

## Recommendations for Surveillance for Children with Leukemia-Predisposing Conditions

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### Abstract

Leukemia, the most common childhood cancer, has long been recognized to occasionally run in families. The first clues about the genetic mechanisms underlying familial leukemia emerged in 1990 when Li-Fraumeni syndrome was linked to *TP53* mutations. Since this discovery, many other genes associated with hereditary predisposition to leukemia have been identified. Although several of these disorders also predispose individuals to solid tumors, certain conditions exist in which individuals are specifically at increased risk to develop myelodysplastic syndrome (MDS) and/or acute leukemia. The increasing identification of affected individuals and families has raised questions around the efficacy, timing, and optimal methods of surveillance. As part of the AACR Childhood Cancer Predisposition Workshop, an expert panel met to review the spectrum of leukemia-predisposing conditions, with the aim to develop consensus recommendations for surveillance for pediatric

patients. The panel recognized that for several conditions, routine monitoring with complete blood counts and bone marrow evaluations is essential to identify disease evolution and enable early intervention with allogeneic hematopoietic stem cell transplantation. However, for others, less intensive surveillance may be considered. Because few reports describing the efficacy of surveillance exist, the recommendations derived by this panel are based on opinion, and local experience and will need to be revised over time. The development of registries and clinical trials is urgently needed to enhance understanding of the natural history of the leukemia-predisposing conditions, such that these surveillance recommendations can be optimized to further enhance long-term outcomes. *Clin Cancer Res*; 23(11); e14–e22. ©2017 AACR.

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### Introduction

Leukemia is the most common childhood malignancy, accounting for approximately 31% of all cancers occurring in children younger than 15 years of age and 25% of cancers

among those younger than 20 (1). Although most childhood-onset leukemias are thought to result from sporadic somatic genetic events, they have also been observed in individuals in the context of an expanding array of hereditary conditions. These conditions are caused by germline genetic changes that impact critical cellular processes, such as DNA stability and repair, apoptosis, cell-cycle control, intracellular signal transduction, and transcriptional regulation. Most of these genetic defects perturb blood cell development and contribute to the emergence of abnormal hematopoietic clones. Although some of the leukemia-predisposing syndromes have been recognized for decades [e.g., Li-Fraumeni syndrome (LFS) and familial platelet disorder with associated myeloid malignancy (FPD/AMM)], many have only recently been discovered [e.g., ETV6-associated predisposition to hematopoietic malignancies (also known as thrombocytopenia 5; *THC5*)]. As a result, for many of these predisposition syndromes, the physical and clinical manifestations, laboratory features, leukemia types, and age-specific leukemia risks remain poorly defined. This incomplete understanding has led to a lack of consensus regarding the justification, utility, methods, and timing of surveillance for children affected by these syndromes.

To facilitate consensus recommendations for leukemia surveillance in children and young adults, a panel of pediatric hematologists-oncologists, geneticists, and genetic counselors met to issue as part of the AACR Childhood Cancer Predisposition Workshop. This article will highlight some of the syndromes that were discussed and the recommendations for surveillance that were developed. Because of space limitations, this

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doi: 10.1158/1078-0432.CCR-17-0428

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**Table 1.** Syndromes predisposing to childhood-onset acute leukemia or BMF/MDS

