not harbor constitutional gene mutations, but instead must sustain multiple genetic events within a single cell for tumors to form. Mutations generally occur in continuously proliferating cells (where DNA replication is ongoing) and are caused by prolonged exposure to environmental carcinogens; therefore, nonheritable cancers increase with age and commonly arise from the epithelial cells of barrier tissues. The development of so-called “adult type” cancers in children, including carcinomas of the skin and gastrointestinal (GI) tract, is exceedingly rare and highly suspicious for an underlying genetic predisposition. Children who present with adult type cancers should be carefully examined for a possible genetic cause. In this section, we summarize the heritable basis of several adult type cancers that can manifest during childhood. Table 1 summarizes additional adult type cancers and their underlying genetic causes.

**Basal Cell Carcinoma**

Basal cell carcinoma (BCC) is the major histologic subtype of nonmelanoma skin cancer and the most common malig-
nancy in fair-skinned people. Prior studies have estimated that 700,000 to 1 million cases of BCC are diagnosed each year in the United States. BCC increases with age, with 80% developing in individuals older than age 55. The majority of adult BCCs are sporadic and result from excess exposure to the sun or ultraviolet tanning beds.

Incidence and genetic basis. When diagnosed in children, BCC should raise suspicion for the nevoid basal cell carcinoma syndrome (NBCCS, also known as Gorlin syndrome), caused by germline PTCH1 mutations. PTCH1 encodes a cell surface receptor that transduces signals from the SHH protein. SHH signaling activates GLI family transcription factors that upregulate pro-proliferative genes and reduces expression of cell cycle inhibitors, including p27KIP1 and p18INK4c. NBCCS is characterized by multiple BCCs, as early as age 3 to 4, but more commonly between puberty and age 35 (mean age of onset, 25). They can vary from a few to thousands, as well as in size (1 to 10 mm), and are commonly located in sun-exposed areas. Although generally considered benign, BCCs can metastasize in rare cases. If untreated, BCCs lead to disfigurement, especially on the face. BCCs are typically treated by surgical removal, and ionizing radiation should be avoided in NBCCS as new tumors can arise in the radiation field even after many years.

Children and teenagers with NBCCS are prone to jaw keratocysts, found in 90% of affected individuals. Keratocysts should be surgically removed because they can interfere with tooth eruption and lead to jaw fracture. Patients may also manifest with hydrocephalus, hyperkeratosis, small pit-like findings in the palms and soles, skeletal abnormalities (bifid ribs, hemivertebrae, scoliosis), ocular issues (cataracts, coloboma, microphthalmia), and characteristic facial findings (frontal bossing, hypertelorism, macrocephaly, milia).

