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Genetic predisposition to myelodysplastic syndrome and acute myeloid leukemia in children and young adults

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Abstract

Myelodysplastic syndrome (MDS) is a clonal blood disorder characterized by ineffective hematopoiesis, cytopenias, dysplasia and an increased risk of acute myeloid leukemia (AML). With the growing availability of clinical genetic testing, there is an increasing appreciation that a number of genetic predisposition syndromes may underlie apparent *de novo* presentations of MDS/AML, particularly in children and young adults. Recent findings of clonal hematopoiesis in acquired aplastic anemia add another facet to our understanding of the mechanisms of MDS/AML predisposition. As more predisposition syndromes are recognized, it is becoming increasingly important for hematologists and oncologists to have familiarity with the common as well as emerging syndromes, and to have a systematic approach to diagnosis and screening of at risk patient populations. Here, we provide a practical algorithm for approaching a patient with a suspected MDS/AML predisposition, and provide an in-depth review of the established and emerging familial MDS/AML syndromes caused by mutations in the *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, *SRP72* genes. Finally, we discuss recent data on the role of somatic mutations in malignant transformation in acquired aplastic anemia, and review the practical aspects of MDS/AML management in patients and families with predisposition syndromes.

Keywords

genetic predisposition; bone marrow failure; familial MDS/AML; aplastic anemia; clonal hematopoiesis

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Introduction

Myelodysplastic syndrome (MDS) is defined by the World Health Organization (WHO)[1] as a clonal hematopoietic disorder characterized by ineffective hematopoiesis, cytopenias, single or multilineage dysplasia, and an increased propensity to evolve to acute myeloid leukemia (AML). Primary or *de novo* MDS has been traditionally considered a disease of aging, with the median age of onset in the 7th decade; in contrast, MDS in children and young adults is very uncommon (Figure 1A). Childhood MDS has been historically stratified into the categories of *de novo* or primary MDS, and "secondary" MDS, defined as MDS arising from classical inherited bone marrow failure (BMF) syndromes, acquired BMF, and therapy-related MDS following radiation or chemotherapy (Figure 2A) [1]. Based on recent advances in defining mechanisms of leukemogenesis and the role of clonal hematopoiesis as a predisposition factor to myeloid malignancies, there is an increasing appreciation that states associated with clonal hematopoiesis frequently underlie what was previously considered *de novo* or primary MDS. Such states include age-related stem cell depletion or exhaustion in the elderly [2–4], and acquired or inherited disorders of bone marrow in children and young adults(Figure 2B).

As more patients and families with predisposing conditions are identified, it is increasingly important for the practicing physician to have a working knowledge of the approach to evaluation and management of MDS/AML predisposition syndromes. A number of recent excellent reviews have discussed the diagnostic features of the classical bone marrow failure (BMF) syndromes and well-established familial MDS/AML syndromes [5–10]. However, clinical management guidelines are largely lacking [11]. In this review, we aim to provide a conceptual framework for evaluating an underlying genetic predisposition in the young population with MDS and AML. We will then provide an in-depth review focusing on emerging familial MDS/AML syndromes and MDS predisposition in acquired aplastic anemia. Finally, we will put forth practical considerations for diagnostic assessment and patient management.

Epidemiology of MDS

Myelodysplastic syndrome remains largely a disease of aging, with a median age at diagnosis of 71–76 years [12,13], largely mirroring the frequency of age-related clonal hematopoiesis (Figure 1A). National registry data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) indicates an annual rate of MDS of 0.2 per 100,000 for patients under 40 years of age, but a ~300-fold higher incidence of 58 per 100,000 in patients over 80 years [14].

Approximately 10–20% of myeloid malignancies are associated with cytotoxic therapy, most commonly alkylating agents, ionizing radiation, and DNA topoisomerase II inhibitors [1]. Although this review focuses on the MDS/AML predisposition syndromes that are caused by single gene alterations, there is mounting evidence that a variety of modifier genes incrementally contribute to MDS/AML susceptibility, frequently via interaction with environmental exposures. Several population polymorphisms, such as the poor metabolizing variants of the cytochrome P450 enzymes and the common polymorphisms of detoxifying

enzymes of the glutathione-S-transferase family, have been linked to the development of AML[15–17].

For the 80–90% of MDS which is not therapy-related, there are several differences in disease characteristics between MDS occurring in the young compared to the elderly, suggesting distinct leukemogenic drivers in these age groups (Figure 1B)[18,19]. At the population level, first-degree relatives of the under 21 year-old patients with MDS and AML are at a significantly increased risk of AML/MDS (relative risk 6.5×) compared to the general population; in contrast, this familial aggregation is not seen for the MDS population as a whole, underscoring a significantly greater contribution of genetic factors to leukemogenesis in the young[20].

When, Why, and How to Suspect and Evaluate for an MDS/AML Predisposition Syndrome?

For patients presenting with an apparent primary MDS at an age significantly outside the expected age range (Figure 1A)—loosely defined as younger than 50 years—it is prudent to scrutinize the history for signs suggestive of an underlying predisposition syndrome. These can range from a known history of a classical bone marrow failure (BMF) syndrome or a strong family history of MDS/AML, to more subtle personal or family history and physical exam findings that require familiarity with predisposition syndromes and a high index of suspicion to make the correct diagnosis (Table I). Importantly, the phenotypic spectrum of predisposition syndromes remains largely undefined, and, for many of the syndromes, incomplete penetrance and variable expressivity may limit the ability to diagnose these disorders based solely on personal or family history. Finally, although there are no cytogenetic or molecular findings that are specific for genetic predisposition-associated MDS, there are recurrent chromosomal and molecular findings that should raise suspicion for an underlying genetic predisposition [21–25] (Table II).

Diagnosing an underlying predisposition syndrome significantly impacts both immediate treatment decisions such as the choice and timing of chemotherapy, as well as potential allogeneic stem cell transplantation considerations including the choice of pre-transplant conditioning and screening of sibling donors. Inadvertent transplantation with stem cells from a sibling donor carrying an unrecognized germline predisposition syndrome can lead to devastating complications including failure to engraft, severe transplant-related toxicity, and the development of donor-derived leukemia [26–30]. Longer term implications of having an underlying predisposition syndrome frequently include an increased risk of non-hematologic malignancies, particularly in disorders such as Fanconi Anemia (FA) and Dyskeratosis Congenita (DC) [22,31,32]. Such conditions require genetic counseling and conscientious cancer screening of both the patient and their affected family members. Thus, it is imperative that pediatric and young adult patients, as well as older patients with a suggestive personal or family history undergo a rapid and systematic evaluation for an underlying MDS/AML predisposition syndrome. Importantly, although transformation to MDS/AML is the most feared late complication of genetic predisposition syndromes, refractory cytopenias and associated complications are the most common cause of mortality in this population,

and establishing the correct diagnosis is equally important for patients with predisposition presenting with cytopenias as for those presenting with MDS/AML.

From a practical standpoint, the expanding availability of clinical next-generation sequencing (NGS) has revolutionized screening for familial MDS/AML, with NGS assays rapidly emerging as the new standard at tertiary care centers [33–37]. Although there are a number of caveats to accurate interpretation of NGS results (Table III), in cases where a patient's presentation is phenotypically ambiguous, NGS can often outperform candidate gene testing and ancillary testing both in efficiency and cost [33,38,39]. Whenever possible, genetic testing should be performed on constitutional tissue, preferably on skin fibroblasts, in order to exclude somatic mutations and to avoid false-negatives due to peripheral blood somatic mosaicism[40]. Although clinical whole exome sequencing (WES) is being increasingly utilized in the diagnosis of rare genetic disorders, currently we do not recommend familial MDS/AML screening with WES because of the substantial burden of proof required to establish disease causality for rare or novel genetic variants[41].