Gene (syndrome)	Inheritance (OMIM#)	Hematopoietic malignancies	Associated manifestations
<i>TP53</i> (Li-Fraumeni)	AD (151623)	Low hypodiploid B-ALL (tMDS/AML)	High risk of other cancers (9)
<i>PAX5</i> (susceptibility to ALL 3)	AD (615545)	B-ALL	
<i>CEBPA</i> ( <i>CEBPA</i> -associated predisposition to AML)	AD (601626)	AML	
<i>ETV6</i> (thrombocytopenia, type 5)	AD (616216)	B-ALL (MDS, AML, MM)	Thrombocytopenia
<i>RUNX1</i> (FPD/AMM)	AD (601399)	AML (T-ALL)	Thrombocytopenia
<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i> (mismatch repair cancer syndrome)	AR (276300)	NHL (T-ALL, B-ALL, AML)	Parents at risk for colon cancer (10)
Down syndrome/trisomy 21	Sporadic (190685)	ALL, AML	Multisystem
<i>BLM</i> (Bloom syndrome)	AR (210900)	NHL (AML, MDS, ALL)	Short stature, photosensitivity, immunodeficiency, other cancers (11)
<i>NBN</i> (Nijmegen breakage syndrome)	AR (251260)	NHL (T-ALL)	Cerebellar ataxia, skeletal abnormalities, immunodeficiency, other cancers (11)
<i>ATM</i> (ataxia-telangiectasia)	AR (208900)	T-ALL (NHL, HL, AML)	Cerebellar ataxia, immunodeficiency, ocular telangiectasias (11)
<i>NFI, PTPN11, CBL</i> , others (RAS-activating syndromes)	AD (162200, 163950, 613563)	JMML (tMPN, AML, MDS)	Cafe au lait spots, Lisch nodules, neurofibromas, schwannomas, brain tumors (NFI); dysmorphic facies, congenital heart anomalies, short stature, cryptorchidism (PTPN11; ref. 8)
<i>FANCA-E, BRCA, RAD51D</i> , others (Fanconi anemia)	AD, AR, XLR (607139, 613899)	AML (MDS, ALL)	Short stature, skeletal anomalies, other malformations, head and neck cancer, BMF (11)
<i>TERT, TERC, DKC1</i> , others (dyskeratosis congenita)	AD, AR, XLR (305000)	AML (MDS) <sup>a</sup>	Nail dystrophy, lacy skin pigmentation, oral leukoplakia, BMF, pulmonary fibrosis, hepatic fibrosis, head and neck cancer (11)
<i>ELANE, HAX1</i> , others (severe congenital neutropenia)	AD, AR, XLR (202700, 605998)	AML (MDS)	Neutropenia, recurrent infections, neurocognitive abnormalities
<i>RPS19, RPL5, RPL11</i> , others (Diamond-Blackfan anemia)	AD, AR (603474)	MDS (AML) <sup>a</sup>	Macrocytic anemia, short stature, congenital anomalies
<i>SBDS</i> (Shwachman-Diamond syndrome)	AR (260400)	MDS (AML)	Short stature, pancreatic insufficiency, BMF
<i>GATA2</i>	AD (601626, 614172)	MDS (AML)	Immunodeficiency, lymphedema, deafness, hypertelorism, hydrocele, other congenital anomalies
Monosomy 7	AR (252270)	MDS (AML)	
<i>SAMD9</i> (MIRAGE syndrome)	AD (617053)	MDS	Adrenal hypoplasia, severe infections, developmental delay, chronic diarrhea, thrombocytopenia, anemia
<i>SAMD9L</i> (ataxia-pancytopenia syndrome)	AD (159550)	MDS, AML	Ataxia, BMF

Abbreviations: AD, autosomal dominant; AML, acute myeloid leukemia; AR, autosomal recessive; B-ALL, B-cell acute lymphoblastic leukemia; BMF, bone marrow failure; HL, Hodgkin lymphoma; JMML, juvenile myelomonocytic leukemia; MIRAGE, myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; T-ALL, T-cell acute lymphoblastic leukemia; tMDS, therapy-associated myelodysplastic syndrome; tMPN, transient myeloproliferative disorder; XLR, X-linked recessive.

<sup>a</sup>The risk for childhood MDS/AML in dyskeratosis congenita and Diamond-Blackfan anemia remains to be defined.

article does not include specific syndromes such as those associated with germline *ANKRD26* and *DDX41* mutations, for which there are currently no published reports of leukemia or myelodysplastic syndrome (MDS) in affected children. For a more comprehensive description of the leukemia-predisposing conditions, the readers are referred to Table 1 and several excellent recent reviews (2–7), some of which describe management suggestions for affected children (3) and adults (7). For recommendations regarding surveillance for solid tumors in those syndromes in which leukemia occurs among a spectrum of other cancers, see other articles in this *CCR* Pediatric Oncology Series (8–11).

## The Leukemia Predisposition Syndromes

### Syndromes in which leukemia occurs among a spectrum of other cancers

**LFS (OMIM #151623).** LFS is an autosomal dominant cancer predisposition syndrome caused by germline mutations in the *TP53* gene, which encodes the critical TP53 tumor suppressor protein. LFS is characterized by a high risk for a number of tumor types, including acute leukemia (9, 12). Indeed, leukemia was one of the defining cancers of LFS in its original descriptions and

accounts for 3% to 5% of all LFS cancers (12, 13). The relative risk of leukemia in individuals with LFS is estimated to be 6-fold higher than the general population, developing predominantly in *TP53* mutation carriers less than 45 years old (14). The leukemias occurring in affected children tend to be low-hypodiploid acute lymphoblastic leukemia (ALL), most commonly of B-cell origin, although other leukemia subtypes and therapy-associated leukemias have also been reported (15). Low-hypodiploid ALL is defined by leukemia cells containing 32 to 39 chromosomes; remarkably, up to 40% of children with low-hypodiploid B-ALL harbor germline *TP53* mutations (16). Childhood hypodiploid ALL is associated with a poor prognosis, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) is often recommended, particularly for those with minimal residual disease after completion of induction (17). Thus, a diagnosis of low-hypodiploid ALL in a child should trigger genetic counseling and consideration of testing for LFS, as the result may influence therapeutic decision making and donor choice. For example, if a matched related HSCT is to be used, relatives who test negative for the familial *TP53* mutation would be the preferred donors. In addition, knowing the germline *TP53* mutation status of the patient may be a consideration in determining pretransplant

conditioning regimens, particularly with respect to use of total body irradiation (9). Strategies for tumor surveillance have been described for LFS (7, 12, 18), but their impact on improving outcomes for those who develop leukemia remains unknown.