### TABLE 1. Adult Type Cancers that Can Present in Children and Underlying Genetic Syndromes

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Genetic Syndrome(s)</th>
<th>Age of Cancer Onset (avg; years)</th>
<th>Gene</th>
<th>Locus</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocortical carcinoma</td>
<td>LFS</td>
<td>Females: 11.5 (0.5–38) Males: 3 (2–3.5)</td>
<td>TP53</td>
<td>17p13.1</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>BWS</td>
<td>Early childhood</td>
<td>1p15 methylation defects</td>
<td>1p15</td>
<td>Non-heritable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>NBCCS</td>
<td>25; earliest 3-4</td>
<td>PTCH1</td>
<td>9q22.32</td>
<td>AD</td>
</tr>
<tr>
<td>Brain</td>
<td>Gliomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LFS</td>
<td>15-20</td>
<td>TP53</td>
<td>17p13.1</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>LS</td>
<td>30-50, can occur in teens</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Multiple</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>CMMRD</td>
<td>8</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Multiple</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Medulloblastoma</td>
<td>FAP</td>
<td>15</td>
<td>APC</td>
<td>5q22.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>NBCCS</td>
<td>2</td>
<td>PTCH1</td>
<td>9q22.32</td>
<td>AD</td>
</tr>
<tr>
<td>Breast</td>
<td>LFS</td>
<td>30; can occur &lt; 20</td>
<td>TP53</td>
<td>17p13.1</td>
<td>AD</td>
</tr>
<tr>
<td>Colorectal</td>
<td>LS</td>
<td>44-61*, earliest in teens</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Multiple</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>CMMRD</td>
<td>6*, range: 5-28</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>Multiple</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>FAP</td>
<td>Majority by 40-50*, can occur in childhood</td>
<td>APC</td>
<td>5q22.2</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>PJS</td>
<td>42*, can occur &lt; 20</td>
<td>STK11</td>
<td>19p13.3</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>JPS</td>
<td>30s-40s*, can occur &lt; 20</td>
<td>BMPRIA</td>
<td>10q23.2</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Bloom</td>
<td>35*; can occur &lt; 20</td>
<td>BLM</td>
<td>15q26.1</td>
<td>AR</td>
</tr>
<tr>
<td>Thyroid</td>
<td>PHTS</td>
<td>39; can occur in childhood/teens*</td>
<td>PTEN</td>
<td>10q23.31</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>MEN2A</td>
<td>20s-30s; can occur in childhood/teens*</td>
<td>RET</td>
<td>10q11.21</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>MEN2B</td>
<td>10-20; earliest 2 mo*</td>
<td>RET</td>
<td>10q11.21</td>
<td>AD</td>
</tr>
<tr>
<td>Renal cancer</td>
<td>TS (angiomyolipoma)</td>
<td>9-10</td>
<td>TSC1, TSC2</td>
<td>9q34.13, 16p13.3</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>VHL (RCC)</td>
<td>40, can occur at younger ages (rarely before 16)</td>
<td>VHL</td>
<td>3p25.3</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>HLRCC</td>
<td>44, can occur at 10-20</td>
<td>FH</td>
<td>1q43</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Paraganglioma/ Pheochromocytoma</td>
<td>Hereditary PGL/PCC</td>
<td>20s-40s; earliest 5-8</td>
<td>SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX</td>
<td>Multiple</td>
</tr>
<tr>
<td></td>
<td>MEN2A/B</td>
<td>20s-30s, can occur in teens (2A and 2B)</td>
<td>RET</td>
<td>10q11.21</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>VHL</td>
<td>30, can occur in children</td>
<td>VHL</td>
<td>3p25.3</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>NF1</td>
<td>42, can occur &lt; 20</td>
<td>NF1</td>
<td>17q11.2</td>
<td>AD</td>
</tr>
</tbody>
</table>

Abbreviations: LFS, Li-Fraumeni syndrome; AD, autosomal dominant; BWS, Beckwith-Wiedemann syndrome; NBCCS, nevoid basal cell carcinoma syndrome; LS, Lynch syndrome; CMMRD, congenital mismatch repair deficiency; AR, autosomal recessive; FAP, familial adenomatous polyposis; PJS, Peutz-Jeghers syndrome; JPS, juvenile polyposis syndrome; PHTS, PTEN hamartoma tumor syndrome; MEN2A/B, multiple endocrine neoplasia type 2A/2B; TS, tuberous sclerosis; RCC, renal cell carcinoma; HLRCC, hereditary leiomyomatosis and renal cell carcinoma; PGL/PCC, paraganglioma/pheochromocytoma; VHL, von Hippel-Lindau; NF1, neurofibromatosis type 1.

*Without intervention (polypectomy/colectomy/thyroidectomy).
Additional tumors in NBCCS include cardiac and ovarian fibromas, which occur in about 2% and 20% of individuals, respectively.\textsuperscript{24,26} Approximately 5% of children with NBCCS develop medulloblastoma, with the peak age of onset around 2 years.\textsuperscript{24}

NBCCS is primarily diagnosed by physical examination and radiologic imaging based on published diagnostic criteria. Clinical genetic testing for germline \textit{PTCH1} mutations can be pursued; detection frequency ranges from 50% to 85% in individuals with findings of NBCCS.\textsuperscript{24} Molecular testing often confirms the diagnosis in atypical presentations or identifies asymptomatic individuals in families with a known \textit{PTCH1} gene mutation. Individuals carrying a clinical or molecular diagnosis of NBCCS warrant referral to a geneticist or dermatologist with NBCCS expertise for education, coordination of surveillance, and management of the multiple clinical manifestations of this disorder.

