

Germline predisposition to myeloid neoplasms Recommendations for genetic diagnosis, clinical management and follow-up

Nordic guidelines

Version 1.0, May 20th 2019

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Abbreviations

Allo-HSCT	Allogeneic haematopoietic stem cell transplantation
AML	Acute myeloid leukemia
CBC	Complete blood count
CNVs	Copy-number variations
MDS	Myelodysplastic syndrome
MLPA	Multiplex ligation amplification
MN	Myeloid neoplasms
NGS	Next-generation sequencing
NMDSG	Nordic MDS group
SNVs	Single nucleotide variants
VAF	Variant allele frequency
WES	Whole exome sequencing
WGS	Whole genome sequencing

Background

Although the majority of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) cases are considered to be sporadic, the introduction of next-generation sequencing (NGS) into the diagnostic work-up has revealed that hereditary MDS or AML (MDS/AML) are more common than previously thought. Estimates suggest that about 5%-15% of adults and 4-13% of pediatric patients with MDS/AML carry germline pathogenic variants in cancer susceptibility genes¹⁻⁴. At the same time, several new genes associated with familial MDS/AML, with or without syndromic features, have been recently discovered, such as *GATA2*, *ETV6*, *DDX41*, *SAMD9*, and *SAMD9L*⁵⁻²⁰.

In 2016, *myeloid neoplasms with germline predisposition* were included as a new dedicated entity in the revision of the WHO classification of myeloid neoplasms (Table 1), thus acknowledging the clinical importance of recognizing these disorders during the diagnostic work-up of patients with myeloid malignancies²¹. Consideration of MDS/AML germline predisposition syndromes has also been integrated in the clinical management guidelines of patients with MDS/AML of the European Leukemia Net and the National Comprehensive Cancer Network^{22,23,5,6}. In addition, experts in this field have provided recommendations on which patients should be investigated for germline predisposition syndromes, and how such patients and families should be managed²⁴⁻³². For specific disorders such as Fanconi anaemia³³, Shwachman-Diamond syndrome³⁴, Diamond-Blackfan anaemia³⁵, and telomere biology disorders³⁶ consensus guidelines already exist, but for the other rare disorders predisposing for MDS/AML, international recommendations and guidelines for adult patients have not yet been developed³⁷.

Recognition of a specific germline predisposition in the individual patient with MDS/AML is important not only for psychological reasons providing an explanation for the disease, but also because of clinical implications as it may tailor therapy, dictate the selection of donor for allogeneic haematopoietic stem cell transplantation (allo-HSCT) and determine the conditioning regimen³⁸. For disorders with extra-haematopoietic manifestations, a molecular diagnosis may enable prophylactic measures, early intervention or contribute to avoid unnecessary or even harmful medication³⁹. Finally, it allows for genetic counselling and follow-up of at-risk family members³⁹.

The rarity of hereditary MDS/AML combined with the heterogeneous clinical presentation makes identification of these patients challenging. For this reason, the Nordic MDS group (NMDSG) decided to establish a working group with the purpose of creating and implementing common Nordic clinical guidelines to ensure uniformity in diagnostic procedures and management of patients and their family members at risk. The working group members are haematologists, pediatricians and clinical/medical geneticists from Sweden, Norway, Finland and Denmark. The initial focus of the working group was on the adult MDS/AML patients with a germline predisposition, but it is the hope that these guidelines may also be of value in other settings.

This document presents the first version of Nordic recommendations for a diagnostic algorithm, surveillance, and considerations for allo-HSCT for patients and carriers of a germline mutation predisposing to MDS/AML. It will be posted on the NMDSG website (NMDSG.org) and regularly updated. Please contact mette.klarskov.andersen@regionh.dk or panagiotis.baliakas@igp.uu.se if you have any suggestions for further improvement or update.

Summary pages

Pages 5-6 represent a summary of the entire document

Whom to test genetically

A: Patients with positive family history or signs/symptoms indicative of a hereditary condition predisposing to myeloid neoplasms (MN) especially MDS/AML.

A1: Patient with MDS/AML and symptoms/signs of a hereditary condition predisposing to MN development diagnosed before the age of 50.

A2: Two individuals (first or second degree relatives, FDR and SDR, respectively) with MDS/AML or long lasting thrombocytopenia or symptoms/signs indicative of a hereditary condition predisposing to MN development, one of whom diagnosed before the age of 50.

A3: One individual with MDS/AML and two FDR or SDR with a diagnosis of solid tumor malignancy one of whom diagnosed before the age of 50.

A4: ≥ 3 FDR or SDR with MN or long-lasting thrombocytopenia or symptoms/signs indicative of a hereditary condition predisposing to MN development, independently of age.