The complete evaluation for underlying predisposition should include metaphase cytogenetic analysis, and, in appropriate cases, single nucleotide polymorphism array studies to evaluate for smaller copy number changes beyond the resolution of metaphase karyotyping[42]. At present, we still advise to perform ancillary functional testing for the most common forms of inherited BMF: chromosomal breakage and lymphocyte telomere length measurements for the higher risk conditions FA and DC, respectively. Bone marrow flow cytometry is increasingly utilized to rapidly screen for GATA2 haploinsufficiency[43]. Flow cytometry is also used to diagnose paroxysmal nocturnal hemoglobinuria (PNH), a marker of clonal hematopoiesis in acquired aplastic anemia and, to a lesser degree, in MDS and myeloproliferative neoplasms; the presence of a PNH clone strongly suggests underlying acquired BMF and steers away from a diagnosis of inherited BMF[44] (Figure 3).

It is important to recognize that even among families with a strong history of familial MDS/AML, comprehensive genetic characterization for the currently known syndromes will lead to the diagnosis only in a fraction of families. In a 2012 study of 27 families with familial MDS/AML syndromes, Holme and colleagues screened the affected family members for mutations in *RUNX1*, *CEBPA*, *TERC*, *TERT*, *GATA2*, as well as *TET2* and *NPM1*. Pathogenic mutations were identified in 10 of the 27 families, while 17 families remained uncharacterized [45]. The causes for failure of genetic diagnosis are several-fold, including false-negative results due to the technical limitations of genetic testing (Table III) and incomplete identification of predisposition syndromes, exemplified by the discovery of five new syndromes (associated with defects in *GATA2, ANKRD26, SRP76, DDX41*, and *ETV6* genes) since 2011. As more genes and pathways are linked to MDS/AML predisposition, revisiting the diagnostic assessment with additional genetic testing may uncover an etiology. Until that time, it is essential that individuals and families with a clinical history indicative of a familial predisposition syndrome who have negative genetic testing are offered genetic counseling and are followed in manner similar to those with a known familial defect, recognizing that they are likely to carry an as yet unidentified predisposition syndrome [11].

MDS/AML Genetic Predisposition Syndromes

MDS/AML genetic predisposition syndromes can be grouped into four categories: 1) disorders associated with numerical chromosomal abnormalities (e.g. trisomy 21), which are considered unique biologic entities and will not be discussed further in this review, 2) the classical inherited BMF syndromes (e.g. FA and DC), 3) other syndromic predisposition to leukemia (e.g. Li-Fraumeni and Bloom's syndromes), and 4) emerging familial MDS/AML syndromes (e.g. *GATA2* haploinsufficiency or *RUNX1*-associated familial platelet disorder with propensity to myeloid malignancy) (Table IV). Among the classical BMF syndromes, the greatest risk of malignant transformation to MDS and AML is in patients with FA and DC, where the actuarial risk of developing a malignant transformation by the age of 18 years is 75% and 25%, respectively, followed by inherited BMF, unclassifiable, severe congenital neutropenia (SCN) and Shwachman Diamond Syndrome (SDS), where the risk is estimated at 24%, 24%, and 20%[46]. We provide a comprehensive summary of these disorders in Table IV, and refer the reader to several recent excellent recent reviews of BMF syndromes for more details [7,8,47–51]. Here, we will focus on the recent advances in established and emerging familial MDS/AML, as well as on the emerging data on MDS predisposition in acquired aplastic anemia.

ANKRD26-related thrombocytopenia

ANKRD26-related thrombocytopenia (*ANKRD26*-RT or THC2, MIM #188000) is an autosomal-dominant thrombocytopenia caused by single nucleotide substitutions in the 5' untranslated region (5'UTR) of the ankyrin repeat domain 26 (*ANKRD26*) gene, leading to its gain-of-function [52]. A single family with a missense mutation in *ANKRD26* (p.D158G) was also recently reported [53]. The pathophysiology of *ANKRD26*-RT is a subject of active investigation. Electron microscopy studies identified dysfunctional proteasome pathways in platelets and megakaryocytes of *ANKRD26*-RT patients [54]. A recent report showed the loss of runt-related transcription factor 1 (RUNX1) and friend leukemia integration 1 transcription factor (FLI1) binding by the mutated 5'UTR of *ANKRD26* in *ANKRD26*-RT patients, which led to the loss of RUNX1 and FLI1-mediated repression of the ANKRD26 activity. Persistent expression of ANKRD26, in turn, led to increased thrombopoietin/myeloproliferative leukemia virus oncogene (MPL)-mediated signaling and the activation of the MAPK/ERK1/2 pathway, leading to impaired protoplatelet formation[55].

Clinically, *ANKRD26*-RT presents with moderate thrombocytopenia with a normal mean platelet volume (MPV). The diagnosis is most commonly made in adulthood ranging from the age in the early 20s through the 70s; pediatric patients aged 2 to 16 years have also been reported [56,57]. Although hemoglobin and leukocyte values are normal in the majority of patients, elevated hemoglobin and white blood cell counts have been observed and may represent a feature of the disease. Spontaneous bleeding is rare, and a number of patients have undergone surgeries without platelet support, and most women in the studied families gave birth without bleeding complications[56].There are reports of transient normalization of platelet counts in the setting of an acute infection, as well as apparent partial responses to immune thrombocytopenia-directed therapies[57]. Among the roughly 222 reported cases of *ANKRD26*-RT to date, there has been an increased incidence of myeloid malignancies with

4.9% of patients developing acute leukemias, 2.2% developing MDS, and 1.3% developing CML, yielding an estimated risk of these malignancies that is 23-fold, 12-fold, and 21-fold higher than the general population, respectively [58].

Familial AML with mutated *CEBPA*

Familial AML with mutated *CEBPA* (MIM #116897) is an autosomal-dominant familial AML syndrome with a near complete penetrance, caused by germline dominant-negative mutations in the CCAAT enhancer binding protein-α (*CEBPA*)[59], distinct from the more commonly encountered somatic *CEBPA* mutations seen in AML. Most commonly, patients have a germline frameshift mutation in the N-terminal region of the CEBPA protein, which, at the time of progression to AML is frequently accompanied by a second, in-frame somatic C-terminal mutation in the leucine zipper domain which disrupts DNA binding [60,61]. CEBPA functions as a lineage-specific transcription factor, which directs both the transcriptional activation as well as the cell proliferation arrest required for the development of committed myeloid precursor cells [62]. Germline N-terminal mutations cause defective trans-activation and an inability to cause proliferation arrest. The accompanying C-terminal mutations lead to disruption of transcriptional activation of myeloid-specific genes through altered dimerization [62].

Clinically, *CEBPA*-associated familial AML presents with AML at a median age of 24.5 years (range 1.75–46 years) at presentation [59,63,64]. A case of AML in monozygotic twins carrying the same germline *CEBPA* mutation, whose age at onset of AML differed by 13 years, has been reported and highlights variability of presentation [65]. Among sporadic cases of AML, a number of patients are likely to carry a germline *CEBPA* mutation. In a study of 151 patients with an apparently sporadic, cytogenetically normal AML carrying single- or double- *CEBPA* mutants, 5 patients (3.3%) had an underlying germline *CEBPA* mutation; most of these also carried a second, somatic mutation in the C-terminus [61]. While germline CEBPA mutations are associated with highly penetrant familial AML, survival outcomes are favorable, with recurrence typically caused by independent leukemic episodes[64].