**Colorectal Cancer**

Colorectal cancer (CRC) is the third most common cancer in adults, where it accounts for more than 9% of all malignancies.\textsuperscript{27} CRC increases with age with more than 90% of cancers developing in individuals older than age 50.\textsuperscript{27} In adults, approximately 5% to 10% of CRCs occur in the setting of a genetic predisposition, with the most common underlying condition being hereditary nonpolyposis colorectal cancer (HNPPC, also known as Lynch syndrome [LS]). In HNPPC, the average age of CRC onset varies, but is generally in the 40s to 60s.\textsuperscript{28-30} Individuals with HNPPC also develop carcinomas elsewhere in the GI tract, central nervous system cancers (glioblastoma), gynecologic (endometrial), and genitourinary (GU) cancers.\textsuperscript{28-31} HNPPC is caused by heterozygous germline mutations in the \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, and \textit{PMS2} genes, which play a role in DNA mismatch repair (MMR).

**Incidence and genetic basis.** Extremely rare in children, CRC constitutes less than 1% of pediatric cancers with an incidence of 0.3 to 1.5 cases per million children per year.\textsuperscript{31} Like adults, heterozygous germline MMR mutations contribute to CRC in the pediatric age group; Durno et al revealed that 6 of 14 (43%) patients with an HNPPC-associated CRC were less than age 24 (eight were younger than age 18, the youngest was age 12).\textsuperscript{31}

Recently, constitutional mismatch repair deficiency (CMMRD) syndrome was described in which individuals harbor biallelic mutations in the MMR genes.\textsuperscript{30,32} In contrast to HNPPC, patients with CMMRD (two affected MMR genes) exhibit a higher incidence of very early-onset GI cancers in 32% to 37% of patients.\textsuperscript{30,32} Several other childhood cancers are associated with CMMRD, including hematologic malignancies (primarily T-cell leukemias/lymphomas in 15% to 24% of patients) and brain tumors (32% to 48%).\textsuperscript{32} Less common cancers include neuroblastoma and rhabdomyosarcoma.\textsuperscript{32,33}

Age of cancer onset varies, with hematologic malignancies presenting at an average age of 5.5 years, brain tumors at 8 years, and gastrointestinal tumors at 15 to 16 years, and endometrial tumors at 24 years. In one study, gastrointestinal polyps or CRC were the first manifestation of CMMRD in up to one-third of patients.\textsuperscript{33}

CMMRD should be considered in children with the following conditions: CRC or other HNPPC cancers in conjunction with café au lait (CAL) macules and/or hypo-pigmented skin lesions (seen in virtually all CMMRD patients), history of parental consanguinity, and positive family history of HNPPC cancers. Lack of a positive family history does not rule out CMMRD, as many families do not meet clinical criteria for HNPPC.\textsuperscript{32}

To establish a molecular diagnosis, microsatellite instability and/or loss of MMR protein expression by immunohistochemistry (IHC) can be tested on tumor or germline tissues, followed by mutational analysis. IHC analysis for loss of MMR protein expression in tumor is reported to be 100% sensitive and specific for CMMRD.\textsuperscript{32} If the familial MMR mutations are known, it may be possible to proceed directly to genetic testing. Because of the complex genetics and technical challenges associated with MMR testing, professionals with experience in HNPPC and/or CMMRD should coordinate genetic counseling and testing.

Childhood CRC can also represent a rare manifestation of other genetic syndromes, including familial adenomatous polyposis (FAP, caused by mutations in the \textit{APC} gene),\textsuperscript{34} as well as Peutz Jegher (\textit{STK11}),\textsuperscript{35} Bloom (\textit{BLM}),\textsuperscript{36} juvenile polyposis syndrome (\textit{SMAD4, BMPR1}),\textsuperscript{37} or even LFS/LFS-L. In each of these conditions, CRCs generally occur in adults. However, reports exist of affected children. Therefore, these conditions should also be kept in mind and careful physical and genetic evaluation considered for those who present with CRC and the appropriate clinical features.