B: Patients with MN where the diagnostic work-up for the determination of the somatic genomic background has detected variants suspected to be germline

A number of variants that cause MN with germline predisposition can be also detected as somatic in sporadic cases. An indication that a variant may be of germline origin can be the variant's allele frequency (VAF) [near-heterozygous (40 % – 60 %) or near-homozygous (90 %)]. In such cases further testing of extra-haematological tissue for the respective variant is highly recommended after obtaining the patient's consent.

C: Patients not fulfilling the criteria A and B diagnosed with MDS/AML before the age of 50 carrying aberrations of chromosome 7 [monosomy 7/del(7q)/der(7)].

A family or personal history without any suspicion of a hereditary disorder does not exclude an underlying predisposing germline variant. Several reports in the literature favor genetic testing for hereditary conditions predisposing to MN for all young patients. We propose that among young patients (<50 at diagnosis) without a family or personal history only those with aberrations of chromosome 7 (monosomy 7/del(7q) or other aberrations with loss of 7q material), which is particularly common in *GATA2*- and *SAMD9/SAMD9L*-related disorders should be further referred for genetic counselling/testing.

How and what to test

Genetic testing should be performed with the aim to detect both single nucleotide variants (SNVs) and copy-number variations (CNVs). We propose a number of genetic conditions that should be excluded for all patients fulfilling the above-mentioned criteria (Table 1) as well as a respective diagnostic algorithm (Figure 1). Regarding the tissue that should be analysed we recommend fibroblasts obtained after skin biopsy, especially in cases fulfilling criteria A and C. Other alternatives such as blood in remission or sorted T-cells isolated from blood may also be considered.

Surveillance of individuals with a germline predisposition to MDS/AML

All patients including asymptomatic carriers with a germline predisposition to MDS/AML should be referred to and subsequently followed by a haematological center with expertise in hereditary malignancies to ensure adequate monitoring and tailored treatment (Table 3). The haematological center/department is strongly recommended to collaborate closely with a clinical geneticists/medical genetic department with expertise in diagnosing and genetic counselling of hereditary haematologic disorders.

Indication for allo-HSCT

All patients that have developed MN on the basis of a genetic predisposition except those diagnosed with AML associated with germline variants in *CEBPA*, are potential candidates for allo-HSCT. Please note that MDS/AML patients with germline *DDX41* mutations are often older and no specific recommendation regarding allo-HSCT can be made at the moment due to a lack of data. It should be further highlighted that each case should be referred for discussion within an expert transplant panel.

Genetic counselling

All patients with a germline predisposition to MN should be offered genetic counselling. This also includes patients with a positive family history where the genetic pathogenic variant has not been identified. Genetic counselling is mandatory prior to genetic testing of all healthy relatives for germline predisposition for MN including predictive testing of HLA-identical potential family donors.

Which patients should be tested for germline conditions predisposing to myeloid neoplasms

Who should test patients suspected for germline disorders

Diagnostic genetic testing for germline variants in patients with MDS/AML may be performed by the clinical/medical geneticist as part of genetic counseling or requested by a specialized haematologist without prior referral to genetic counselling, depending on the legislation of each country. However, it is important that genetic counselling is offered to all patients investigated for potential germline conditions, even if no pathogenic variant is detected.

Genetic counselling is mandatory prior to genetic testing of all healthy relatives for germline predisposition for myeloid neoplasms (predictive and presymptomatic testing) including predictive testing of HLA-identical potential family donors.

Criteria for whom to test

For the development of the following criteria a number of factors have been considered

- Age
- Family history
- Personal medical history
- Clinical/physical findings
- Genetic characterization of the clonal cells
- Recommendations published in the recent literature
- Our clinical experience thus far

A: Patients with positive family history or signs/symptoms indicative of a hereditary condition predisposing to myeloid neoplasms (MN) especially MDS/AML.

A1: Patient with MDS/AML and symptoms/signs of a hereditary condition predisposing to MN development*¹ diagnosed before the age of 50.

A2: Two individuals (first or second degree relatives, FDR and SDR, respectively) with MDS/AML or long lasting thrombocytopenia or symptoms/signs indicative of a hereditary condition predisposing to MN development*¹, one of whom diagnosed before the age of 50.

A3: One individual with MDS/AML and two FDR or SDR with a diagnosis of solid tumor malignancy*² one of whom diagnosed before the age of 50.

A4: ≥ 3 FDR or SDR with MN or long-lasting thrombocytopenia or symptoms/signs indicative of a hereditary condition predisposing to MN development*¹, independently of age.

*¹: excessive toxicities with chemotherapy or radiation, multiple cancer diagnoses, therapy-related leukaemia, poor mobilization of a sibling candidate donor^{28,40}, consanguinity, skin or nail abnormalities, unexplained liver disease, pulmonary fibrosis or alveolar proteinosis, short stature, microcephaly or characteristic skeletal abnormalities or other congenital abnormalities, Café au lait spots, hypopigmented macules, lymphedema, immune deficiencies, atypical infections, excessive warts.