**Constitutional mismatch repair deficiency (OMIM #276300).** Constitutional mismatch repair deficiency (CMMRD; also known as mismatch repair cancer syndrome or bi-allelic mismatch repair deficiency) is a rare, autosomal recessive syndrome caused by biallelic mutations in the genes encoding the mismatch repair proteins, including *MLH1*, *MSH2*, *MSH6*, *PMS2*, and rarely 3' deletions in *EPCAM*. Heterozygous alterations in these genes cause Lynch syndrome, an autosomal dominant disorder with a population prevalence of 1:400 (10, 19). In contrast to Lynch syndrome, which primarily predisposes to adult-onset cancers of the colon and endometrium, CMMRD confers a very high risk of cancers beginning in childhood and continuing through adulthood (20, 21). Individuals with CMMRD are at particularly high risk for brain, gastrointestinal, and hematopoietic cancers. Approximately one third of affected individuals develop lymphoma or leukemia, with a median age at diagnosis of 6 years (range, 0.4–30 years; ref. 22). Non-Hodgkin lymphomas (NHL), commonly of T-cell origin, are the most frequently reported hematopoietic cancer. Individuals with CMMRD also develop acute leukemias, including T- and B-cell ALL and acute myeloid leukemia (AML). Affected individuals appear to tolerate therapy as well as those without CMMRD, yet they are prone to relapse and development of second primary cancers (22). Expert-based recommendations for surveillance have been published (23, 24). Although these recommendations do not strongly advocate for intensive leukemia surveillance, they note that regular monitoring may add to our knowledge of the natural history of hematopoietic malignancies when they occur in the context of CMMRD (24).

**RAS activation syndromes (neurofibromatosis 1, OMIM #162200; Noonan syndrome OMIM #163950; Noonan-like CBL syndrome, OMIM #613563).** Several overlapping syndromes with multisystem involvement, including neurofibromatosis 1 (NF1), Noonan syndrome, and Noonan-like CBL syndrome (CBL), are characterized by mutations leading to activation of the RAS signaling pathway and increased risk of leukemia. The risk is particularly high for juvenile myelomonocytic leukemia (JMML), a disease inextricably linked with RAS activation, as mutations in RAS pathway genes (somatic or germline) can be found in at least 90% of cases (25). NF1 is caused by mutations in the *NF1* gene and associated with a high risk of solid tumors, including brain tumors, peripheral nerve sheath tumors, and rhabdomyosarcoma (8). Although less frequently encountered, patients with NF1 have a greater than 200-fold increase in the risk for JMML, as well as increased risk of ALL and AML (26). Noonan syndrome is caused by mutation in one of at least seven different genes. Up to 10% of patients with Noonan syndrome caused by mutation in *PTPN11* or *KRAS* develop a transient myeloproliferative disease in infancy that closely resembles JMML. Although it is generally benign and self-resolving, it can cause significant morbidity and mortality, and in rare patients, it can progress to frank JMML (27). Patients with Noonan syndrome caused by mutation in *PTPN11* or *SOS1* are also at increased risk of B-ALL, most with high hyperdiploidy (28). CBL syndrome is caused by germline mutations in the *CBL* gene, which encodes the Casitas B-lineage lymphoma protein, an E3 ubiquitin ligase that functions to negatively regulate intracel-

lular signaling induced by receptor tyrosine kinases (29). Although patients with CBL syndrome are at increased risk to develop myeloproliferation and JMML, in some patients, myeloproliferation regresses despite loss of heterozygosity of the *CBL* locus in hematopoietic cells (27). Existing guidelines for the care of patients with NF1 and Noonan syndrome do not advocate for routine surveillance for leukemia in asymptomatic patients (30, 31). There are currently no guidelines for individuals with CBL syndrome. Recommendations from the AACR Pediatric Cancer Working Group for surveillance for solid tumors in children with NF1 are addressed in a companion article (8), which is part of this CCR Pediatric Oncology Series.