**Medullary Thyroid Cancer**

Thyroid cancer is the ninth most common cancer in adults and comprises 3.6% of all new cancer cases in the United States.\textsuperscript{38} Thyroid cancers usually present between age 45 and 54.\textsuperscript{39} MTC is an aggressive subtype of thyroid cancer that arises from parafollicular C cells and accounts for 5% to 10% of thyroid cancers.\textsuperscript{38,39} As described previously, the majority of MTC will be sporadic but 1% to 7% will be caused by MEN2.\textsuperscript{38,39} This increases up to 25% with a positive family history of MTC (a condition known as familial medullary thyroid cancer [FMTC]), presence of pheochromocytoma and/or hyperparathyroidism (indicative of MEN2A), or other phenotypic features (mucosal neuromas and marfanoid habitus, indicative of MEN2B). All three MEN2 subtypes (FMTC, MEN2A, MEN2B) confer an almost 100% lifetime risk for MTC. When MTC is seen in children, it is most likely because of a genetic germline mutation, most often \textit{RET}. Identification of MEN2 in children with MTC enables surveillance to detect pheochromocytomas and hyperparathyroidism and allows for genetic testing and monitoring of other family members. For mutation-positive individuals who have not yet developed MTC, genetic testing allows for prophylactic thyroidectomy (often before age 5), a life-saving procedure that greatly reduces the likelihood of MTC.\textsuperscript{40}
Adrenocortical Carcinoma
Comprising 0.02% to 0.2% of adult cancers, ACC has an incidence of about 0.72 per million individuals per year in the United States. In Southern Brazil, the incidence is 10 to 15 times higher than the United States, presumably because of the increased prevalence of the R337H founder mutation in TP53, as discussed previously. In adults, the median age of ACC onset ranges from 46 to 55, and 10% develop disease caused by an underlying predisposition with about 5.8% because of LFS, 3% because of HNPCC, 1% to 2% because of MEN1, and less than 1% because of Neurofibromatosis type 1 (NF1) or FAP.

Incidence and genetic basis. ACC represents 0.2% to 1% of all childhood cancers and typically presents during the first 5 years of life (median age 3 to 4 years). Childhood ACC is one of the defining features of LFS, as discussed previously, with approximately 6.5% to 10% of patients with LFS developing ACC. Initially believed that the R337H mutation commonly found in Southern Brazil uniquely predisposes to ACC, it is now recognized that it is also linked to more typical LFS-associated cancers. Based on the strong association between LFS and childhood onset ACC, TP53 genetic testing is strongly recommended for any child with ACC. Testing should not be dismissed in the absence of a positive family history, as up to 25% of TP53 mutations occur as de novo events. As highlighted with the previous hereditary cancer syndromes, it is highly recommended that genetic testing for LFS be completed in the context of genetic counseling and by those familiar with the syndrome.

An additional cause of ACC is Beckwith Wiedemann syndrome (BWS), characterized by macrosomia, visceromegaly, macroglossia, neonatal hypoglycemia, ear anomalies, and abdominal wall defects. Children with BWS are most at risk for Wilms tumor and hepatoblastoma; however, they can also develop rhabdomyosarcoma or ACC. The BWS adrenal phenotype also includes adrenocortical cytomegaly, adrenocortical adenomas, pheochromocytomas, and adrenal cysts. The molecular basis of BWS involves genetic and epigenetic alterations at chromosomal locus 11p15, containing the genes CDKN1C, IGF2, and H19 (normally expressed in a mono-allelic fashion with a parent of origin effect). The 11p15 alterations lead to altered expression of these growth-regulating genes, believed to contribute to the overgrowth phenotype also includes adrenocortical cytomegaly, adrenocortical adenomas, pheochromocytomas, and adrenal cysts. The molecular basis of BWS involves genetic and epigenetic alterations at chromosomal locus 11p15, containing the genes CDKN1C, IGF2, and H19 (normally expressed in a mono-allelic fashion with a parent of origin effect). The 11p15 alterations lead to altered expression of these growth-regulating genes, believed to contribute to the overgrowth and tumor risks in BWS. Abdominal ultrasound screening is recommended for the risk of abdominal tumors in BWS.

During the past 30 years, the pediatric oncology community has seen tremendous advances in cancer genetics and genomics. These new data profoundly increased our knowledge of the heritable basis of cancer, with more than 25 genes in the germ line predisposing to adult type cancers in children (Table 1). Many of these genes are also mutated somatically in nonheritable cancers, and these cancer predisposing syndromes have provided invaluable insights into the processes underlying tumor formation. The challenge now lies in how to best translate this continuously expanding genetic knowledge to the clinic in a meaningful manner to improve the outcomes for affected children and their families.

