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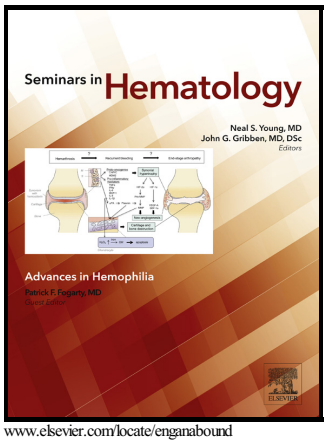

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PRACTICAL CONSIDERATIONS FOR DIAGNOSIS AND MANAGEMENT OF PATIENTS AND CARRIERS

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Key messages:

1. History taking, status at presentation, and physical examination can be considered first screening tools for identification of MDS/AML predisposition syndromes.

2. Therapeutic management, surveillance and prevention must be guided by the nature of the underlying genetic condition.

3. Considerations for diagnosis and management of patients and family carriers should be made in apprehension to hematologist's own daily practice.

Abstract

Newly diagnosed children and adults with MDS or AML need to be screened for presence of a genetic predisposition syndrome because the information on the genetic status is likely to influence clinical care and management of the patient and the family. Scenarios in which genetic counseling is advised include presence of a mutation on somatic screen which can be associated with a germline predisposition, hematologic or cytogenetic characteristics suggestive of an underlying susceptibility syndrome, non-hematological phenotype suspicious for a familial condition, history of previous malignancy, or a family history of cancer, cytopenia, autoimmunity or organ-system manifestation fitting a predisposition syndrome. With increasing complexity on phenotypes, genetics and leukemia risk of the recently recognized predisposition syndromes, specialized clinics for hereditary hematologic malignancies have been initiated to guide genetic testing and support hematologists integrating genetic data into therapeutic strategies and clinical care. Recommendations for surveillance of carriers are currently expert-opinion-based and subject to future modification when a more complete picture for the distinct genetic entities will arise.

Introduction

Traditionally, inherited bone marrow failure syndromes (IBMFS) and Down syndrome have been associated with genetic predisposition to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Within the last fifteen years, other subtle constitutional mutations that render patients susceptible to the development of myeloid neoplasia have been defined [1]. Most of the affected genes are recurrently mutated in sporadic leukemia.

Some of these predisposition genes are involved in megakaryopoiesis and platelet production. They give rise to familial syndromes, which can present with mild to moderate thrombocytopenia and bleeding disorder. The three currently known disorders in this group are: Familial platelet disorder with associated myeloid malignancy (FPD/AML) caused by germline mutations in the *RUNX1* gene [2], thrombocytopenia 5 caused by *ETV6* mutations [3] and thrombocytopenia 2 with disease causing variants in *ANKRD26* [4,5].

Similar to the syndromic nature of the classical IBMFS, some of the recently recognized predisposition syndromes like GATA2 deficiency [6,7) or the telomere biology disorders [8] can exhibit a variable non-hematological phenotype. Other cancer susceptibility syndromes like AML with germline *CEBPA* mutations [9] and myeloid neoplasms with pathogenic *DDX41* variants [10] are limited to the hematopoietic system, and most of these patients have normal blood counts prior to diagnosis of MDS/AML. Other genetic predisposition syndromes for MDS/AML like heterozygous germline mutations in *SRP72* [11] or duplication of the *ATG2B* and *GSKIP* gene [12) have been described in few families only.

Penetrance in these recently described autosomal-dominant inherited predisposition syndromes is variable. There is a wide interfamilial and intrafamilial variation in phenotype. With increasing availability of molecular testing, heightened awareness and collaborative research the number of afflicted patients and carriers will rise rapidly. In addition, it is likely that new susceptibility disorders caused by cooperating effects in less damaging mutations in

multiple genes will be discovered. Thus, it will become increasingly challenging integrating all aspects of leukemia susceptibility into clinical care. This chapter summarizes practical considerations of diagnosis and management for patients and carriers focusing on the recently defined predisposition syndromes.

Screening for predisposition syndromes at diagnosis of MDS/AML: physical examination and history taking

Early identification of an underlying predisposition syndrome in a patient with newly diagnosed MDS or AML is crucial because the genetic information is likely to influence the personalized care of the affected individual. All newly diagnosed patients with MDS and AML should therefore be screened for presence of a genetic predisposition syndrome by a meticulous physical examination and a carefully taken medical history. Although these screening tools are simple and easily performed, they are often omitted. Naturally, initial physician-patient contacts in malignant disorders focus on emergency care and issues related to therapy and overall prognosis. However, once these immediate challenges are handled, physicians are encouraged to complete their physical examination with respect to presence of non-hematological stigmata of underlying genetic disorders.