**Fanconi anemia (OMIM #227650 and others).** Fanconi anemia is a genetically and phenotypically diverse syndrome, characterized by DNA damage repair defects, bone marrow failure (BMF), and cancer predisposition. It is caused by biallelic mutations in one of at least 19 genes involved in DNA damage repair (32). Most patients have congenital anomalies, including short stature, abnormal thumbs, and café au lait spots, although some patients have no physical manifestations and are only diagnosed when presenting with cytopenias. BMF presents in childhood in most patients (33). Patients with Fanconi anemia have a very high relative risk of solid tumors and leukemia. Head and neck squamous cell cancer is the most common solid tumor, with a relative risk of about 600 in those with Fanconi anemia compared with those without the condition, usually presenting in adulthood (34, 35). AML is the most common hematologic malignancy, accounting for more than 80% of leukemias (35). Patients with biallelic mutations in *FANCD1/BRCA2* have the most distinctive phenotype with severe congenital anomalies and a cumulative incidence of leukemia of 80% by 10 years of age and of any malignancy of more than 90% by 7 years of age (35). Guidelines for the management of patients with Fanconi anemia, including leukemia surveillance, have been published and advocate for proactive monitoring of the peripheral blood and bone marrow for progressive BMF, MDS, and/or clonal evolution (11, 36).

#### Syndromes in which leukemia is the primary malignant manifestation

**Susceptibility to ALL 3 (OMIM #615545).** Germline mutations in *PAX5*, the gene encoding a critical B-cell transcription factor, have recently been shown to increase the risk for precursor B-ALL. Three unrelated families have been described thus far in which multiple individuals carried identical missense mutations (p.G183S) affecting the octapeptide domain of the encoded paired box 5 protein, suggestive of autosomal dominant inheritance (37, 38). All individuals with leukemia who were tested were carriers of this mutation and diagnosed with a specific subtype of B-ALL characterized by somatic loss of the wild-type *PAX5* allele, mostly by the formation of an isochromosome 9 or dicentric rearrangements involving 9q. Multiple *PAX5* mutation carriers unaffected by leukemia were also identified, suggesting reduced penetrance, but more families are needed to provide an accurate risk estimate. As all leukemias were diagnosed in childhood in the reported kindreds, it has been speculated that the risk for developing leukemia strongly decreases after the first decade of life. No recommendations for leukemia surveillance specific to this syndrome have been reported.

**GATA2-associated predisposition to MDS/AML (OMIM #614038; #614172).** Pathogenic variants in *GATA2*, the gene encoding the

GATA2 transcription factor, are related to autosomal dominant predisposition to MDS with progression to AML (39, 40). Non-syndromic as well as syndromic presentations have been described, with syndromic cases showing immune deficiency in MonoMAC syndrome (41) and lymphedema in Emberger syndrome (42). Most germline mutations are missense and occur in highly conserved codons encoding a C-terminal zinc finger domain (ZF2) required for DNA binding and involved in protein:protein interactions. Other mutations occur throughout the five coding exons and can lead to total loss of gene function. In one report, up to 7% of primary pediatric MDS cases were attributed to germline GATA2 mutations (43). Furthermore, in adolescents with MDS and monosomy 7, as many as 72% appear to harbor germline GATA2 mutations, and the majority of these are *de novo* (43). Germline mutations in GATA2 were also associated with trisomy 8 (43). At present, all described germline mutations predispose individuals to MDS/AML, infectious diseases, and cytopenias, but data suggest that only complete haploinsufficiency or loss of function of GATA2 predispose to lymphedema (40). Human papillomavirus and Epstein-Barr virus infections contribute to development of additional neoplasms, which also cause significant morbidity and mortality (40). Although there are some clear cases of unaffected GATA2 mutation carriers, about 50% of patients present in childhood or young adulthood with associated illnesses, including hematopoietic malignancy (40). Somatic mutations in *ASXL1* are found in the hematopoietic tissues of 30% of individuals with germline GATA2 mutations, and in four of five of those tested who developed chronic myelomonocytic leukemia, suggesting that a cooperative second "hit" is required for malignant transformation (44). To correct hematopoietic and immunologic defects, the emerging standard of care involves allo-HSCT from a GATA2 mutation-negative donor, particularly for those with worsening MDS and severe or recurrent infections. Routine evaluation of the bone marrow for dysplasia, excess blasts, or abnormal cytogenetics has been advocated by some investigators, as it may inform the timing of allo-HSCT (40).

***CEBPA-associated predisposition to AML (OMIM #601626; #116897).*** Familial AML due to germline mutations in *CEBPA*, the gene encoding a key transcription factor involved in the development of granulocytes from common myeloid progenitors (45, 46), is an autosomal dominant condition in which AML typically occurs earlier and more frequently than is the case in sporadic AML. At least 45% of individuals with germline *CEBPA* mutations develop AML, most commonly in the third decade, but onset has been reported as early as the first few years of life (47, 48). Approximately 5% to 14% of all AML patients have mono-allelic or biallelic somatic *CEBPA* mutations in their leukemic cells. Among those whose leukemias exhibit biallelic mutations, 7% to 11% harbor one of these mutations in the germline (49). Germline mutations occur most often as frameshift mutations affecting the 5' end of the gene. Leukemias developing in the context of *CEBPA*-associated predisposition to AML usually show acquisition of somatic mutations affecting the 3' end of the remaining *CEBPA* allele (47). Rarely, 3' end *CEBPA* mutations have been reported as germline events in families exhibiting incomplete leukemia penetrance (48). Individuals with germline *CEBPA* mutations tolerate AML therapy, and long remissions can be induced. Nevertheless, mutation carriers are prone to recurrent disease, with subsequent leukemias harboring distinct somatic 3'