PREDISPOSITION TO HEMATOLOGIC MALIGNANCIES
Childhood leukemia is the most common pediatric cancer and accounts for more than a third of all new cancer diagnoses in children and adolescents. Despite its high frequency, only a small proportion of childhood leukemia cases are truly familial or caused by known hereditary cancer syndromes. The genetic epidemiology of childhood leukemia has been actively investigated for many decades, with growing evidence for a genetic (or inherited) contribution to leukemia risk. Both ALL and acute myeloid leukemia (AML) can be seen with a variety of hereditary cancer syndromes; however, leukemia is very rarely seen as the only presenting cancer. The categories of leukemia-associated inherited cancer syndromes can be divided into six main groups: genetic instability/DNA repair syndromes, cell cycle/differentiation, bone marrow failure syndromes, telomere maintenance, immunodeficiency syndromes, and transcription factors/pure familial leukemia syndromes.

Single Nucleotide Polymorphisms and Genome-Wide Association Studies (GWAS)
The earliest studies of childhood ALL risk investigated SNPs within candidate genes based on leukemia biology, and fell within categories of folate metabolism/transport, xenobiotic metabolism/transport, immune function, DNA repair, and cell cycle. Hundreds of studies found mixed results, but the most suggestive SNPs within genes associated with ALL risk included MTHFR C677T (folate metabolism), CYP1A1 TP235C (xenobiotic metabolism), GSTM1 deletion (xenobiotic metabolism), NAT2*5 (xenobiotic metabolism), XRCC1 G28152A (DNA repair), and HLA-DRB4 (encoding HLA-DR53 immune antigen). More recently, leukemia risk has been investigated by GWAS with SNP microarrays. Although an agnostic approach, these GWAS reports consistently identify SNPs in the following genes associated with growth regulation, hematopoiesis, and lymphocyte development: IKZF1 (7p12.2), CDKN2A (9p21.3), ARID5B (10q21.2), and CEBPE (14q11.2). GWAS in multiethnic populations (including African Americans and Hispanic Americans) demonstrated novel susceptibility variants at the BMI1-PIP4K2A (10p12.31–12.2) locus. These risk alleles, including their association with ALL hyperdiploid subtype, have now been validated in multiple studies with children of many different ethnic/racial backgrounds. These SNPs are among the strongest cancer susceptibility variants identified through GWAS with a nearly 3-fold risk of disease, suggesting that inherited genetic factors may contribute greatly to childhood ALL. Nevertheless, by some estimates, these SNPs account for only 8% of genetic variation in ALL risk, and additional susceptibility variants have yet to be discovered.
Inherited Syndromes
The known hereditary cancer syndromes associated with leukemia risk account for nearly 60 different genes. Each syndrome has a different risk for ALL or AML (and sometimes bone marrow myelodysplastic syndrome [MDS]). We will briefly describe some of these syndromes, with a focus on the limited recommendations for screening and early detection. The reader is directed to Table 2 for more comprehensive information on the causative genes and is associated with multiple CAL spots, pediatric brain tumors, colorectal cancers, and pediatric hematologic malignancies including both ALL and AML.72-76 Any child presenting with ALL with multiple CAL spots and/or a family history of LS-related tumors (colorectal, endometrial, gastric, ovarian) should be considered for MMR testing. If identified, both parents often will be obligate carriers of heterozygous MMR defects and will have LS (HNPCC). There are currently no standard screening recommendations for leukemia risk in CMMRD. Fanconi anemia (FA) is a well-described autosomal recessive (AR) disorder that leads to increased chromosomal breakage through defects in DNA repair.77 The primary features of FA include bone marrow failure, distinct physical characteristics, growth failure, and increased risk for AML and solid malignancies. Bone marrow failure often occurs between the ages of 5 and 15, more than a third will develop leukemia by age 30, and nearly half will develop MDS by age 50 (removing other competing health concerns).78,79 Because of high sensitivity to DNA damaging agents, including radiation, treatment for FA-related malignancies, is complicated by the high rate of secondary malignancy. Regular CBCs and annual bone marrow evaluation for morphology, cellularity, and cytogenetics has been recommended in FA.77 Ataxia telangiectasia (A-T) is caused by AR mutations in ATM leading to deficient DNA repair characterized by progressive ataxia and central nervous system (CNS) degeneration, growth deficiency, ocular and facial telangiectasia, immunodeficiency, and an increased risk for malignancy (10% to 38% risk).80,81 Patients with A-T have a 70-fold increased risk for ALL and an up to 5-fold increased risk for T-cell lymphoid malignancies.82 Similar to FA, patients with A-T are very sensitive to ionizing radiation and require tailored treatment plans for their cancers to reduce the risk for secondary malignancy. No formal hematologic surveillance has been recommended in A-T, although parents are often advised to monitor for indications of underlying malignancy such as weight loss, bruising, and localized pain or swelling.81

