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. See all articles in the online-only CCR Pediatric Oncology Series.

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 review this 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
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; 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...
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 malignancies when they occur in the context of CMMRD (24). Although these recommendations do not strongly advocate for routine surveillance for leukemia in asymptomatic patients, they note that regular monitoring is 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.

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 octopeptide 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). Nonsyndromic 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 monoallelic 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 #612616). 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 heterogeneous 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)].
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. 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 long-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) 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

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

<table>
<thead>
<tr>
<th>At diagnosis</th>
<th>At follow-up^*</th>
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<tbody>
<tr>
<td>Genetic counseling/testing of patient and other family members</td>
<td>Patient counseling and education</td>
</tr>
<tr>
<td>Medical history</td>
<td>• Review recurrence risks</td>
</tr>
<tr>
<td>• Prior cytopenias, bleeding history, nononcologic manifestations</td>
<td>• Discuss reproductive/family planning for children reaching adolescence or young adulthood</td>
</tr>
<tr>
<td>Family history</td>
<td>• Review leukemia signs and symptoms</td>
</tr>
<tr>
<td>• Review and document types of cancer and leukemia, ages at cancer or leukemia onset</td>
<td>• Discuss advances in the field</td>
</tr>
<tr>
<td>• Include history of antecedent cytopenias and/or bleeding</td>
<td>Interval medical history</td>
</tr>
<tr>
<td>Physical examination</td>
<td>Update family history</td>
</tr>
<tr>
<td>• Signs of leukemia, lymphoma</td>
<td>• Review and document any new individuals with cancer or leukemia</td>
</tr>
<tr>
<td>• Other syndrome specific findings, including signs of solid tumors</td>
<td>• Document types of cancer and leukemia, ages at cancer or leukemia onset</td>
</tr>
<tr>
<td>CBC</td>
<td>Physical examination</td>
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<tr>
<td>• Manual differential</td>
<td>CBC^c</td>
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<tr>
<td>• Reticulocyte count</td>
<td>Bone marrow evaluation^d</td>
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<td>• Blood smear with morphology</td>
<td>• Aspirate ± biopsy</td>
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<tr>
<td>Bone marrow evaluation</td>
<td>• Morphology</td>
</tr>
<tr>
<td>• Aspirate and biopsy</td>
<td>• Cytogenetics</td>
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<tr>
<td>• Morphology</td>
<td>Discuss enrollment in registries or other research studies</td>
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<tr>
<td>• Cyto genetics</td>
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<tr>
<td>Patient/family education about signs and symptoms of cancer, including leukemia</td>
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<td>HSCT consultation</td>
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<tr>
<td>• Consider HLA typing and genetic testing of potential familial donors</td>
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<tr>
<td>Discuss enrollment in registries or other research studies</td>
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Abbreviation: CBC, complete blood count.

^a 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.

^b 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.

^c 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.

^d 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).
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.

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