GATA2 haploinsufficiency

GATA2 haploinsufficiency is an autosomal dominant MDS/AML predisposition syndrome caused by loss-of-function mutations or deletions in the *GATA2* gene, leading to a spectrum of clinical abnormalities previously described as Primary Lymphedema with Myelodysplasia (Emberger Syndrome, MIM#137295), and monocytopenia and mycobacterial infection syndrome (MONOMAC, Immunodeficiency 21, or DCML, MIM# 614172)[66–70]. GATA2 is a critical transcriptional regulator of hematopoiesis, interacting with a number of transcription factors including SPI1, FLI1, TAL1, LMO2 and RUNX1 to regulate hematopoietic stem cell survival and cell renewal [71]. Haploinsufficiency of GATA2 causes reduced primitive hematopoietic stem cell proliferation and survival, as well as defective lymphatic development [72,73]. In addition to its crucial role in hematopoiesis, GATA2 is expressed at high levels in lymphatic vessel valves, and is an important regulator

of genes involved in lymphatic valve morphogenesis, a function likely responsible for the primary lymphedema in GATA2 haploinsufficiency families[74].

Clinically, among the 57 patients with GATA2 haploinsufficiency in the National Institutes of Health (NIH) cohort [66], the median age of initial presentation was 20 years, ranging from 5 months to 78 years. The patients' presenting symptoms ranged from viral infections in 32% of cases, disseminated non-tuberculous mycobacterial infections in 28%, MDS/AML in 21%, lymphedema in 9%, and invasive fungal infections in 4%. By the end of the study follow-up, 53 of the 57 patients (93%) had at least one of the following cardinal symptoms--severe viral or non-tuberculous mycobacterial infections, MDS/AML, pulmonary alveolar proteinosis, or lymphedema[66]. Clinical presentation with a congenital mild neutropenia (median neutrophil count of 1.5 grams/Liter, range 0.5–1.2 g/L), associated with monocytopenia, warts, infections, and MDS/AML, has also been described, adding *GATA2* to the list of genes implicated in chronic neutropenias [75].

Extended mononuclear cell profiling of 20 patients and 6 asymptomatic relatives with GATA2 haploinsufficiency revealed dendritic cell, monocyte, B, and natural killer (NK) lymphoid deficiency, with an elevated Fms-like tyrosine kinase 3 ligand (Flt3L) level [76]. Clinical progression correlated with increasingly elevated Flt3L levels, depletion of specific lymphocyte subsets (transitional B cells, CD56-bright NK cells, and naive T cells), and accumulation of terminally differentiated NK and CD81 memory T cells. It has been suggested that monitoring of Flt3L levels and hematologic parameters such as circulating CD34+cells can be used for surveillance of transformation to MDS in this syndrome [76]. Patients present with an accumulating number of symptoms over time, with the fraction of symptomatic patients rising from 50% at the age of 20 years to 86% at the age of 40 years. The overall survival has been estimated as 96%, 77%, and 45% at 20 years, 40 years, and 60 years of age, respectively[66]. Progression to myelodysplasia in patients with GATA2 haploinsufficiency is frequently associated with monosomy 7 and trisomy 8 [66–70], as well as acquisition of somatic *ASXL1* mutations in 30% of patients [77].

RUNX1-associated familial platelet disorder with propensity to myeloid malignancy

RUNX1-associated familial platelet disorder with propensity to myeloid malignancy (FPD/AML, MIM# 601399) is an autosomal-dominant familial MDS/AML predisposition syndrome, caused by inherited mutations in the hematopoietic transcription factor *RUNX1*, associated with life-long moderate thrombocytopenia and platelet function defects[78]. Inherited mutations lead to RUNX1 haploinsufficiency through large intragenic deletions often a part of the 21q22 syndrome; smaller insertions or deletions; or by nonsense, frameshift, missense mutations in the Runt DNA binding domain [79,80]. RUNX1-mutant cells from FPD/AML patients were shown to have defective hematopoietic differentiation, with reduced hematopoietic progenitors and impaired differentiation of megakaryocytes [81]. Dominant-negative effects have also been described [79,80].

There is significant heterogeneity both in age of presentation, which ranges from early childhood into the sixth decade, as well as in the clinical course [82,83]. In a study of five

pedigrees with FPD/AML, the age at onset of platelet abnormalities ranged from 7 to 60 years, with MDS/AML diagnosed between 6 and 75 years; a number of patients presented with MDS/AML as the initial finding[29,84]. There is commonly a history of mild to moderate bleeding tendency, which is frequently accompanied by thrombocytopenia. However, individuals with FPD/AML without a bleeding history and even with apparently normal platelet counts have been reported, highlighting the inadequacy of a blood count as a screening test [29]. Instead, the diagnosis is made by DNA sequencing of the RUNX1 gene from a non-hematopoietic tissue material (e.g. skin fibroblasts), in conjunction with deletion/duplication testing (e.g. using a high-density single nucleotide polymorphism array) to ensure detection of structural genomic abnormalities [82].

The rate of MDS/AML transformation in FPD/AML is estimated at 20–60%, with a high degree of variability within families [29,84]. Although a definitive correlation between the type of *RUNX1* mutation and the resultant risk of leukemia has not been established, mutations with a dominant-negative effect appear to have a higher risk, consistent with a likely need for a "second-hit" event to initiate malignant transformation [80]. A study of 8 patients with FPD/AML showed that in the majority of patients (6 of 8), malignant transformation was associated with a somatic acquisition of a second *RUNX1* mutation [83]. However, recent data indicate that malignant transformation may be mediated by recurrent somatic mutations in *CDC25C* gene in up to a half of FPD/AML patients. *CDC25C* mutations act to enhance mitotic entry and appear to be an early driver event of malignant transformation, followed by acquisition of additional mutations, most notably somatic mutations in *GATA2* [85]

Emerging Familial MDS/AML Syndromes

Despite the considerable progress in the identification of hereditary MDS/AML predisposition syndromes, most cases of familial MDS/AML remain uncharacterized, and there is a growing recognition of the existence of additional MDS/AML syndromes. Since 2012, three additional syndromes have been identified, linked to germline mutations in *SRP72*, *DDX41* and *ETV6* genes.

SRP72-associated familial aplasia and myelodysplasia

SRP72-associated familial aplasia and myelodysplasia (Bone marrow failure syndrome 1, MIM# 614675) is an autosomal-dominant disorder caused by mutations in the *SRP72* gene. Mutations in *SRP72* were detected in two kindreds with aplasia and MDS; both families had auditory abnormalities (deafness in one family and possible labyrinthitis in the other family). The age at onset of cytopenias and/or MDS ranged from 11 to 76 years. SRP2 is a component of the signal recognition particle, responsible for halting the translation of nascent secretory or extracellular proteins, and directing them to the endoplasmic reticulum. Mutations in SRP72 cause reduced localization of the mutant protein in the endoplasmic reticulum, and represent a novel pathway in the pathophysiology of bone marrow failure and MDS [86].

DDX41-associated familial MDS/AML syndrome

DDX41-associated familial MDS/AML syndrome is a recently identified autosomal-dominant syndrome presenting in mid to late adulthood, caused by the germline mutations in the DEAD-Box helicase *DDX41*, leading to altered pre-mRNA splicing and RNA processing [87]. Initially identified in an index family with three generations of family members affected by AML and high-risk MDS, *DDX41*-associated familial MDS/AML syndrome was subsequently found in 8 additional patients (~1%) from an unselected cohort of 1034 patients with MDS and secondary AML.