Cell Cycle/Differentiation
Characterized by RAS signaling pathway dysfunction, the rasopathies are inherited as autosomal dominant syndromes with varying leukemia risk and specific physical traits. Individuals with NF1 have a 200- to 500-fold increased risk for juvenile myelomonocytic leukemia (JMML), and 10% to 14% of children with JMML may have a clinical diagnosis of NF1.83 Noonan syndrome (NS), mostly commonly caused by PTPN11 mutations, is noteworthy among the rasopathies for its association with self-resolving myeloproliferative syndrome (MPD/TMD)84 and also JMML.85 CBL syndrome is the most recently described leukemia-related rasopathy and primarily causes JMML, along with specific dysmorphic features.86,87 Because of both its rarity and recent recognition, the true prevalence and leukemia risk in CBL syndrome is still being described. No formal leukemia screening exists for children with the rasopathies, although any bruising, petechiae, fevers, and fatigue should lead the clinician to consider leukemia. Given the strong association between JMML and the rasopathies, any newly diagnosed patient with JMML should be carefully examined for clinical signs of NF1, NS, and CBL syndrome. Any patient with NS and MPD/TMD may benefit from close observation before treatment to monitor for transient disease.

Bone Marrow Failure Syndromes
Many different bone marrow failure syndromes have been associated with varying degrees of bone marrow failure in different precursor cell lines, including Diamond Blackfan anemia (DBA), Shwachman-Diamond syndrome (SDS), congenital amegakaryocytic thrombocytopenia (CAMT), thrombocytopenia and absent radii (TAR) syndrome, and severe congenital neutropenia (Kostmann) syndrome. Although all leukemias have been described in these syndromes, MDS and AML seem to be the most common with risks ranging from 5% to 25%.88-91 Other studies have found up to a 25% risk for AML.92,93 For DBA and SDS, proposed leukemia surveillance includes CBCs several times a year with bone marrow aspirate/biopsy in the event of another cytopenia or a change in response to treatment (although bone marrow examination every 1 to 3 years has been suggested for SDS).94,95 Careful follow-up of any leukemia-related signs or symptoms has been offered as management for the other bone marrow failure syndromes.

Telomere Maintenance and Immunodeficiency Syndromes
Please see Table 2 for a list of telomere maintenance and immunodeficiency syndromes associated with leukemia risk. Although leukemia screening recommendations are not based on large clinical trials for these syndromes because of their rarity, it has been suggested to consider annual CBCs and bone
### TABLE 2. Hereditary Cancer Syndromes Associated with Leukemia and Hematologic Malignancies