*²: other haematological malignancies or cancer forms suggestive of constitutional mismatch repair deficiency syndrome, Li-Fraumeni syndrome, *BRCA2* related syndromes (such as sarcomas, adrenocortical carcinomas, brain tumors, gastrointestinal, genitourinary, breast, ovarian and pancreas cancer)

It should be noted that a number of conditions included in criterion A may appear with atypical or no clinical stigmata, therefore a detailed personal and family history including a three generations pedigree is needed. In order to facilitate the obtainment of such a history the use of a questionnaire proposed by Churpek et al. from the Chicago group is recommended³¹.

B: Patients with MN where the diagnostic work-up for the determination of the somatic genomic background has detected variants suspected to be germline (near heterozygous or near homozygous).

A number of variants that cause MN with germline predisposition can be also detected as somatic in sporadic cases. Classical examples are variants within the *RUNX1*, *GATA2*, *TP53*, *ETV6* and *CEBPA* genes. Analysis of such variants with the advent of NGS panels is performed routinely as part of the diagnostic work-up for MDS/AML patients, especially in young individuals. An indication that a variant may be of germline origin can be the variant's allele frequency (VAF) [near-heterozygous (40 % – 60 %) or near-homozygous (90 %)]. In such cases further testing of extra-haematological tissue for the respective variant is highly recommended after obtaining the patient's consent. The detection of a pathogenic germline variant through a somatic gene panel is more likely in younger MDS/AML patients (<50 years), but may also be identified in older age groups. Particularly, variants in the *DDX41* gene are associated with MDS/AML between 55-65 years of age. Furthermore, the type of variant may be of importance, for example truncating variants in the *DDX41* gene are usually of germline origin.

It should be highlighted that the majority of the NGS panels used in the current clinical setting are designed for the detection of somatic variants, therefore a normal result does not preclude the possibility of a germline variant in regions not included in the actual analysis.

C: Patients not fulfilling the criteria A and B diagnosed with MDS/AML before the age of 50 carrying aberrations of chromosome 7 [monosomy 7/del(7q)/der(7)].

A family or personal history without any suspicion of a hereditary disorder does not exclude an underlying predisposing germline variant. *De novo* mutations, gonadal mosaicism, genetic reversion, variable penetrance and expressivity may explain the absence of distinctive clinical features. It is well established that early cancer debut strongly implies heredity¹. Several reports in the literature favor genetic testing for hereditary conditions predisposing to MN for all young patients^{5,41}. That said and for the time being, our working group proposes that among young patients (<50 at diagnosis) without a family or personal history only those with aberrations of chromosome 7 (monosomy 7/del(7q) or other aberrations with loss of 7q material), which is particularly common in *GATA2*- and *SAMD9/SAMD9L*-related disorders,^{16,17,42-44} should be further referred for genetic counselling/testing.

Preliminary data suggest that specific somatic gene variants may likewise be over-represented in some disorders predisposing for MN^{10,45-47}. They may in the future prove to be useful indicators to identify patients with MN who do not meet the standard criteria for genetic testing for a predisposing germline variant⁴⁷.

We think that testing all young patients independently of family/personal history could be performed primarily in the context of clinical trials rather than in a clinical setting, at least for the time being. If, however, resources are available and national guidelines approve genetic counselling/investigation for MDS/AML predisposing syndromes could be offered to all young patients.

Limitations of the proposed criteria to take into consideration

It is important to highlight that the current criteria are focused mainly on known genetic predisposition syndromes for MDS/AML. The proposed age threshold of 50 years at the time of diagnosis is arbitrary and conditions such as predisposition for MDS/AML due to germline *DDX41* mutations or patients debuting at a later age than expected may be underrepresented. Moreover, a number of genetic aberrations predisposing to the development of myeloid neoplasms may have not yet identified, therefore some patients may not fit the aforementioned criteria. However, they may still be eligible for genetic counselling/investigation. In case of any

clinical suspicion of a hereditary condition not included in the following criteria, a referral to an institution with expertise in the field is recommended.

How should patients with MN and suspicion of germline predisposition be genetically investigated

Genetic testing should be performed with the aim to detect both single nucleotide variants (SNVs) and copy-number variations (CNVs). It is not our goal to provide guidelines on the actual technique that should be used in each laboratory, as long as the genetic testing is performed following validated and accredited methodologies. Instead we propose a number of genetic conditions that should be excluded for all patients fulfilling the above-mentioned criteria (Table 1). For the diagnostic procedure of the well described IBMFS, Fanconi anaemia, telomere biology disorders, Shwachman-Diamond syndrome and Diamond-Blackfan anaemia, we refer to the respective international guidelines³³⁻³⁶. As a suggestion and in order to provide solid and timely genetic testing for patients fulfilling criteria A and C we propose upfront the performance of either whole exome sequencing (WES), whole genome sequencing (WGS) or large NGS panels complemented with the *in silico* CNV calling and/or laboratory analysis for CNVs, such as microarrays testing or MLPA (multiplex ligation amplification). At the moment WGS is, however, not widely established in the clinical setting, but is being investigated as an alternative method in the Nordic countries.