In contrast to other predisposition syndromes, *DDX41*-associated familial MDS/AML presents later in adulthood with an age at presentation ranging from 44 to 88 years among the 19 published cases. All patients presented with advanced disease, such as MDS with excess blasts (RAEB-1/2), and primary and secondary AML. Approximately half of the patients had bi-allelic *DDX41* mutations due to a second, somatic event in the wild type allele. In addition to the second-hit somatic *DDX41* mutations, additional somatic mutations were frequently found, most commonly mutations in *TP53*, *RUNX1*, and *LUC7L2*. Of note, de novo, somatic mutations in the *DDX41* gene have been reported in myeloid neoplasms and *DDX41* locus is involved in 26% of cases of MDS with del(5q) [87].

ETV6-associated familial thrombocytopenia and hematologic malignancy

ETV6-associated associated familial thrombocytopenia and hematologic malignancy is a recently identified autosomal-dominant syndrome caused by germline mutations in the ETS family transcriptional repressor variant 6 (*ETV6*), causing altered DNA binding and ETV6 protein mislocalization [88,89]. Interestingly, *ETV6* is a tumor suppressor gene that is frequently disrupted by somatic alterations, such as the ETV6-RUNX1 fusion commonly seen in childhood leukemias. In contrast, patients with germline *ETV6* mutations present with bleeding, thrombocytopenia, red cell macrocytosis, and are frequently misdiagnosed as having immune thrombocytopenia [88,89]. Among the reported cases of *ETV6*-associated familial thrombocytopenia and hematologic malignancy, there was a high prevalence of a variety of hematologic malignancies, including acute lymphoblastic leukemia (ages at presentation of 3 to 37 years), MDS RAEB-1 (age of 21 years), CMML (age of 81 years), mixed-phenotype acute leukemia (age of 50 years), and multiple myeloma (age of 51 years); there also appears to be a predisposition to non-hematologic malignancies including skin cancer and colon cancer.

Clonal Hematopoiesis and MDS Predisposition in Acquired Aplastic Anemia

Acquired aplastic anemia (AA), a rare blood disease associated with MDS/AML predisposition in both children and adults, is distinct from the inherited predisposition syndromes in that it is not inherited but caused by immune destruction of early hematopoietic cells, leading to peripheral cytopenias and marrow aplasia [90]. With improved patient outcomes after the introduction of immunosuppressive therapy[91], it became apparent that survivors of aplastic anemia are at high risk of transformation to

hematologic malignancies, with a 10-year cumulative incidence of 10% and 7% for MDS and AML, respectively [92].

Recent targeted sequencing studies, aimed at identifying markers of malignant transformation in AA, found malignancy-associated somatic mutations in 5% to 54% of patients [93–99](Figure 4). The substantial spread in mutation frequency can be largely explained by differences in methodologies in the individual studies: including the differences in patients' age, inclusion or exclusion of patients with malignant transformation, composition of targeted gene panels, and assay sensitivity (Figure 4). Across all studies, the recurrently mutated genes in aplastic anemia include *PIGA*, mutated in 25–50% of AA patients, as well as the MDS-associated genes *ASXL1*, *BCOR*, *DNMT3A*, and *TET2*, which can be found in 18–25% of adult AA patients without MDS transformation [94,95]. In addition to the above genes, a diverse range of additional somatic mutations, not known to be associated with malignancy, is commonly seen [96,98–100], along with copy number-neutral loss of heterozygosity (CN-LOH) of the short arm of chromosome 6 at the site of the HLA locus, found in ~13% of AA patients [101,102]. Emerging data from whole exome sequencing performed in young AA patients without morphologic evidence of MDS, suggest that acquired clonal hematopoiesis is present in the majority of AA patients, including children as early as 1 year from diagnosis, with a diverse mutation spectrum [100].

Available studies, many of which included post-AA MDS patients, indicate that acquired mutations in *ASXL1* and *DNMT3A* are associated with a worse overall survival and with an increased risk of malignant transformation; importantly, the majority of patients harboring these mutations did not progressed to MDS over the limited study period [94,97,98]. Conversely, mutations in *PIGA* and *BCOR/BCORL1* genes have been linked to a more favorable prognosis [98]. Genetic analysis of AA patients upfront, accompanied by long-term follow-up, is needed to characterize the complete spectrum and prognostic significance of genetic alterations in AA. In the absence of definitive longitudinal studies, we recommend a cautious approach in interpreting findings of clonal hematopoiesis in AA. In older patients and those with a long duration of disease, shown to be at a greater risk of somatic mutations [94,98,100], screening for MDS-associated mutations in *ASXL1* and *DNMT3A* may be helpful in guiding long-term surveillance. Importantly, detection of MDS-associated somatic mutations alone does not necessarily signify disease transformation, and, at present, the role of mutations in guiding therapy has not been established.

Management of Patients and Family Members with MDS/AML Predisposition Syndromes

Although there are well-established guidelines for managing older adults with MDS/AML[103], as well as pediatric patients with *de novo* AML, treatment guidelines for younger adults and children with MDS predisposition syndromes are lacking[11], with published experience largely limited to evaluation and therapeutic algorithms for patients with classical inherited BMF syndromes. Here, we will describe general considerations for management of young patients with emerging MDS/AML predisposition syndromes (Table V), and will review the published experience for patients with classical inherited BMF.

Genetic Counseling, Surveillance, and Considerations for Preventive Therapy

All patients with an MDS/AML predisposition syndrome should be offered genetic counseling, and their family members should be offered genetic counseling and site-specific genetic testing. For patients in whom an underlying predisposition syndrome is identified prior to the onset of MDS or AML, management should include regular hematologic and bone marrow surveillance, syndrome-specific cancer surveillance, and, for syndromes associated with the highest risk disease of MDS transformation (e.g. Severe Congenital Neutropenia (SCN) and Fanconi Anemia), consideration of preventive stem cell hematopoietic stem cell transplantation (HSCT) prior to the onset of high risk clonal cytogenetic abnormalities.

Up to 35% of patients with SCN requiring over 8 mcg/kg/day of granulocyte colony stimulating factor (G-CSF) develop MDS/AML after 15 years of G-CSF use[104], with event-free survival of 57% and 27% when HSCT is performed after the development of MDS or AML, respectively, in this patient population[105–108]. In contrast, outstanding event-free and overall survival of 75% and 89% respectively have been achieved with HSCT for patients with SCN prior to the onset of MDS/AML, leading to the recommendation that all SCN patients with matched related donors and perhaps closely matched unrelated donors strongly consider HSCT in early childhood prior to developing clonal abnormalities[107]. Similarly, patients with Fanconi Anemia have excellent 5-year survival of over 90% when transplant is performed at a young age for the indication of bone marrow aplasia[109]; in contrast, 5-year overall survival drops to 33% in FA patients who develop advanced MDS or leukemia[110]. Because outcomes are somewhat better in patients who undergo transplant as soon as classic cytogenetic changes are detected[111], many centers now implement routine bone marrow screening for all FA patients even with stable blood counts and proceed to transplant based on cytogenetics even if full MDS criteria are not met. For FA patients with mutations in *FANCD1/BRCA2* that carry an extremely high risk for leukemic transformation, preemptive HSCT even without cytogenetic abnormalities has been proposed [112].

In contrast to these classical BMF syndromes, many emerging MDS predisposition syndromes (Table III) have not been fully defined, with their phenotypic spectrum, penetrance, and risk of transformation MDS/AML unknown, with no defined role of preventive HSCT. In all cases, a referral to a tertiary cancer center specializing in MDS predisposition should be strongly considered, and, at the minimum, patients and families with known or suspected MDS predisposition syndromes should be followed with close hematologic surveillance (Table V).