*CEBPA* mutations. These data suggest that the recurrent leukemias reflect development of second primary AML rather than relapse (47). Because of the high rate of development of multiple AMLs within germline *CEBPA* mutation carriers, allo-HSCT has been recommended as a curative therapy (7). However, given the long remissions between leukemia occurrences, chemotherapy-only regimens may be appropriate.

#### **Leukemia predisposition syndromes with associated thrombocytopenia**

***Thrombocytopenia, type 5 (OMIM #616216).*** Thrombocytopenia, type 5 (THC5) is an autosomal dominant syndrome of thrombocytopenia, red cell macrocytosis, and leukemia predisposition that is associated with germline mutations in the gene encoding the transcription factor *ETV6* (50–53). The thrombocytopenia is variable and generally not severe, but some patients have an increased risk of bleeding (50, 51). Bone marrow evaluation may reveal dysplasia and/or hypolobulated megakaryocytes. About one fourth of *ETV6* mutation carriers have been reported to develop acute leukemia and/or MDS. Although rare cases of AML and other myeloid malignancies have been described, most of the leukemias developing in individuals with THC5 are lymphoid with a B-cell precursor phenotype. Indeed, in a cohort of over 4,000 apparently sporadic B-ALL cases, approximately 1% were found to harbor germline *ETV6* variants thought to contribute to leukemogenesis (52). Less often, solid tumors have been observed, and a recent report suggests that a germline *ETV6* variant is associated with increased risk of colorectal cancer as adults (54). Therefore, it is possible that germline *ETV6* mutations lead to a more general cancer predisposition, with B-ALL as the greatest risk.

***FPD/AMM (OMIM #601399).*** FPD/AMM is an autosomal dominant condition caused by germline mutations in *RUNX1*, a transcription factor and master regulator of hematopoiesis, that increases risk for myeloid malignancies and occasionally T-ALL (55–57). The clinical presentation varies but typically includes a lifelong mild to moderate bleeding tendency due to quantitative and/or functional platelet defects (58). Individuals with FPD/AMM who have apparently normal platelet counts and no bleeding history have also been reported (55). The incidence of transformation to MDS/AML in individuals with germline *RUNX1* mutations is variable among families but ranges up to 40% or more, with patients presenting at any age (reported range of 6–76 years; mean 33 years; ref. 58). The evolution to leukemia may depend on the type of germline mutation, and recent studies report that those exerting a dominant-negative effect have a higher risk for leukemia development (55, 59). These dominant-negative mutations typically disrupt the DNA-binding or transactivating capacities of *RUNX1* (60), likely deregulating expression of hematopoietic stem and progenitor cell target genes. Transformation to AML is often associated with acquisition of a second somatic mutation involving the remaining *RUNX1* allele (61). Additional acquired mutations involve *GATA2* and *CDC25C* (reported in a Japanese cohort) as well as genes encoding signaling intermediates (*FLT3*, *KRAS*, *KIT*, *MPL*, *CBL*, *NOTCH1*), tumor suppressors (*TP53*, *WT1*, *PHF6*, *BCORL1*), cohesins (*RAD21*), splicing factors (*SRSF2*, *SF3B1*), or proteins involved in regulating DNA methylation (*TET2*, *DNMT3A*; refs. 62–64). In addition to germline mutations, 21q chromosomal deletions causing *RUNX1* haploinsufficiency may lead to



thrombocytopenia and rarely to MDS/AML (65). Chromosomal translocations or somatic mutations involving *RUNX1* have also been observed in sporadic ALL, AML, chronic myelomonocytic leukemias, and early-stage MDS syndromes, highlighting the importance of *RUNX1* in leukemogenesis (66).