Like the classical IBMFS, some of the recently discovered predisposition syndromes can display overlapping dysmorphic changes of the head (facies, eyes, ears, oral cavity, and microcephaly), skeleton (forearm, fingers, and toes) and skin (pigmentation, warts, hair and nails). Growth abnormalities (short stature), developmental delay or behavioral problems (autism, aggressive behavior) may be present. Importantly, changes in other organ systems such as pulmonary (telomere biology diseases) or lymphatic vessel system (GATA2 deficiency) can raise the suspicion for presence of a specific disorder and thus direct genetic testing.

Similar to obtaining a complete physical status, medical and family history taking is often a multistep process. Patients and families may need some time to gather the necessary information and clinical records. While constructing a formal family pedigree spanning three or more generation is typically reserved for genetic counseling, a robust family history of first and second degree relatives needs to be obtained in all patients with myeloid neoplasia at diagnosis [13].

Check-lists and other quality control measures may simplify screening procedures for predisposition syndromes in a busy hematology practice. In addition, they can increase awareness and educate medical staff. However, it is important to recognize that there is currently no scientific evidence that these screening measures capture a significant proportion of patients with underlying inherited disorders. Furthermore, the level of suspicion sufficient to initiate genetic testing is neither defined nor addressed in expert opinions.

Scenarios at diagnosis of MDS/AML requiring genetic testing for predisposition syndromes

Criteria for initiating screening for predisposition syndromes of MDS/AML are poorly defined. There are different scenarios, which require genetic counselling of the patient and subsequent testing (Table 1).

With implementation of MDS/AML panel diagnostics into clinical practice the question whether a specific gene mutation is somatic or possibly germline arises more frequently. Genes altered in inherited predisposition syndromes are key regulators of cellular function and hence often acquired drivers of clonal development in sporadic malignancy. While standard sequencing cannot distinguish between germline and somatic, there are clues from the somatic analysis, which indicate that a germline mutation is likely. They include a near-heterozygous or near-homozygous allelic frequency and/or the presence of multiple mutations within one of these genes [14]. In these cases expansion on the patient's history,

counseling and germline testing are appropriate next steps. For instance, an 18 year old male diagnosed with MDS and excess blasts (MDS-EB) and i) a *RUNX1* mutation and a history of thrombocytopenia may have *RUNX1* germline disease, ii) a *GATA2* mutation, autism and a hydrocele is likely to suffer from GATA2 deficiency, and iii) a *TERT* or *TERC* mutation and a hypocellular bone marrow will be diagnosed of a telomere biology disorder. In other instances, a high probability of underlying genetic disease calls for prompt germline analysis: approximately 10% of patients with AML and biallelic *CEBPA* mutations will have CEBPA-familial leukemia [15], and 60% of individuals with a pathogenic variant of the *DDX41* gene have inherited disease [16]. There is a clear need to develop and integrate algorithms for identification of probable inherited disease into the interpretation of targeted sequencing panels at diagnosis of MDS/AML.

Hematologic parameters can also trigger testing for a predisposition syndrome. Preceding monocytopenia [6] or lack of B-cells [17] may point to GATA2 deficiency, while pale appearing platelets can lead to *ANKRD26* germline mutations with alpha granule deficiency [4]. Bleeding diatheses and prior thrombocytopenia may indicate *RUNX1*, *ETV6* or *ANKRD2*6 germline disorder. Thrombocytopenia is due to megakaryocytic dysplasia, which can be considered as preleukemic abnormality reflecting disturbed maturation secondary to the transcription factor or transferase defect [18]. Dysmegakaryopoiesis with small megakaryocytes with hypolobulation, small amount of mature eosinophilic cytoplasma and micromegakaryocytes is also noted in other susceptibility syndromes like GATA2 deficiency [19] and is consistent with but not specific for these disorders. Importantly, presence of atypical megakaryocytes is not a sign of overt MDS. Furthermore, low grade MDS like refractory cytopenia of childhood (RCC) cannot be reliably distinguished from IBMFS or leukemia predisposition syndromes by histopathological means only [20].