Interpretation of Cytogenetic Changes: all clones are not created equal

While many acquired cytogenetic abnormalities in patients with known predisposition syndromes portend a high risk of malignant transformation and serve as an indication for therapy including HSCT (Table II), a phenomenon unique to patients with bone marrow failure is that certain somatic mutations or chromosomal aberrations may serve to correct the

defective gene function in hematopoietic cells, and, consequently, decrease, rather than increase, the risk of developing MDS/AML. Such changes include the well-described somatic reversion seen in hematopoietic stem cells in FA patients [113], as well as isochromosome 7q or CN-LOH of chromosome arm 7q, resulting in enhanced SBDS protein expression in patients with Shwachman-Diamond Syndrome (SDS)[114,115]. The development of other clonal abnormalities, such as interstitial deletions involving chromosome arm 20q in patients with SDS, while not corrective of the underlying genetic defect, appear to be benign and can remain stable for years, can disappear spontaneously, and do not appear to increase the risk of developing MDS[116]. Common patterns of clonal evolution in acquired aplastic anemia similarly do not seem to increase the risk for MDS, and include somatic *PIGA* mutations, deletion of chromosome arm 13q, and 6p CN-LOH[101,117]. 13q deletion in particular may convey a favorable prognosis to aplastic anemia therapy, rather than increase the risk of additional clonal evolution[117].

Pre-transplant therapy in patients with MDS/AML secondary to an underlying genetic predisposition

Given that myeloid neoplasms arising from genetic predisposition syndromes are caused by malignant clonal emergence within primitive hematopoietic stem and progenitor cells[118], the curative treatment of choice in suitable transplant candidates presenting with MDS and secondary AML is hematopoietic stem cell transplantation (HSCT). The role of pre-transplant chemotherapy for purposes of reducing disease burden pre-HSCT and improving post-HSCT disease-free survival in these patients continues to be debated. In general, for young patients with MDS, pre-HSCT intensive chemotherapy similar to that used for *de novo* pediatric AML does not result in a survival benefit compared to HSCT alone[119]. Given the added concern for prolonged pancytopenia and significant non-hematologic toxicity in patients with certain types of genetic predisposition such as FA, we recommend against the use of intensive chemotherapy prior to HSCT for patients with underlying bone marrow failure conditions presenting with MDS without evidence for transformation to AML. For patients with inherited predisposition and AML, intensive chemotherapy prior to HSCT may be indicated but often results in substantial morbidity. Currently, novel approaches are being explored to reduce this morbidity, such as sequential chemotherapy followed directly by HSCT during the period of chemotherapy-induced aplasia in patients with Fanconi Anemia[120].

The hypomethylating agents 5-azacitidine and decitabine are increasingly being utilized as a cytoreduction strategy prior to HSCT in adults with high risk MDS and AML[121–123]. In contrast, there are few published data on the use of these agents in children, primarily limited to the use of 5-azacitidine as a bridge to HSCT in children with juvenile myelomonocytic leukemia[124] and of decitabine as a bridge to HSCT in a few children with refractory or relapsed AML[125]. Although likely the agents of choice in this setting, hypomethylating agents should be used cautiously in the setting of inherited BMF due to a potential risk of profound myelosuppression, requiring close monitoring for cytopenias and a prompt and established plan for HSCT rescue.

Considerations for HSCT in Patients with MDS/AML predisposition syndromes

A critical reason to pursue genetic confirmation of an underlying predisposition syndrome for all pediatric and younger adult patients with MDS or AML is to determine whether prospective familial HSCT donors possess the same genetic predisposition. Given the incomplete penetrance, divergent time to disease onset, and variable expressivity of the manifestations of predisposition syndromes [126], a thorough donor evaluation is paramount. This should include a comprehensive donor physical examination and medical history, family medical history, and genetic screening for any siblings or other related donors. In cases with a compelling history of a familial MDS/AML but no established genetic diagnosis, a consideration could be made for selecting a fully matched unrelated donor.

Equally important, an identification of certain genetic predisposition syndromes may dictate the optimal conditioning intensity for HSCT. While most centers recommend myeloablative conditioning regimens for young patients with MDS/AML, patients with genetic disorders such as Fanconi Anemia, Dyskeratosis Congenita, and Shwachman-Diamond Syndrome have greatly increased toxicity with conventional conditioning, and regimens with considerably reduced alkylating agent and/or radiation dosing should be utilized in these populations[109,127,128]. Interestingly, the presence of underlying bone marrow aplasia in patients with early stage, hypocellular MDS evolving from acquired aplastic anemia and congenital amegakaryocytic thrombocytopenia may allow for reduction in conditioning intensity with preserved disease-free survival, though these reduced intensity regimens still require prospective study in larger cohorts[129–131].

Conclusions

With the growing knowledge of mechanisms of leukemogenesis and clonal hematopoiesis, there is an increasing appreciation that a number of genetic predisposition syndromes may underlie apparent *de novo* presentations of MDS/AML, particularly in children and younger adults. Having an underlying predisposition syndrome significantly impacts both immediate treatment decisions such as the choice and timing of chemotherapy as well as the potential allogeneic stem cell transplantation including the choice of pre-transplant conditioning and screening of sibling donors, as well as patient and family surveillance. It is increasingly important for hematologists and oncologists to have a degree of familiarity with the common as well as emerging syndromes, and to have a systematic approach to diagnosis and screening of this high-risk patient population.

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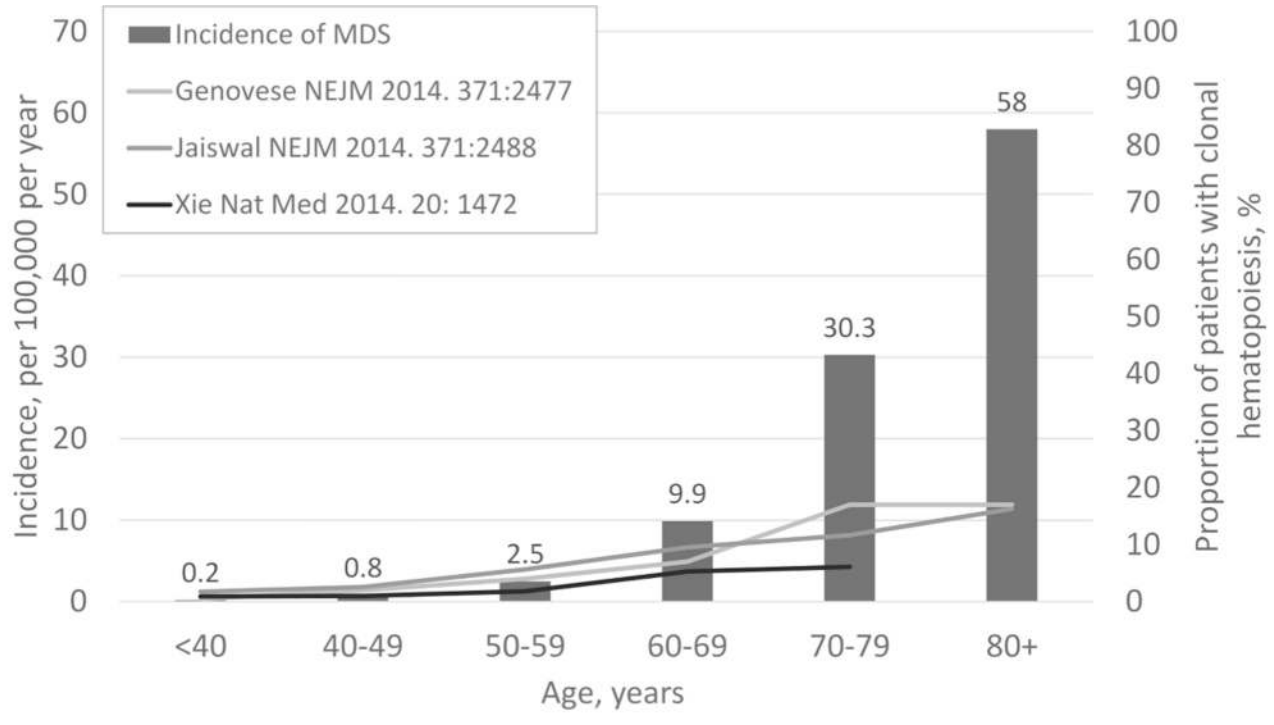
A