If a potential germline variant has been detected in a somatic gene panel as part of the diagnostic work up for MN (see Criteria B above), further testing of extra-haematological tissue for the respective variant is highly recommended after obtaining the patient's consent. The patient may ideally be referred to genetic counselling for further information prior to testing of extra-haematological tissue.

Diagnostic algorithm

Please see Figure 1 for a proposal for a diagnostic algorithm. It should be highlighted that for specific syndromes such as *GATA2*-related disorders and *ANKRD26* even noncoding regulatory regions should be covered. Functional analyses may be of value in Fanconi anaemia, telomere biology disorders and Diamond-Blackfan anaemia especially when a variant of uncertain significance is detected. For laboratories performing such functional tests, see Table 2.

Tissue for genetic testing

Regarding the tissue that should be analysed we recommend fibroblasts obtained after skin biopsy, especially in cases fulfilling criteria A and C. In selected cases other alternatives such as blood in remission may also be appropriate. In cases included in criterion B a stepwise procedure with targeted analysis of sorted T-cells isolated from blood may be the first step. In case of confirmation of the pathogenic variant in the T-cells, a skin biopsy should also be performed. For carrier testing of healthy family members DNA from a whole blood sample can be used. Carrier testing, presymptomatic and predictive testing of healthy relatives always requires genetic counselling before and after genetic testing.

Genetic counselling

All patients with a germline predisposition to MN should be offered genetic counselling. This also includes patients with a positive family history where the genetic pathogenic variant has not been identified. If the patient has not already received genetic counselling as part of the diagnostic procedures, it is important to refer to such counselling to ensure identification and counselling of family members at risk.

Surveillance of individuals with a germline predisposition to MDS/AML

The overall goal of surveillance and monitoring of patients with a germline predisposition to MDS/AML is to ensure intervention prior to development of high-risk disease. However, uncertainty regarding penetrance and age-adjusted risk of MDS/AML transformation makes it highly challenging to time such intervention correctly. In addition, germline disorders presenting as cytopenia, IBMFS or MDS may benefit more from surveillance as opposed to germline predisposition disorders presenting primarily as overt AML, especially if they occur in the context of a cancer syndrome with more than one organ involvement.

As very little evidence-based data exist on the efficacy and benefit of surveillance in individuals with germline predisposition to MDS/AML, published recommendations for surveillance are solely based on expert opinion^{27,29,39,42,48}. For the classical IBMF syndromes like Fanconi anaemia, Shwachman-Diamond syndrome, Diamond-Blackfan anaemia, and telomere biology disorders guidelines for surveillance already exist and should be followed when indicated in both children and adults^{33-36,49}.

For whom is surveillance indicated

These recommendations for surveillance are intended for

A: Individuals with a deleterious or likely deleterious genetic variant associated with a germline predisposition regardless of clinical presentation.

B: Individuals who fulfil the clinical diagnostic criteria for a myeloid neoplasm with a germline predisposition even if the pathogenic genetic variant is undetermined.

The recommendations do in general not apply to individuals with a variant of uncertain significance (VUS) in whom clinical diagnostic criteria for a specific predisposition disorder are absent.

If presymptomatic testing is impossible due to an unidentified pathogenic variant, and the family history is highly suggestive of hereditary MDS/AML, first-degree relatives to an affected relative may in selected cases be considered for surveillance after genetic counselling.

Surveillance and follow-up at a haematology center with specialized expertise in disorders associated with germline predisposition to MDS/AML

All patients including asymptomatic carriers with a germline predisposition to MDS/AML should be referred to and subsequently followed by a haematological center with expertise in hereditary malignancies to ensure adequate monitoring and tailored treatment. The haematological center/department is strongly recommended to collaborate closely with a clinical geneticists/medical genetic department with expertise in diagnosing and genetic counselling of hereditary haematologic disorders. If the patient has not already received genetic counselling as part of the diagnostic procedures, it is important to refer to such counselling to ensure identification and counselling of relatives at risk.

All patients should undergo physical examination at regular intervals, be educated about presentation and symptoms of MDS/AML and signs of other relevant conditions, and informed of limitations and benefits associated with surveillance.

Start of surveillance programs of asymptomatic mutation carriers must be individualized according to the typical age of myeloid neoplasm in the specific disorder and in the family. As

examples *DDX41* associated MDS/AML presents in mid to late adulthood¹³ whereas bone marrow failure syndromes typically present in childhood.