#### Recently described leukemia predisposition syndromes

**Ataxia-pancytopenia syndrome (OMIM #159550) and myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy syndrome (OMIM #617053).** Ataxia-pancytopenia syndrome (APS) and myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) syndrome are caused by mutations in *SAMD9L* and *SAMD9*, respectively, likely resulting in gain of function (67, 68). These genes are both located on chromosome 7q21.2 and have overlapping functions in the processes involved in endosome fusion (68, 69). APS was described many years ago as a familial syndrome associated with progressive ataxia, BMF, and AML (70), and only recently has it been attributed to germline heterozygous missense mutations in *SAMD9L* (67). The phenotype is variable, with the onset of neurologic symptoms ranging from 10 to 62 years of age and inconsistent presence of anemia and/or thrombocytopenia, which appear not to correlate with the severity of neurologic findings (67). AML was described in two children with APS, one of whom had a prior history of MDS (70). MIRAGE syndrome is a recently described multisystem disorder identified through the study of individuals with adrenal hypoplasia, severe infections, developmental delay, chronic diarrhea, pulmonary dysfunction, thrombocytopenia, and usually anemia (68). Two of 11 patients with *SAMD9* variants developed MDS. These diseases share an association with monosomy 7, which leads to loss of heterozygosity of the mutated *SAMD9L* or *SAMD9* genes during progression of MDS/BMF. This observation has suggested a common pathophysiology in bone marrow dysfunction and leukemogenesis. As reported, these disorders are otherwise quite distinct. Currently, there is no published information discussing leukemia surveillance for these conditions.

#### Considerations Regarding Surveillance for Leukemia and/or MDS

Tumor surveillance is directed at the early detection of neoplasms, with the overall aim to minimize morbidity and mortality by allowing for the prompt initiation of treatment. Surveillance is often instituted for individuals with predisposition to solid tumors, where early detection may enable less extensive surgical approaches and allow for other reductions in therapy, but it can also prove beneficial for individuals at risk for hematopoietic cancers. However, it is important to recognize that there are inherent differences in the natural history of acute lymphoid versus myeloid malignancies (or MDS), and that these differences may impact decisions regarding the types and frequency of surveillance testing. For example, due to the rapid onset of acute malignancies such as NHL, ALL, and some cases of hereditary AML, there is limited evidence that surveillance facilitates early detection, improves outcomes, or confers other medical benefits. In contrast, some hereditary forms of AML, particularly those occurring in the context of MDS or BMF syndromes (11), may be more indolent, evolving over months to years. In children with these conditions, it is often possible to detect progressive cytopenias, bone marrow dysplasia, and the emergence of abnormal

clones exhibiting specific cytogenetic abnormalities or somatic mutations that are harbingers of eventual leukemia. For some of these children, such as those with *GATA2*-associated predisposition to MDS/AML, Fanconi anemia, Shwachman–Diamond syndrome (SDS), and severe congenital neutropenia (SCN), outcomes are improved when allo-HSCT is undertaken before acute leukemia develops (3). In these cases, preemptive treatment with allo-HSCT may preclude the need for intensive AML therapies, which cause prolonged cytopenias and can increase the risk for infection, relapse, second primary neoplasms, and even treatment-related deaths. By correcting the hematopoietic defect, allo-HSCT can also minimize or reverse other comorbidities, such as immunodeficiency and pulmonary alveolar proteinosis in *GATA2*-associated predisposition to MDS/AML (71). Consensus guidelines for the management of Fanconi anemia (36), dyskeratosis congenita (72), SDS (73), and Diamond–Blackfan anemia (74) have been published. They share features that were considered by the panel in developing the recommendations outlined below (Table 2).

#### Surveillance Recommendations

##### 1. Referral to centers with expertise in hereditary hematologic malignancies

Consultation with, or referral to, hematologists-oncologists, geneticists, genetic counselors, or other providers familiar with the leukemia predisposition syndromes enables coordinated and comprehensive care. Counseling of children and families who have or are thought to have leukemia-predisposing syndromes requires knowledge of the biology of these diseases and the unique social and ethical issues associated with genetic testing of children for cancer predisposition (75, 76). Such expertise facilitates genetic testing by informing which tissue should be analyzed (e.g., peripheral blood vs. cultured skin fibroblasts) and the type of testing to be done (e.g., single gene, gene panel, comprehensive gene testing, targeted familial mutation testing, etc.). Expert providers may also guide referral to appropriate specialists and lead discussions with families about recurrence risk, management of oncologic and nononcologic features, cancer surveillance, and patient and family involvement in research.

At each visit, patients should undergo a complete history and physical examination to assess for signs and symptoms of leukemia, MDS, and/or other nononcologic comorbidities. Providers should collect and document changes in the family history, discuss new scientific and clinical developments, and offer patients and families the opportunity to be enrolled in new registries or other clinical or translational research investigations. At a minimum, patients should be seen annually; however, a patient's medical and/or family history or provider preference may dictate more frequent visits (see below, "Surveillance testing").

##### 2. Education about the signs and symptoms of leukemia

Patients and family members should be provided with information about the manifestations of leukemia and MDS, such as progressive fatigue, pallor, fever, petechiae, bruising, splenomegaly, and lymphadenopathy. They should be made aware that the presence of these signs and symptoms should prompt a visit to a physician for evaluation, including physical examination and laboratory testing for possible hematologic abnormalities [e.g., complete blood count (CBC)].