Conventional karyotypes can provide important clues. Simultaneous presence of del(7q) and monosomy 7 in an infant with cytopenia can be indicative of a germline mutation in *SAMD9*/*SAMD9L* [21,22], trisomy 8 and/or monosomy 7 in an adolescent may indicate

GATA2 deficiency [7]. Isochromosome i(7)(q10) and del(20)(q) are particularly frequent in Shwachman-Diamond syndrome [23], while gain of chromosome 1q and 3q26q29 are the most common aberrations in MDS/AML in Fanconi anemia [24].

A patient's non-hematological phenotype can raise the suspicion of classical IBMFS, a telomere biology disorder or GATA2 deficiency. The combination of pulmonary fibrosis or cryptogenetic liver cirrhosis and cytopenia is pathognomonic for a telomere biology disorder, which also needs to be considered in young patients with bone marrow failure/hypoplastic MDS-EB when Fanconi anemia is excluded or with the presence of squamous cell carcinoma [25]. Warts, hydrocele or other lymphatic malformation, autism or aggressive behavior, sensorineural hearing loss, pulmonary alveolar proteinosis, immunodeficiency or nontuberculous mycobacteria infection may be indicative of GATA2 deficiency [6,7].

The hematologic neoplasia can be part of a cancer spectrum, and the patient may have experienced another malignancy. Referring to all familial cancer conditions in which MDS/AML is not the defining malignancy is beyond the scope of this review. Presence of a complex karyotype in MDS/AML following cytotoxic therapy can be a strong indicator of Li-Fraumeni syndrome, a particularly pleiotropic hereditary cancer syndrome hematologists need to be familiar with [26]. Lastly, a family history positive for of cancer, cytopenia, autoimmunity or manifestation of any organ-system fitting a predisposition syndrome can provide an important thread for the patient's further work-up.

Genetic testing: Methods, tissue and interpretation

While current standard diagnostic MDS/AML of next generation sequencing (NGS)-panels can identify mutations possibly altered in germline, they are not designed for predisposition screening. Comprehensive clinical testing in hereditary MDS/AML predisposition syndromes is offered by a number of reference laboratories in the USA, Europe and Asia. Given the phenotypic overlap of these susceptibility syndromes, a gene-panel based approach is often

preferred as it offers the ability to analyze multiple genes simultaneously and is cost effective [27]. Because panel diagnostics may not capture all exonic and intronic alterations, Sanger sequencing is applied when clinical suspicion of a defined predisposition syndrome is high [7]. In some conditions like in RUNX1 mutated disease intragenic deletions and duplications undetectable by sequencing are frequent emphasizing the need for array analyses of mutation-negative cases [28].

For patients with a hematologic malignancy, cultured skin fibroblasts are the preferred tissue for germline mutation testing [29]. A 3-mm skin-punch biopsy or a skin ellipse taken at the site of bone marrow sampling or during implantation of a venous device can provide high quantity and quality of germline DNA. While cultures of fibroblasts can take 3 - 6 weeks until sufficient DNA for testing is available, DNA from epithelial cells of hair follicles is readily available for timely studies [7]. Buccal swabs or saliva are frequently contaminated with hematopoietic cells and should be avoided, although negative results may be clinically useful. DNA from nail clippings has successfully been utilized in chimerism studies after HSCT [30] indicating that this tissue is not a preferred source for genetic testing as it can contain hematopoietic cell DNA. In the absence of a skin biopsy some investigators utilize DNA from mesenchymal cells cultured from bone marrow aspirates [31]. Since dysfunction of stromal cells can result in MDS and secondary leukemia [32], results from these studies have to be interpreted with caution.

With massive parallel sequencing an increasing number of novel sequence variants are detected in patient specimens. Guidelines for the classification of these variants into (i) pathogenic, (ii) likely pathogenic, (iii) uncertain significance, (iv) likely benign, or (v) benign have been published [33]. For individuals with variants of uncertain significance additional clinical or laboratory studies with respect to possible presence of a genetic disorder or family studies are discouraged. Instead, enrollment in clinical registries based at academic institutions specialized in hereditary hematologic malignancy can be advised. With lack of

functional studies or other gold standard tests, available evidence can result in conflicting interpretations of the five-tier system of classification for variants [34]. It can be extremely disturbing for an affected family when laboratories provide different assessments of variant pathogenicity to individual family members. In such instances, education and counseling of affected individuals by a team of specialists in clinical genetics and molecular testing is critical.