Work-up for patients with a germline predisposition to MDS/AML

Baseline

Initially all patients should have a diagnostic work-up for MDS/AML including a complete blood count (CBC) with manual differential and a bone marrow aspirate/biopsy with cytogenetic analysis and testing for somatic mutations on a myeloid gene panel according to the NMDSG guidelines. These investigations serve to exclude MDS or a manifest bone marrow failure disorder and as a baseline for subsequent comparison. It is important to recognize that asymptomatic carriers may present with varying blood counts ranging from normal CBC, mild cytopenia to severe aplastic anaemia. Also, carriers of *RUNX1*, *ANKRD26* and *ETV6* variants may have thrombocytopenia or bleeding tendency without thrombocytopenia at baseline^{20,50-55}.

Follow-up

At the moment it is debatable how often routine follow-up investigations should be performed to monitor for disease progression.

Complete blood counts. The working group agreed that CBC should be repeated every 6 months particularly in high-risk patients i.e. those with pathogenic variants in *GATA2*, *RUNX1* or Fanconi complex genes.

If changes to abnormal values in blood counts develop, CBC should be repeated within a few weeks, other causes of cytopenia should be excluded, and a bone marrow biopsy/aspirate should be performed. Even a slight drop in thrombocytes just below normal range should warrant further investigations. See below.

Bone marrow aspirate/biopsy. Bone marrow aspirate/biopsy should not be routinely repeated if the CBC values are stable and other indications of progressive disease are absent. American guidelines in children and adults recommend annual bone marrow aspirate/biopsy in high-risk disorders^{39,48}, because blood counts may not be sensitive enough as a marker for progression. However, it is the experience of the working group that asymptomatic carriers do not in general consent to annual bone marrow aspirate/biopsies and that the lack of compliance is not outweighed by the benefits of the procedure.

If deterioration of blood counts occurs on consecutive CBC, a bone marrow biopsy/aspirate is mandatory to examine for changes in bone marrow cellularity, dysplasia, blast percentage, clonal cytogenetic evolution, and somatic mutations.

Regarding clonal cytogenetic evolution it is important to note that some acquired aberrations like monosomy 7/del(7q)/der(1;7) and a complex karyotype are associated with high risk of malignant transformation, whereas others do not increase leukemic risk and can remain stable for long periods of time or even disappear. Isochromosome 7q and del(20q) in Shwachman-Diamond syndrome are examples of cytogenetic aberrations without associations to disease progression^{56,57}.

Testing of peripheral blood for somatic mutations. There was consensus in the working group about the potential value of annual testing for somatic gene mutations with a NGS gene panel targeting myeloid genes with high coverage and reading depth. This recommendation is based on recent reports which highlight the emergence of clonal haematopoiesis associated with increased risk for the development of AMD/AML in hereditary conditions, mainly those related to germline *GATA2* and *RUNX1* mutations^{47, 6,45,46}. The frequency of testing for somatic mutations and the clinical implications are, however, undefined in most other patients with

germline predisposition to MDS/AML. Nevertheless, appearance in the blood of a new somatic mutation or an increase in variant allele frequency of an already existing clone should lead to further investigations including a bone marrow aspirate/biopsy in exactly the same way as emerging cytopenia (see “Complete blood count” above). The emergence of a clone should not solely be an indication for clinical action⁶. The gene, the VAF, the number of pathogenic variants as well as the dynamics over time should be taken into account. It should also be noted that the above-mentioned myeloid NGS panels are designed to include the great majority of potential somatic genomic aberrations that occur at the MDS/AML transformation, however they are restricted in their targets and a normal result cannot exclude somatic variant in genes not included in the panel-design.

For an overview of baseline and follow-up investigation of individuals with a germline predisposition see Table 3.

Management and surveillance of other organ dysfunction

Patients with germline predisposition to MDS/AML with risk of other organ dysfunction must be referred by the haematologist or the clinical/medical geneticist to a hereditary cancer clinic or to relevant medical disciplines/specialties to ensure screening for solid tumors and organ dysfunction depending on the specific risks and according to existing guidelines^{10,33-36}.

Referral to genetic counselling when family planning is relevant

Patients with germline predisposition to MDS/AML should be referred to genetic counselling when family planning is ongoing and preferably before pregnancy. At genetic counselling the couple should be informed about the risk in their offspring of inheriting the predisposition and options, if any, for prenatal diagnostics.

Recommendations for allo-HSCT

This section contains recommendations regarding indication, timing, donor selection, conditioning and follow-up of allogeneic HSCT for patients with “myeloid neoplasms with germline predisposition”. Please note that especially the timing and the indication for allo-HSCT are based on expert-opinion due to the novelty and rarity of these syndromes.

Indication for allo-HSCT

All patients of a suitable age, who have developed MN on the basis of a genetic predisposition except those diagnosed with AML associated with germline variants in *CEBPA*, are potential candidates for allo-HSCT. It should be highlighted that each case should be referred for discussion within an expert transplant panel that may even include international specialists in the field.

Timing of allo-HSCT

The exact diagnosis according to the WHO 2016 classification for myeloid neoplasms influences when allo-HSCT ought to be performed in the course of the neoplasm.