B

MDS Characteristics	Children and Young Adults	Older Adults and the Elderly
Underlying etiology of MDS	Genetic predisposition is common	*de novo* MDS is common
Familial aggregation	Present	Absent
Cytogenetic abnormalities	Monosomy 7, del 7q are relatively more common	Isolated 5q- and complex cytogenetics are relatively more common
Molecular abnormalities	Spliceosomal mutations are rare	Spliceosomal mutations are common

Figure 1. Incidence and Characteristics of Myelodysplastic Syndrome by Age at Diagnosis

A. Incidence of Myelodysplastic Syndrome by Age at Diagnosis. Histogram plot depicts the incidence rates of MDS stratified by age-group, as reported by the United States Surveillance, Epidemiology, and End Results (SEER) database analysis through 2011[14]. Overlying line plot depicts the percentage of individuals without a diagnosis of hematologic malignancy who have detectable clonal hematopoiesis with somatic mutations [2–4]. B. Characteristics of MDS in children and young adults, compared to MDS in older adults (age > 60 years). The solid black line separates childhood and young adult MDS (left) from older adults and the elderly (right). Clinical, cytogenetic and molecular features that occur at a higher frequency in a particular age group are listed above the corresponding age categories.

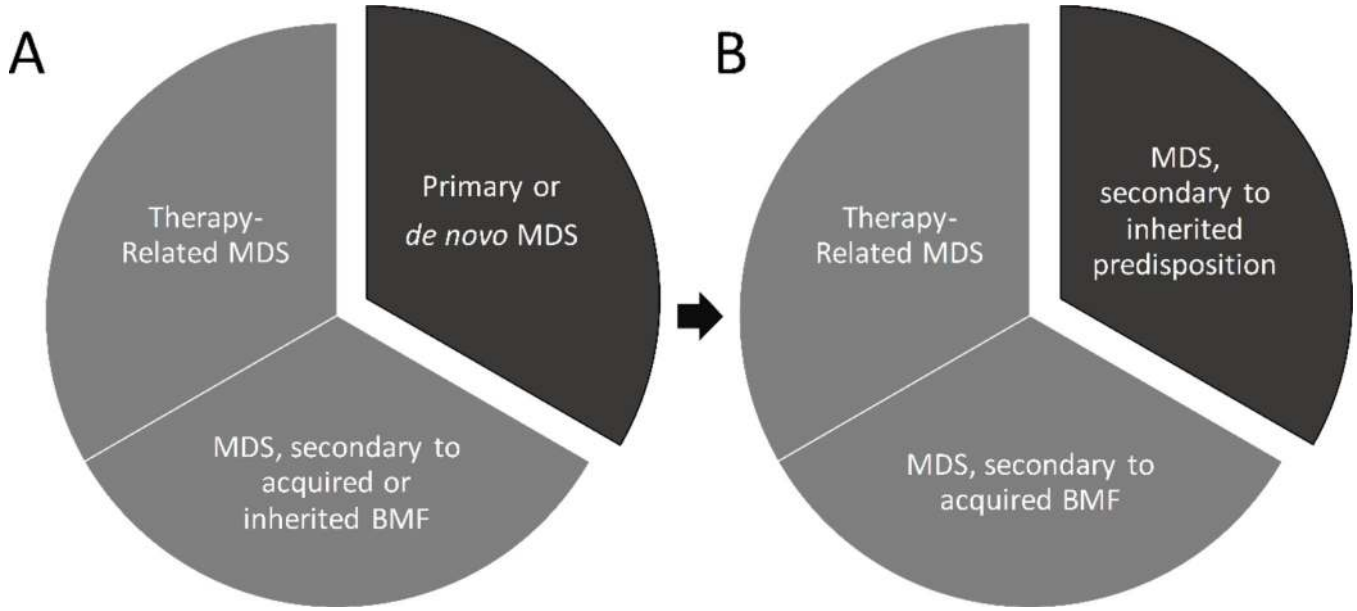


Figure 2. Classification of Childhood and Young Adult MDS

A. Childhood MDS has been historically classified into the categories of *de novo* or primary MDS, and "secondary" MDS, defined as therapy-related MDS following exposure to cytotoxic therapies, or MDS secondary to well-described inherited bone marrow failure (BMF) syndromes or acquired BMF [1]. B. Proposed revised classification of childhood and young adult MDS: 1) therapy-related MDS, 2) MDS secondary to acquired BMF, and 3) MDS secondary to inherited predisposition syndromes, including classical BMF syndromes as well as emerging MDS/AML predisposition syndromes.