**Table 2.** Recommended surveillance for children with predisposition to leukemia or MDS

At diagnosis	At follow-up <sup>a</sup>
Genetic counseling/testing of patient and other family members	Patient counseling and education
Medical history <ul style="list-style-type: none"> <li>• Prior cytopenias, bleeding history, nononcologic manifestations</li> </ul>	<ul style="list-style-type: none"> <li>• Review recurrence risks</li> <li>• Discuss reproductive/family planning for children reaching adolescence or young adulthood</li> <li>• Review leukemia signs and symptoms</li> <li>• Discuss advances in the field</li> </ul>
Family history <ul style="list-style-type: none"> <li>• Review and document types of cancer and leukemia, ages at cancer or leukemia onset</li> <li>• Include history of antecedent cytopenias and/or bleeding</li> </ul>	Interval medical history
Physical examination <ul style="list-style-type: none"> <li>• Signs of leukemia, lymphoma</li> <li>• Other syndrome specific findings, including signs of solid tumors</li> </ul>	Update family history <ul style="list-style-type: none"> <li>• Review and document any new individuals with cancer or leukemia</li> <li>• Document types of cancer and leukemia, ages at cancer or leukemia onset</li> </ul>
CBC <ul style="list-style-type: none"> <li>• Manual differential</li> <li>• Reticulocyte count</li> <li>• Blood smear with morphology</li> </ul>	Physical examination CBC <sup>b</sup> Bone marrow evaluation <sup>c</sup> <ul style="list-style-type: none"> <li>• Aspirate ± biopsy</li> <li>• Morphology</li> <li>• Cytogenetics</li> </ul>
Bone marrow evaluation <ul style="list-style-type: none"> <li>• Aspirate and biopsy</li> <li>• Morphology</li> <li>• Cytogenetics</li> </ul>	Discuss enrollment in registries or other research studies
Patient/family education about signs and symptoms of cancer, including leukemia	
HSCT consultation <ul style="list-style-type: none"> <li>• Consider HLA typing and genetic testing of potential familial donors</li> </ul>	
Discuss enrollment in registries or other research studies	

Abbreviation: CBC, complete blood count.

<sup>a</sup>The interval between visits should be no more than 12 months in asymptomatic patients at lower risk of developing MDS/AML. More frequent visits (perhaps every 3–6 months) are recommended for those with higher risk of MDS/AML. The development or worsening of cytopenias or other concerning signs or symptoms may necessitate more frequent visits.

<sup>b</sup>CBC should be considered at least annually in those with normal blood counts or stable single cytopenias (see text for exceptions). Initially, for those with higher risk of MDS/AML, CBC evaluations every 3 to 4 months are suggested to determine the trajectory of blood counts. If the CBC is stable, this interval can be lengthened. Regardless of the genetic condition, if the CBC and/or differential worsen or become abnormal, they should be repeated within 2 to 4 weeks and/or a bone marrow examination should be performed.

<sup>c</sup>Annual clinical bone marrow evaluation is recommended for those at higher risk of MDS/AML, even with stable blood counts. Clinical bone marrow evaluation may be omitted in asymptomatic children with stable blood counts and lower risk of MDS/AML (e.g., LFS, Down syndrome/trisomy 21, PAX5, ETV6, CMMRD, Bloom syndrome, ataxia-telangiectasia, RASopathies, dyskeratosis congenita, Diamond-Blackfan anemia). For these latter patients, consideration could be given to completing a bone marrow evaluation for research purposes to better understand the natural history of these disorders. More frequent clinical bone marrow evaluations are recommended for those with new or worsening cytopenias.

### 3. Consultation with a transplant specialist

In recognition that allo-HSCT may be a component of care, particularly for children with worsening MDS or BMF, discussions with a transplant specialist should occur soon after a diagnosis is established. Early HLA typing of the child, siblings, and parents should also be considered. If the germline leukemia-predisposing mutation is known for the patient, genetic testing of siblings and parents should also be performed and mutation carriers excluded as stem cell donors. Pre- and posttest genetic counseling should be provided for family members being tested, as the results can have far-reaching implications beyond donor selection (77). Currently, the role for preemptive allo-HSCT for individuals with leukemia-predisposing syndromes is not known.

### 4. Surveillance testing

All patients and families should be counseled about the potential benefits and limitations of surveillance. Laboratory evaluations to monitor for leukemia and MDS include the CBC and differential, bone marrow aspiration/biopsy, and bone marrow cytogenetics. Although surveillance can be considered for all patients, the use and frequency of specific tests may vary depending on the (i) leukemia-predisposing condition, (ii) patient and family preferences, (iii) availability of insurance or other financial resources to cover the costs of testing, and (iv) differences in health care approaches throughout the world.