A: Myeloid neoplasm with germline predisposition without a pre-existing disorder or organ dysfunction

Patients with germline *CEPPA* mutations have no absolute indication for allo-HSCT in CR1 because they can experience long remissions after conventional chemotherapy⁵⁸, but the risk of new leukemic clones is still high for which reason allo-HSCT may be considered at some time point in these patients. MDS/AML patients with germline *DDX41* mutations are often older and no specific recommendation regarding allo-HSCT can be made at the moment due to a lack of data^{13,14}.

B: Myeloid neoplasm with germline predisposition and pre-existing platelet disorder

For the time being there is no indication for allo-HSCT until the development of a manifest MN.

C: Myeloid neoplasm with germline predisposition and other organ dysfunction

These syndromes show high risk of developing MN with a relatively early onset. Therefore, allo-HSCT could be considered before transformation occurs to prevent mortality due to other manifestations (*GATA2* related disorders) and to spare the patient the side effects of myeloablative conditioning and reduce the risk for relapse¹⁰. In some individuals even organ dysfunctions or life threatening immunodeficiency can be an indication for allo-HSCT.

Donor selection

It is crucial to refrain from using an affected family member or an asymptomatic known carrier as donor in order to avoid graft failure and/or donor derived leukemia³⁸. In families with an identified germline predisposing pathogenic variant we recommend genetic testing of any potential compatible donor in the absence of any signs/symptoms before HSCT. The genetic testing of a potential donor must be performed only after genetic counselling in respect of the individual's integrity and right "not to know" his or her carrier status. This procedure may take time, and in such cases a well-matched unrelated donor may be first choice to avoid harmful delay of the transplantation.

In families with a positive family history where the underlying genetic cause has not been identified an unrelated donor may be preferred even in the presence of phenotypically "healthy" matching family donors. However, donor selection must depend on availability and match.

Conditioning regimen

Individuals with IBMFS, like Fanconi anaemia and telomere biology disorders, show an increased sensitivity to chemotherapy and specific dose-reduced conditioning regimens are recommended (for more information please see the respective treatment recommendations)^{33,36,49}.

Reduced intensity conditioning transplantation can also be used for patients with *GATA2* related syndromes before they have transformed because functional and numeric defects in the immune and hematopoietic stem cells will allow it⁵⁹.

Once the patients have developed a myeloid neoplasm more intensive conditioning regimens can be considered.

Follow up after allo-HSCT

Allogeneic HSCT increases the risk for secondary tumors but many patients which fall into the category "myeloid neoplasm with genetic predisposition and other organ dysfunction" have a specifically high risk so they should be monitored even more closely after allo-HSCT.

Concluding remarks

Germline predisposition to myeloid neoplasms is a new and rapidly emerging field, which significantly impacts therapy and care of involved patients and family members. Hence it is crucial that haematologists and clinical/medical geneticists have the basic knowledge to suspect a germline disorder. These Nordic guidelines are intended to support clinicians when dealing with patients with a potential germline predisposition to MDS/AML. The working group is aware that the criteria for genetic testing are conservative which reflect that genetic testing is not widely available in all Nordic countries. However, this approach is aimed at identifying highly penetrant germline disorders, and as mentioned above the recommendations need to be updated and revised regularly.

At present we lack understanding on many biological and clinical aspects of the well-known and new germline disorders with increased risk of MDS/AML. Joint research projects and registries are urgently needed, and we strongly encourage haematologists and clinical/medical geneticists with special interest and expertise in the field to actively take part in such research activities.

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Table 1. Overview of germline conditions predisposing to myeloid neoplasms (adapted from WHO 2016 book chapter and NCCN MDS v1.2019)

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction						
Acute myeloid leukemia with germline <i>CEBPA</i> mutation	<i>CEBPA</i>	AD	AML	>80%	-	DNA sequencing including del/dup analysis
Myeloid neoplasms with germline <i>DDX41</i> mutation	<i>DDX41</i>	AD	MDS, AML	Unknown, probably high but mostly in older age	CML, CMML and lymphomas have also been reported	DNA sequencing
Chromosome 14q32 duplication syndrome	14q32 genomic duplication	AD	AML, MPNs, CMML	High penetrance in the 5 families reported	-	Del/dup analysis
Myeloid neoplasms with germline predisposition and pre-existing platelet disorders						
Myeloid neoplasms with germline <i>RUNX1</i> mutation (Familial platelet disorder with associated myeloid malignancy)	<i>RUNX1</i>	AD	MDS, AML	~45%	Thrombocytopenia and abnormal platelet function; clonal hematopoiesis; ALL	DNA sequencing including del/dup analysis
Myeloid neoplasms with germline <i>ANKRD26</i> mutation	<i>ANKRD26</i>	AD	AML, MDS, CML	8%	Moderate thrombocytopenia with mild bleeding manifestations	DNA sequencing of 5'UTR
Myeloid neoplasms with germline <i>ETV6</i> mutation	<i>ETV6</i>	AD	ALL, AML, MDS	Unknown	Thrombocytopenia and mild bleeding manifestation	DNA sequencing