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Prevalence</th>
<th>Leukemia Type</th>
<th>Leukemia Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA Repair/Genetic Instability</td>
<td>Li-Fraumeni syndrome</td>
<td>TP53</td>
<td>1/5,000-1/20,000</td>
<td>ALL, MDS, AML</td>
<td>1%-3%</td>
</tr>
<tr>
<td></td>
<td>Biallelic mismatch repair syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2</td>
<td>1/775,000</td>
<td>ALL, AML</td>
<td>Unknown, but high</td>
</tr>
<tr>
<td></td>
<td>Werner syndrome</td>
<td>WRN</td>
<td>1/20,000-1/40,000 in Japan (founder mutation); 1/200,000 in United States[19]</td>
<td>AML, MDS</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>Rothmund-Thomson</td>
<td>RECQL4</td>
<td>Unknown, rare</td>
<td>MDS</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>Bloom syndrome</td>
<td>BLM</td>
<td>1/100 carrier frequency in Ashkenazi Jewish population</td>
<td>AML, ALL, MDS</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Fanconi anemia</td>
<td>FANCA-C, FANCY-D, FANCE-G, FANCI-J, FANCL-P</td>
<td>1/360,000; 1/300-1/700 carrier frequency for AR forms depending on population[7,18]</td>
<td>MDS/AML</td>
<td>7% MDS; 9% (500-fold) AML 500-fold AML</td>
</tr>
<tr>
<td></td>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>1/40,000-1/700,000</td>
<td>ALL</td>
<td>70-fold leukemia</td>
</tr>
<tr>
<td></td>
<td>Nijmegen breakage syndrome</td>
<td>NBS1</td>
<td>1/100,000; carrier frequency of founder mutation approximately 1/955 (Eastern Europe, Bavaria) — 1/34 (Sorbs)][11,12]</td>
<td>ALL, TLBL/ALL</td>
<td>Unclear</td>
</tr>
<tr>
<td>Cell cycle/differentiation (RAS pathway dysfunction)</td>
<td>Noonan syndrome</td>
<td>PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1</td>
<td>1/1000-1/2500</td>
<td>TMD, JMML, CMML, ALL</td>
<td>Unknown, but high</td>
</tr>
<tr>
<td></td>
<td>CBL syndrome</td>
<td>CBL</td>
<td>Unknown; 3/65 patients with JMML were found to have germ line CBL mutation</td>
<td>JMML</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Neurofibromatosis type 1</td>
<td>NF1</td>
<td>1/3,000</td>
<td>CMML/JMML, AML</td>
<td>11% MDS 200- to 500-fold JMML</td>
</tr>
<tr>
<td>Bone marrow failure</td>
<td>Diamond blackfan anemia</td>
<td>RPS19, RPS24, RPS27, RPL35A, RPL5, RPL11, RPS7, RPS26, RPS10, GATA1</td>
<td>1/200,000-1/100,000,000[13]</td>
<td>MDS/AML, ALL</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RPS19</td>
<td></td>
<td>MDS/AML, ALL</td>
<td>5%-24%</td>
</tr>
<tr>
<td></td>
<td>Shwachman-Diamond</td>
<td>SBDS</td>
<td>1/76,000[14]</td>
<td>MDS/AML, ALL</td>
<td>5%-24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPL</td>
<td>1/22,500 in the Jewish population, [5] rare in other populations</td>
<td>MDS/AML</td>
<td>Unknown, rare reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBMMA Del IgY12</td>
<td>1/200,000-1/100,000[15]</td>
<td>MDS/AML</td>
<td>Unknown, rare reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ELANE, G6PC3, GF1, HAX1, CSF3R</td>
<td>15/1,000,000-10/1,000,000 [16]</td>
<td>MDS/AML</td>
<td>8% to 25%</td>
</tr>
<tr>
<td>Telomere maintenance</td>
<td>Dyskeratosis congenital</td>
<td>CTCL, DHC1, TERC, TERT, TINF2, NOP10, NHP2, WRAP53</td>
<td>Unknown, rare[17]</td>
<td>MDS/AML</td>
<td>3%-33%</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Wiskott-Aldrich</td>
<td>WAS</td>
<td>4/100,000,000 males[20]</td>
<td>ALL</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Bruton’s agammaglobulinemia</td>
<td>BTK</td>
<td>6/1100,000[21]</td>
<td>ALL</td>
<td>Unknown, rare</td>
</tr>
<tr>
<td>Transcription Factor</td>
<td>Familial AML caused by CEBPA mutations</td>
<td>CEBPA</td>
<td>Unknown, rare</td>
<td>MDS/AML</td>
<td>Unknown, younger onset</td>
</tr>
<tr>
<td></td>
<td>Familial platelet disorder</td>
<td>RUNX1</td>
<td>Unknown, rare</td>
<td>MDS/AML</td>
<td>35% AML; young onset</td>
</tr>
<tr>
<td></td>
<td>MonoMac</td>
<td>GATA2</td>
<td>Unknown, rare; approximately 25 families have been reported[22]</td>
<td>MDS/AML</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>Familial PAX5 syndrome</td>
<td>PAX5</td>
<td>Unknown, rare</td>
<td>ALL</td>
<td>Unknown, but high</td>
</tr>
<tr>
<td></td>
<td>Familial SH2B3 syndrome</td>
<td>SH2B3</td>
<td>Unknown, rare</td>
<td>MDS/AML</td>
<td>Unknown, but high</td>
</tr>
<tr>
<td>Unknown</td>
<td>Familial mosaic monosomy T</td>
<td>Unknown</td>
<td>Unknown, rare</td>
<td>MDS/AML</td>
<td>Very high, early onset</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>Down Syndrome</td>
<td>Trisomy 21</td>
<td>1/1,660</td>
<td>TMD, AML, ALL</td>
<td>10% TMD, 1%-2% ALL-AML</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; TLBL, T-cell lymphoblastic lymphoma; TMD, myeloproliferative syndrome; JMML, juvenile myelomonocytic leukemia; CML, chronic myelomonocytic leukemia.
marrow evaluation for morphology and cytogenetics (and more frequently if abnormal findings are present).96-99