Genetic counselling and identification of carriers

Genetic counseling is a key component of the evaluation for possible hereditary cancer risk. Germline genetic testing should be performed in the context of appropriate pre- and post-test counseling [13]. For all patients with MDS/AML and a potential underlying predisposition referral to genetic counseling is recommended. Timely counseling is of particular importance for patients with somatic testing or hematological, cytogenetic or non-hematologic manifestations indicative for the presence of a hereditary condition. Without counseling these individuals might be unprepared for the potential familial implications of the results of the diagnostic work-up of MDS/AML [35].

In the process of genetic counseling the patient's clinical and laboratory data are reviewed and the patient is educated regarding the genetic etiology of MDS/AML. Benefits, limitations and possible outcomes of germline testing are explained, and the patient's personalized risk of the likelihood of a hereditary condition is assessed. Counseling will help the patient to understand the implications of testing offered for planning of his or her own treatment, identification of family members at risk, and future screening or preventive strategies. It will also address the patient's emotional needs around the diagnosis of MDS/AML and familial inheritance. Depending on their personal preferences, not all patients wish to peruse germline testing and not all family or medical histories may warrant testing [36].

Genetic counseling includes obtaining and analyzing a multigenerational medical family history. Most families are complex and it is generally not possible to gather complete information during the initial counseling visits. Following a diagnosis of inherited cancer pedigrees can be replenished once the patient moved beyond his or her initial stress and can actively engage in the appropriate family conversations. Families seeking genetic counseling for familial clustering of MDS/AML are often asked to collect the necessary information ahead of time to alleviate the work load of the first counseling visit. Patients can use a growing number of online tools (e. g. https://familyhistory.hhs.gov/) to collect, print and bring the family medical history to the initial counseling visit.

Genetic test results need to be effectively communicated to patients and their families. The detection of a pathogenic mutation may have immediate implications for other clinically affected family members. Other families members may decide to accept predictive testing to learn about their inherited susceptibility. In a situation where many families are hit twice, by malignancy and genetic disease, low-threshold offers for psychosocial support are particularly warranted.

When a child or adolescent is diagnosed of MDS/AML and an underlying predisposing condition, parents are challenged to balance their emotions while struggling to make the best decision for their child's medical care and for their family. How parents cope with this extremely demanding situation will reflect on the child's ability to grasp age-adjusted information on inheritance and genetic testing. Children who can read often search the internet. Providing them with relevant information in an understandable language will require the combined effort of dedicated care takers and support groups.

The fact that non-affected siblings may be carriers can add another dimension in family relationships. Next to the classical IBMFS, all recently discovered MDS/AML predisposition syndromes (with the exception of *DDX41* mutations [10] can clinically present or typically

occur in childhood. Published guidelines recommend predictive testing in asymptomatic children only if screening and intervention programs starting in childhood can reduce morbidity and mortality [37]. Although empirical evidence on safety and efficacy of surveillance measure is lacking, parents often easily decide in favor of testing their children because of a range of perceived advantages [37].

Adults with susceptibility syndromes may seek reproductive counseling for prenatal testing options including in vitro fertilization and preimplantation genetic diagnosis (PGD). Considering the wide range of clinical presentation of predisposition syndromes within families and the limited knowledge on penetrance, natural history or future therapy options, counseling affected couples is a particular challenge. Studies on the process of decision-making and long-term psychological impact of PGD in Fanconi anemia [38] can assist medical professionals to better understand expectations and needs of affected individuals.

Specialized clinics for hereditary hematologic malignancies

Adult and pediatric hematologists delivering care for patients with hematologic neoplasia need to have sufficient knowledge on predisposition syndromes to screen for these underlying disorders and to refer patients for genetic counseling when appropriate. Confidence of hematologists with regards to understanding and applying genetic testing is often low [39], and many physicians cooperate with specialized clinicians and institutions to integrate genetic data into clinical care.