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
Myeloid neoplasms with germline predisposition and other organ dysfunction						
GATA2 deficiency syndrome	GATA2	AD	MDS, AML	>80%	Immunodeficiency (B-/NK-/CD4-cell lymphocytopenia, monocytopenia), susceptibility to viral infections, warts, disseminated nontuberculous mycobacterial infections, lymphedema, sensorineural hearing loss, pulmonary alveolar proteinosis	DNA sequencing (including intronic regions) and del/dup analysis
MIRAGE syndrome	SAMD9	AD	MDS, AML with monosomy 7	High, spontaneous resolution through revertant mosaicism possible	Cytopenias and marrow failure; growth restriction, infection susceptibility, adrenal hypoplasia, genital phenotypes, and enteropathy.	DNA sequencing
Ataxia-pancytopenia syndrome	SAMD9L	AD	MDS, AML with monosomy 7	High, spontaneous resolution through revertant mosaicism possible	Cytopenias and marrow failure; gait disturbance, nystagmus, cerebellar atrophy and white matter hyperintensities; immunodeficiency	DNA sequencing

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
Bone marrow failure syndrome 1 (BFMS1/SRP72)	<i>SRP72</i>	AD	MDS	Unknown	Congenital sensorineural deafness	DNA sequencing
Fanconi anaemia	<i>FANCA</i>	XLR	MDS, AML	~10%	Bone marrow failure, short stature, skin pigmentation (café-au-lait or hypopigmented spots), skeletal anomalies (thumbs, arms), congenital heart disease, ear anomalies, renal malformations, squamous cell carcinomas)	DNA sequencing including del/dup analysis Chromosomal breakage analysis
	<i>FANCB, FANCC, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCM, PALB2, RAD51C, SLX4</i>	AR				
Severe congenital neutropenia	<i>ELANE, CSF3R, GFI1, SRP54</i>	AD	MDS, AML	21-40%	Severe neutropenia	DNA sequencing including del/dup analysis
	<i>HAX1, G6PC3, JAGN1, VPS45</i>	AR				
	<i>WAS</i>	XLR				
Shwachman-Diamond syndrome	<i>SBDS</i>	AR	MDS, AML, ALL	5-24%	Neutropenia, pancreatic insufficiency, short stature, skeletal abnormalities	DNA sequencing including del/dup analysis
Diamond-Blackfan anaemia	<i>RPS19, RPS17, RPS24, RPL35A, RPL5, RPL11, RPL15, RPL26,</i>	AD	MDS, AML, ALL	~5%	Anemia and marrow erythroid hypoplasia. Small stature, congenital anomalies (e.g.	DNA sequencing including del/dup analysis

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
	<i>RPS7, RPS26, RPS10, RPS29</i>				craniofacial, cardiac, skeletal, genitourinary)	Elevated erythrocyte adenosine deaminase
	<i>GATA1</i>	XLR				
Telomere biology disorders	<i>DKC1</i>	XLR	MDS, AML	2-30%	Bone marrow failure, nail dystrophy, abnormal skin and pigmentation, oral leukoplakia, early hair graying, pulmonary fibrosis, hepatic fibrosis, squamous cell carcinoma	DNA sequencing including del/dup analysis Telomere length analysis
	<i>TERT, TERC, TINF2, RTEL1, PARN, ACD</i>	AD				
	<i>NOP10, NHP2, WRAP53, RTEL1, TERT, CTC1, PARN, ACD</i>	AR				
Down syndrome	Trisomy 21	95% De novo, 5% translocation	Transient abnormal myelopoiesis/ AML, Acute megakaryoblastic leukemia, ALL	10% (transient abnormal myelopoiesis) ~2-3% ALL, AML	Down syndrome: multiple congenital anomalies, dysmorphic features, intellectual disability	Karyotype
RASopathies	<i>CBL, KRAS, NF1, PTPN11</i>	AD	JMML, AML	~10%	Short stature, facial features, cardio-thoracic defects, coagulopathy	DNA sequencing
Constitutional mismatch repair deficiency	<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	AR	ALL, lymphomas, AML, MDS	Unknown, risk ~30% for lymphoma/ALL	Café-au-lait spots, brain tumors, colorectal cancer, osteosarcoma, and other solid tumors.	DNA sequencing including del/dup analysis