The group agreed that surveillance via invasive or frequent laboratory testing is most likely to benefit children at greatest risk

for MDS, or AML that occurs in the context of MDS (e.g., Fanconi anemia, SDS, SCN, *GATA2*-associated predisposition to MDS/AML, familial monosomy 7, FPD/AMM, *CEBPA*-associated predisposition to AML), versus those at greatest risk for ALL, NHL, or JMML (e.g., LFS, susceptibility to ALL 3, CMMRD, *THC5*, Down syndrome/trisomy 21, Bloom syndrome, ataxia telangiectasia, RASopathies). With this in mind, the recommendations below were developed. It is important to recognize that these recommendations were designed for patients who are asymptomatic with stable hematologic parameters. At a minimum, it was agreed that laboratory testing should be completed annually; however, the frequency and type of testing may need to be customized depending on a patient's specific clinical situation. Children who have completed treatment for a primary hematopoietic malignancy should be closely monitored for recurrence as one would do for any patient regardless of the presence of an underlying predisposition. However, due to the increased risk for second hematopoietic malignancies and/or MDS, children with predisposing conditions should eventually be transitioned to longer-term or even life-long surveillance, as outlined below.

(i) **CBC.** All patients should have a CBC with manual differential at the initial visit. This CBC will establish a baseline for future comparison. Of particular importance within the CBC are (i) examination for leukemic blasts or dysplastic changes; (ii) enumeration of the platelet count for those at risk for thrombocytopenia; and (iii) examination of the MCV, because macrocytosis

can be a manifestation of MDS. Given the paucity of data to support the utility of frequent CBCs as a screening tool for ALL and NHL, it was suggested that follow-up CBC testing be minimized for children whose underlying genetic condition places them at highest risk for acute lymphoid malignancies. Rather, these children could undergo follow-up CBCs only when there are symptoms or physical examination findings concerning for these malignancies.

In contrast, for children at high risk for MDS/AML, routine follow-up CBCs should be used to monitor for disease progression. For the highest risk diseases, such as Fanconi anemia, CBCs should be performed every 3 to 4 months, even if counts are stable (36). For other conditions, CBCs should be performed more frequently initially (perhaps every 3–4 months), with the length of time between evaluations lengthening to every 6 to 12 months if the blood counts remain stable. Regardless of the underlying genetic condition, if a patient develops cytopenia of one or more lineages, the CBC should be repeated within 2 to 4 weeks. For those whose CBC worsens or remains abnormal over two or more measurements, a bone marrow aspirate/biopsy with cytogenetics should be performed.

**(ii) Bone marrow aspiration and biopsy with cytogenetic analysis.** A baseline bone marrow aspirate and biopsy with cytogenetic analysis should be considered for all patients, particularly those with significant abnormalities on the CBC at diagnosis and those at greatest risk for MDS. Although the group did not recommend routine follow-up bone marrow aspirate or biopsy for children at greatest risk for ALL or NHL, annual follow-up bone marrow evaluation with cytogenetic analysis should be offered for children at greatest risk for BMF and/or MDS/AML. In these children, the bone marrow should be examined for changes in cellularity; worsening dysplasia; evidence of leukemic blasts; evolution of hematopoietic clones with abnormal, high-risk cytogenetics (e.g., monosomy 7); or development of high-risk somatic mutations. Although the risk of disease progression associated with newly

acquired somatic mutations has yet to be defined, if these or any of the other features noted are present, or if the patient develops a progressive transfusion requirement, allo-HSCT should be considered.

## Conclusions

Despite examination of the best scientific evidence available, the working group found that much of the published data regarding surveillance for individuals with hereditary predisposition to leukemia are currently found in small case series or are based on provider and/or family preference. Nonetheless, the potential benefits and limitations of surveillance were thoroughly considered, and the above recommendations developed. As diagnostic technologies improve and our understanding of the leukemia risks in these conditions increases, the recommendations presented above will require updating. Similarly, as more is learned about the prognostic implications of clonal hematopoiesis and acquired somatic mutations, it is likely that these parameters will be incorporated into future protocols. Creation of research networks and registries for patients with leukemia-predisposing conditions will enable collection of the critical data needed to inform development of improved surveillance and treatment guidelines for children and adults with these complex conditions.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Acknowledgments

The authors express their great thanks to Michael Powell, Jocelyn Voorhees, and the American Association for Cancer Research for organizing this meeting. They are also grateful to Lucy Godley and Akiko Shimamura for their careful review of this manuscript and many helpful comments.

Received February 14, 2017; revised March 27, 2017; accepted April 20, 2017; published online June 1, 2017.

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*Clin Cancer Res* 2017;23:e14-e22.

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