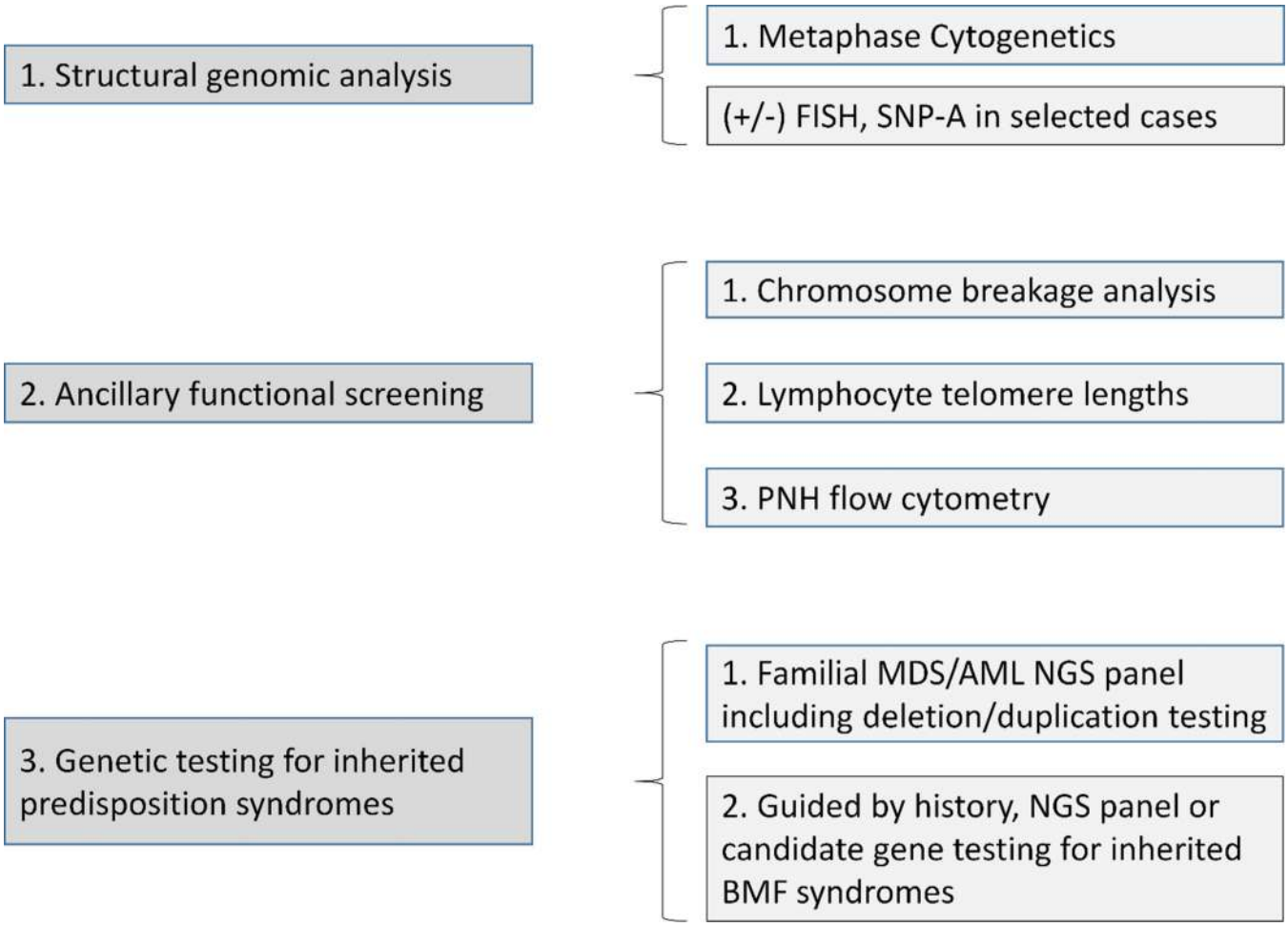
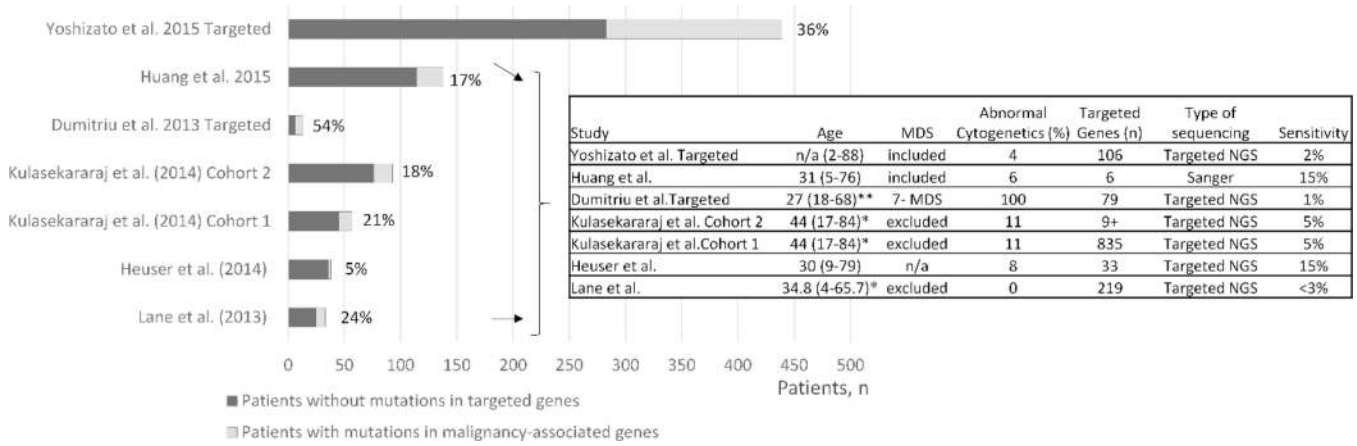


Figure 3. Proposed Evaluation Algorithm for an MDS/AML Predisposition Syndrome

The complete evaluation for underlying predisposition should include metaphase cytogenetic analysis, and, in appropriate cases, single nucleotide polymorphism array (SNP-A) and fluorescent in situ hybridization (FISH) to evaluate for smaller copy number changes beyond the resolution of metaphase karyotyping. Ancillary functional testing should include chromosomal breakage and lymphocyte telomere length measurements to screen for Fanconi Anemia and Dyskeratosis Congenita, respectively. Flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH) can help screen for acquired bone marrow failure, with the presence of a PNH clone suggesting absence of inherited BMF. For most cases, we recommend genetic testing with next-generation sequencing (NGS) technology to screen for known familial MDS/AML syndromes, with any additional BMF testing or gene-specific testing as guided by the patient's history.



Study	Age	MDS	Abnormal Cytogenetics (%)	Targeted Genes (n)	Type of sequencing	Sensitivity
Yoshizato et al. Targeted	n/a (2-88)	included	4	106	Targeted NGS	2%
Huang et al.	31 (5-76)	included	6	6	Sanger	15%
Dumitriu et al.Targeted	27 (18-68)**	7- MDS	100	79	Targeted NGS	1%
Kulasekararaj et al. Cohort 2	44 (17-84)*	excluded	11	9+	Targeted NGS	5%
Kulasekararaj et al.Cohort 1	44 (17-84)*	excluded	11	835	Targeted NGS	5%
Heuser et al.	30 (9-79)	n/a	8	33	Targeted NGS	15%
Lane et al.	34.8 (4-65.7)*	excluded	0	219	Targeted NGS	<3%

Figure 4. Hematologic Malignancy-Associated Somatic Mutations As Detected in Targeted Sequencing Studies of Patients with Acquired Aplastic Anemia

A histogram summarizing published targeted sequencing studies of patients with acquired aplastic anemia. Individual studies are listed along the Y-axis, with the number of patients included in each study is plotted along the X-axis. The dark gray bar shows the corresponding number of patients without detected somatic mutations in targeted genes; light colored bar shows the number of patients with identified somatic mutations, with the corresponding percentage of patients with mutations stated to the right of each bar plot. An embedded table depicts salient characteristics of each study, if available: Age, age at diagnosis in years, median (range); MDS, whether patients with post-AA MDS were included or excluded from the study; Sensitivity, minimal % mutant allele frequency detected in each study. n/a: not available; *, the listed age corresponds to a larger patient cohort; **, age at sequencing.

Table I

Clinical Features Suggestive of an Underlying MDS/AML Predisposition Syndrome

Age at MDS Diagnosis
Childhood
Young adulthood (e.g. < 50 years)
Personal or Family History
Known history of bone marrow failure or aplastic anemia
History suggestive of a genetic predisposition syndrome:
Hematologic prodrome
life-long cytopenias (e.g. "ITP", thrombocytopenia, easy bleeding)
Associated conditions
pulmonary fibrosis
hepatic fibrosis
endocrinopathies
frequent infections (e.g. HPV, non-tuberculous mycobacteria)
lymphedema
Unusual Cancer History
cancers at a young age (particularly head and neck, esophageal, anogenital)
multiple cancers
unusually severe complications of chemotherapy or radiation
Physical Exam Findings
Short stature
Skin, mucosal, hair, or nail changes
café-au-lait spots
hypopigmentation
nail dystrophy
oral leukoplakia
premature graying
Skeletal malformations
thumb abnormalities
radius abnormalities
hip dysplasia
metaphyseal dysplasia
Other congenital malformations
Disease Features
Characteristic chromosomal abnormalities (e.g. monosomy 7)
Characteristic molecular findings (e.g. bi-allelic mutations in familial MDS-associated genes)

Table II

Characteristic Chromosomal and Molecular Abnormalities Commonly Associated With MDS/AML Predisposition Syndromes