Transcription Factors/Pure Familial Leukemia Syndromes

These rare syndromes are caused by mutations in genes that code for hematopoietic transcription factors. The most recent single gene leukemia syndromes include Familial PAX5 syndrome100,101 and Familial SH2B3 syndrome.102,103 The lifetime risk for hematologic malignancy is unknown, but considered to be high. Alterations in the associated genes (CEBPA, RUNX1, GATA2, PAX5, SH2B3, and monosomy 7) are known to occur in leukemia cells, and, therefore, the clinician must be careful to discriminate between somatic mutations and germline mutations when evaluating an individual for the syndromes associated with germline alterations in these genes. This becomes important when deciding what samples (blood vs. buccal) to send for germline testing if the patient has a current leukemia diagnosis. Surveillance following leukemia treatment includes routine clinical standard of care for these syndromes, but no formal guidelines exist for preleukemic surveillance in affected family members (although some regular interval of measuring CBCs may prove beneficial).104 Familial mosaic monosomy 7 offers an exception with recommended annual screening of peripheral blood karyotype, CBC, and hemoglobin F levels to identify early bone marrow abnormalities such as cytopenias and bone marrow dysplasia.105

Congenital Syndromes/Aneuploidies

These syndromes remain outside the scope of this article, although Trisomy 21 (Down syndrome [DS]) has long been associated with an extremely high risk of childhood leukemia, including a 10- to 20-fold increased risk of ALL or AML, and an up to 500-fold risk of acute megakaryoblastic leukemia (AMKL).106,107 Childhood leukemia also has been described with other congenital conditions or birth defects, but these are based on limited case reports, and actual leukemia risk and required surveillance is difficult to determine.108-110 These other non-DS leukemia-associated congenital disorders include Goldenhar’s syndrome,111 Rubinstein-Taybi syndrome,112 Treacher Collins syndrome,113 Poland’s anomaly,113 Klippel-Feil syndrome,114 and Hypomelanosis of Ito.115 As next generation sequencing becomes more common, more leukemia-associated congenital disorders with specific mutations contributing to leukemia risk may be discovered.

Summary

More than 60 different genes have been associated with hereditary cancer syndromes that include an increased risk for childhood leukemia. However, the hereditary basis for childhood leukemia is now only beginning to be understood. Similar to the other inherited syndromes, the insight provided by these leukemia-associated syndromes will have diagnostic and possibly therapeutic implication for all children and adults diagnosed with leukemia or other hematologic malignancies. Although formal guidelines for leukemia surveillance are currently lacking for many of these syndromes, recognition of hematologic symptoms by patients and their providers should prompt further clinical investigation.

ACKNOWLEDGEMENT

This work supported by a grant from the Canadian Institutes for Health Research (MOP-300105) to DM, and through the Primary Children’s Hospital (PCH) Pediatric Cancer Program, supported by the Intermountain Healthcare Foundation and the Primary Children’s Hospital Foundation to JDS.

Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.


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