With the increasing complexity of phenotypes, genetics and leukemia risk of predisposition syndromes, specialized clinics dedicated for the evaluation and monitoring of patients with hematologic malignancy and suspected germline predisposition have been established at academic institutions [14, 29]. Patients referred to such a hereditary hematologic malignancy clinic undergo standard assessment by a genetic councilor and hematologist. Based on this evaluation a formal recommendation is made for the referring physician which describes the

level of suspicion for presence of a predisposition syndrome and details a plan for further evaluation or genetic testing [29]. Once the test result is available, the interdisciplinary team of the clinic can advise on interpretation of variants and develop strategies for surveillance with the patient and the primary care hematologist.

Despite the recent discoveries of a growing number of predisposition syndromes, most patients referred to a hereditary malignancy clinic for evaluation of familial clustering of MDS/AML have negative results on clinical-based testing despite a striking family history [14, 40, 41]. These patients can be offered repetitive testing at later time points once updated information or screening for newly discovered predisposition genes becomes available. In addition, participation in research studies with research-based testing may help to gain insight into pathways and genes involved.

Clinics specialized in hereditary hematologic malignancies have the obligation to educate patients, families and the public on hereditary hematologic malignancies and to perform clinical and translational research. One of their major tasks is coordinating clinical research efforts on designing evidence-based clinical surveillance and management recommendations for affected patients and mutation carriers [29]. Patients generally generously donate their tissue for translational and basic research with the expectation that description of rare variants, new phenotypes, novel syndromes or unique therapeutic approaches could possibly benefit their family or others struck by a predisposition syndrome.

Therapy of MDS/AML in patients with a genetic predisposition syndrome

Clinical care and therapy for patients with MDS/AML due to an underlying genetic predisposition depends on the nature of the condition and the age of patient. Among the currently known disorders, only Down syndrome and *CEBPA*-associated familial AML are associated with myeloid neoplasia and a favorable prognosis in the absence of

hematopoietic stem cell transplantation (HSCT). Survival for patients with myeloid leukemia of Down syndrome and intensity-reduced AML therapy is in the order of 80% - 90% [42]. For *CEBPA*-associated familial AML probability of 5-year survival is approximately 70% and superior to that of sporadic *CEBPA*-associated AML [15].

For most genetic predisposition syndromes, allogeneic HSCT is the only curative therapy once MDS/AML has developed. Apart from the usual HSCT considerations, feasibility of HSCT for affected patients is primarily dependent on the patient's age and co-morbidities, which may originate from the non-hematological phenotype. In young individuals with MDS-EB or monosomy 7 HSCT is recommended early after diagnosis [43]. For patients with other karyotypes or significant cytopenia HSCT must be carefully considered given the risk of HSCT-related complications for many of the genetic disorders; long-term survival is significantly inferior compared to HSCT in individuals with sporadic MDS. Patients with myelodysplasia-related AML may need cytoreductive therapy prior to HSCT. While outcome of HSCT in pediatric cohorts with predisposition syndromes and MDS/AML has been published by several investigators [7,44], experience in HSCT in adult patients with these disorders is sparse [45].

When a family member qualifies as a potential donor for a patient with a predisposition syndrome care must be taken that the donor is not a (yet) asymptomatic carrier. With a germline mutation in the patient identified, genetic testing on the donor's blood can be performed in a timely fashion. In the absence of a known genetic alteration but a strong family history a matched unrelated donor for HSCT is preferred over an HLA compatible sibling [46]. For young patients with MDS, it is strongly advised to exclude bone marrow pathology in a potential family donor even in the presence of normal blood counts and irrespective of family history. A bone marrow aspirate for cytology and cytogenetic analysis as well as a bone marrow biopsy for histopathology with evaluation of cellularity are recommended. These investigations need to be performed well in advance of the planned

transplant date. Excluding a family donor in case of unexpectedly decreased bone marrow cellularity will avoid graft failure [47]. When in doubt, early initiation of an unrelated donor search is advisable.

Surveillance and prevention

Lifetime risk of MDS/AML varies among the different familial syndromes. For *RUNX1* germline mutations, less than half of the persons carrying a mutation will develop MDS/AML; the prevalence of malignancy in families ranges from 20% to 60% [48]. No information is currently available to predict which carrier will develop malignancy or when. The risk of myeloid neoplasia is considerably higher in GATA2 deficiency approaching 90% at 60 years of age [6]. Clinical phenotype in *GATA2* germline carriers is substantially biased by the nature of the cohort studied [6, 7]. Like *GATA2*, *CEBPA* germline mutations are highly penetrant, with AML presenting at a median age of 25 years (range, 1.75-46 years) [49]. Mean age of onset of MDS/AML in germline *DDX41* mutation carriers is 62 years with younger age of onset for some mutations [10]. For individuals with germline *TERT* or *TERC* mutations life time risk of MDS/AML is unknown because the range of diseases affected by telomere length disequilibrium has recently been extended to include idiopathic pulmonary fibrosis and others [25].