Recurrent Cytogenetic Abnormalities	
Syndrome	**Common Karyotype Abnormalities**
Fanconi Anemia	+1q,+ 3q, +13q; 7q-, 20q-; Monosomy 7
Dyskeratosis Congenita	Monosomy 7
Severe Congenital Neutropenia	Monosomy 7; 7q-; trisomy 21
Shwachman-Diamond Syndrome	7q-, 20q-; Isochromosome 7q; Monosomy 7
Acquired Aplastic Anemia	Monosomy 7; Trisomy 8; 13q-; Complex
Characteristic Molecular Abnormalities	
Familial MDS/AML Syndromes	Bi-allelic mutations in familial MDS/AML-associated genes (e.g. *CEBPA, RUNX1, DDX41*)
	Mutations in MDS/AML associated genes at a heterozygous allele frequency (50%)

Table III

Caveats to Interpretation of Next-Generation Sequencing (NGS) Results in the Diagnosis of MDS/AML Predisposition Syndromes

Incomplete knowledge/Variants of unknown significance
Benign variants misclassified as pathogenic
True pathogenic variants that have not been previously described
Mutation outside of NGS capture area
Mutation in a gene not known to be linked to a disease
Mutation in a known gene linked to the disease, but outside of the region of NGS capture
Mutation in a distant regulatory region
Technical limitations
Inadequate sequencing depth over the pathogenic region
Failure to detect large insertions or deletions
Wrong tissue tested
False-negative in peripheral blood of a patient or sibling with reversion mosaicism (e.g. FA)

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Table IV

Summary of Known MDS/AML Predisposition Syndromes

Syndrome	Pathogenic Mechanism	Inheritance	Gene(s)	Selected Findings	Diagnostic Test	Risk of MDS/AML
Classical Inherited BMF Syndromes						
Congenital Amegakaryocytic Thrombocytopenia	Thrombopoietin receptor	AR	*MPL*	None	gene sequencing	unknown
Diamond-Blackfan Anemia	Ribosome biogenesis	AD, XLR	*RPS19, RPS17, RPS24, RPL35A, RPL5, RPL11, RPS7, RPS26, RPS10, GATA1*	Small stature, congenital anomalies (e.g. head and neck, cardiac, thumb)	Elevated erythrocyte adenosine deaminase and HgF; gene sequencing	1–20%
Dyskeratosis Congenita	Telomere maintenance	XLR, AD, AR	*DKC1, TERT, TERC, TINF2, RTEL1, NOP10, NHP2, WRAP53, CTC1, PARN*	Nail dystrophy, lacy skin pigmentation, oral leukoplakia, pulmonary fibrosis, hepatic fibrosis, cancer predisposition	Telomere lengths; gene sequencing	30%
Fanconi Anemia	Homologous DNA repair, impaired tolerance of reactive metabolites	AR, XLR	*FANCA, FANCC, FANCD1/BRCA2, FANCD2, FANCE,FANCF, FANCG/XRCC9, FANCI, FANCJ/BACH1/BRIP1, FANCL, FANCM, FANCN/PALB2, FANCO/RAD51C,FANCP/SLX4, FANCQ(ERCC4), FANCB*	Radial anomalies, café-au-lait spots, short stature, microcephaly, GU anomalies, hip dysplasia, cancer predisposition	Chromosome breakage studies; gene sequencing	40%
Severe Congenital Neutropenia	Various	AR	*ELA2, HAX1, GFI1*	Neutropenia, frequent Infections	gene sequencing	10%
Shwachman-Diamond Syndrome	Ribosome biogenesis	AR	*SBDS*	Short stature, pancreatic insufficiency, skeletal abnormalities	stool studies; gene sequencing	20–30%
Other Inherited Syndromes Associated with MDS/AML						
Bloom Syndrome	DNA repair	AR	*BLM*	Short stature, immunodeficiency, microcephaly, high-pitched voice, hypogonadism	gene sequencing	15–25%
Li-Fraumeni Syndrome	TP53	AD	*TP53, CHEK2*	Cancer predisposition	gene sequencing	8%
Neurofibromatosis Type I	Ras signaling	AD	*NF1, SPRED1*	café-au-lait spots, axillary/inguinal freckling, neurofibromas, Lisch nodules, optic gliomas,	gene sequencing	<1%

Syndrome	Pathogenic Mechanism	Inheritance	Gene(s)	Selected Findings	Diagnostic Test	Risk of MDS/AML
				bony dysplasia		
Noonan Syndrome	Ras signaling	AD	*PTPN11, KRAS, RAF1, SOS1, CBL*	Short stature, facial dysmorphology, congenital heart defect	gene sequencing	unknown
Wiskott-Aldrich Syndrome	Cytoskeletal protein	XLR	*WASP*	immunodeficiency, microthrombocytopenia, eczema	gene sequencing	
Familial MDS/AML						
ANKRD26-related thrombocytopenia	MAPK signaling	AD	*ANKRD26*	None	gene sequencing	8%
Familial AML with mutated CEBPA	CEBPA transcription regulation	AD	*CEBPA*	None	gene sequencing	100%
DDX41-associated familial MDS/AML	DEAD/H-box helicase	AD	*DDX41*	Long latency; presentation in >40 year old adults with high risk MDS and AML	gene sequencing	unknown
ETV6-associated familial thrombocytopenia and hematologic malignancy	ETV6 transcription factor	AD	*ETV6*	Thrombocytopenia, bleeding, macrocytosis, increased incidence of hematologic and non-hematologic malignancies. Possible association with myopathy, GERD, esophageal stricture, reading disability	gene sequencing	unknown
GATA2 Haploinsufficiency	GATA2 transcription regulation	AD	*GATA2*	MonoMac Syndrome (monocytopenia, nontuberculous mycobacterial infections), Emberger Syndrome (lymphedema and monosomy 7), cutaneous warts, deafness	gene sequencing, bone marrow flow cytometry	unknown
RUNX1-associated familial platelet disorder with propensity to myeloid malignancy	RUNX1 transcription regulation	AD	*RUNX1*	Thrombocytopenia and bleeding tendency	gene sequencing	20–60%
SRP72-associated familial aplasiaand myelodysplasia	SRP72 component of signal recognition particle	AD	*SRP72*	Deafness	gene sequencing	unknown

AD, autosomal dominant; AR, autosomal recessive; XLR, X-linked recessive.

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Table V

Principles of Counseling and Management of Patients with MDS/AML Predisposition Syndromes

Patients with An Established Genetic Diagnosis		
Evaluation at Diagnosis		
	Referral to a specialty center	
	Referral for genetic counseling	
	Complete blood count (CBC) with differential	
	Baseline bone marrow biopsy, with morphology, cytogenetic analysis, and molecular testing	
	HLA typing of patient and full siblings	
	Additional evaluation as dictated by specific syndrome	
		Cancer screening
		Bleeding evaluation
		Immunological profiling
Counseling and Screening of Relatives		
	Referral for genetic counseling	
	Mutation-specific genetic testing	
Follow-Up and Surveillance		
	CBC with differential every 3–6 months	
	Bone marrow biopsy with any change in blood counts, or annually for higher-risk syndromes	
	Cancer surveillance program (syndrome-specific)	
Treatment Considerations		
	Consideration of early HSCT with development of dysplasia or cytogenetic abnormalities	
	Limited use of pre-HSCT cytotoxic therapy	
	Comprehensive donor screening	
	Disease-specific transplant planning	
Patients with A Strong History of Familial MDS/AML but no Established Genetic Diagnosis		
	Referral to a specialty center	
	Referral for genetic counseling	
	Complete blood count (CBC) with differential every 6 months, or more frequently with evolving blood counts	
	Bone marrow biopsy including morphology and cytogenetics, with any change in blood counts	
	Periodic reassessment of genetic diagnosis (e.g. every 3–5 years)	
	Additional management and surveillance guided by specific personal and family history	