With more cases of MDS/AML diagnosed of an underlying predisposition syndrome, penetrance may be less than expected suggesting that genetic modifiers play a more potent role. Variable penetrance and anticipation with offspring developing symptoms before their parents or grandparents complicate the development of guidelines for surveillance. Current recommendations for hereditary leukemia are expert-opinion-based and in large part modeled after clinical guidelines for Fanconi Anemia and Li-Fraumeni syndrome [29].

For individuals diagnosed as asymptomatic carrier initial investigations recommended include a physical examination, a complete blood count (CBC) and a bone marrow

examination with cytogenetic analysis for exclusion of MDS/AML as well as evaluation of the carrier's bone marrow morphology in an unaffected state. In addition, marrow and blood can be biobanked for future reference and/or research. Enrollment in research studies and clinical registries should be offered to all affected individuals.

Recommendations for surveillance depend on the nature of the predisposition syndrome and on the carrier's perceived individual risk. For young adults with GATA2 deficiency screening including bone marrow examinations with cytogenetics performed at least annually can be recommended. These individuals may also benefit from a targeted NGS approach. Emergence of key somatic events like mutations in *SETBP1* or *ASXL1* is known to be associated with rapidly progressive disease [50, 51]. Germline mutations might influence the selection of early events and/or acquisition of subclonal mutations [52, 53, 49] which in turn could facilitate monitoring of carriers at risk.

In the absence of evidence-based data hematologists often recommend a physical examination and CBC every 6 - 12 months for surveillance of susceptibility to MDS/AML [29]. A decline in platelet count or hemoglobin concentration, an increase in mean corpuscular volume (MCV) of red cells or any significant change in white blood count (WBC) need to trigger an in depth evaluation. Compliance with these recommendations may be limited specifically in conditions with low penetrance (*RUNX1* germline mutation) or long latency to MDS/AML (*DDX41* germline mutations). Furthermore, in CEBPA-associated familial AML, regular CBCs may not ensure early diagnosis of malignancy since the condition lacks a MDS pre-phase.

Preventive measures decreasing the risk of MDS/AML in familial predisposition syndromes are currently unknown. In telomere biology disorders androgen therapy can improve bone marrow failure possibly by telomere elongation [54]. Because short telomeres have been implicated in genetic instability, one might speculate that mitigation of telomere erosion by

androgens can abrogate early molecular steps in chromosomal instability and clonal development. Particularly for familial disease with additional susceptibility for solid tumor, avoidance of risk factors like alcohol and nicotine and prophylactic vaccination including HPV immunization is recommended, although formal proof of efficacy of these measures is pending.

For most families, the diagnosis of a leukemia predisposition syndrome initiates a life-long confrontation with existential questions. Providing affected children and young asymptomatic carriers the necessary emotional support and guidance while they grow up is a particular challenge. Developmentally appropriate information can provide practical knowledge and help children to understand what is going on in their families and why certain tests are recommended. Adolescent carriers often perceive their predisposition syndrome as severe burden for life. Physicians, counselors and psychologists need to enable them to become proactive with issues concerning their health, relationships and future plans.

Summary

Adult and pediatric hematologists are increasingly confronted with genetic predisposition syndromes for MDS/AML in daily clinical care. Accurate diagnosis of these conditions has impact on treatment, surveillance, prevention and counseling. A sophisticated grasp of clinical genetics and molecular techniques will help care takers to keep up with this rapidly evolving field and manage their patient's care adequately.

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Table 1: Scenarios when genetic testing for predisposition genes is advised in newly diagnosed patients with MDS/AML.

Scenarios for germline testing of MDS/AML predisposition genes	
1.	Somatic testing identified a mutation associated with germline predisposition
2.	Hematologic or cytogenetic characteristics of MDS/AML suggestive of germline predisposition
3.	Non-hematological phenotype of patient suggestive of genetic syndrome known to predispose to cancer
4.	Previous malignancy
5.	Family history cancer, cytopenia, autoimmunity or organ-system manifestation fitting a predisposition syndrome