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
Bloom syndrome	<i>BLM</i>	AR	ALL, AML/MDS, lymphoma	15%	growth deficiency, photosensitive skin changes, immunodeficiency, early-onset diabetes, microcephaly, high-pitched voice, hypogonadism, risk for other cancers	DNA sequencing including del/dup analysis
<i>LIG4</i> syndrome	<i>LIG4</i>	AR	MDS	Rare (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6096036/)	Short stature, microcephaly, Immunodeficiency combined; pancytopenia & myelodysplastic syndrome	DNA sequencing including del/dup analysis
Li Fraumeni syndrome	<i>TP53</i>	AD	ALL, MDS, AML	2-4%	High risk for cancer (50% by age 30 years and 90% by age 60 years) especially high risk for adrenocortical carcinoma, brain cancer, breast cancer, choroid plexus carcinoma, colon cancer, lung carcinoma, sarcoma, other tumors.	DNA sequencing including del/dup analysis
Other bone marrow failure syndromes	<i>MECOM</i>	AD	MDS, AML	Unknown	Skeletal/cardiac abnormalities, neurological defects	DNA sequencing
	<i>ERCC6L2</i>	AR				

Abbreviations: AD, autosomal dominant; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; AR, autosomal recessive; CML, Chronic Myeloid leukemia; CMML, chronic myelomonocytic leukemia; JMML, juvenile myelomonocytic leukemia; MDS, myelodysplastic syndrome; XLR, X-linked recessive. Risks for development of myeloid malignancies have been based on: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia, McGee et al 2016, ASH educational book 2016/2017 and GeneReviews (<https://www.ncbi.nlm.nih.gov>).

Table 2. Laboratories (public and/or academic) performing functional analyses, that may be of value in diagnosis of Fanconi anemia, telomere biology disorders and Diamond-Blackfan anaemia.

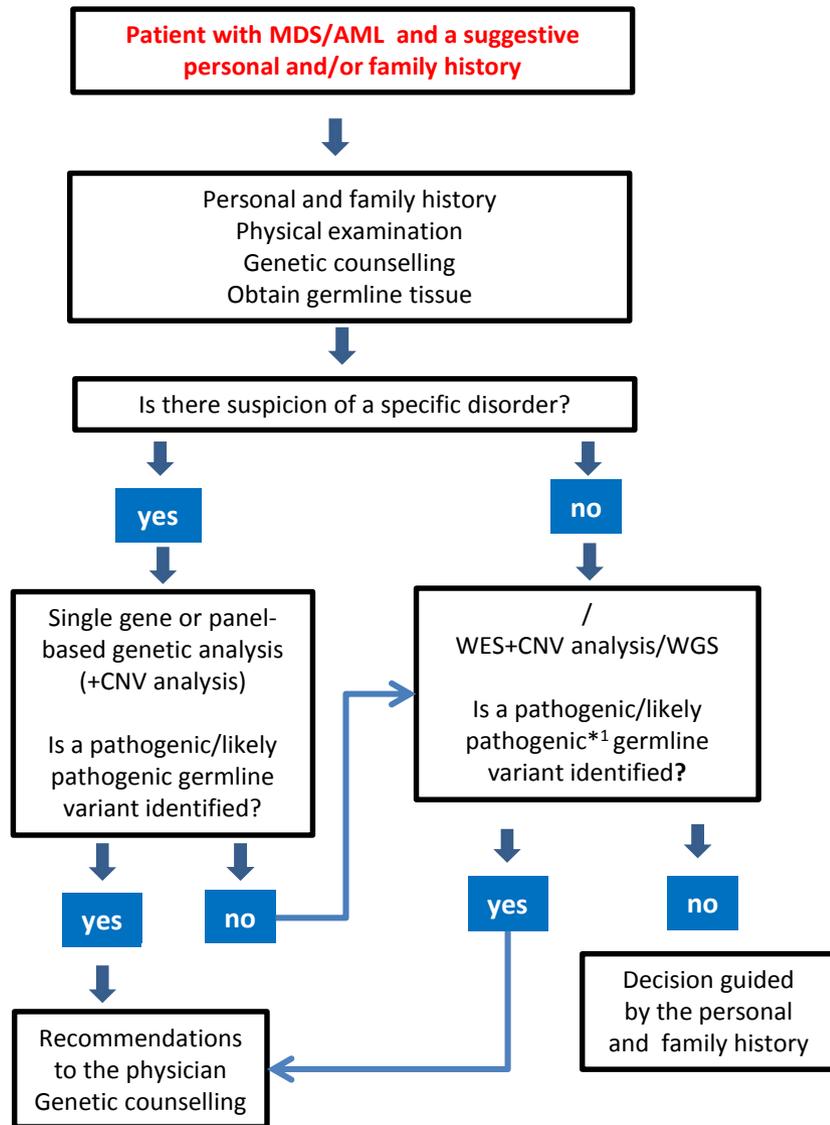
Disorder	Test	Address	Contact prior to sampling and shipping
Fanconi anaemia	Chromosome breakage analysis (FA) with mitomycin	Department of Clinical Genetics Aarhus University Hospital. www.kga.auh.dk Brendstrupgårdsvej 21 C 8200 Aarhus N Denmark	KliniskGenetiskAfdeling@auh.rm.dk Tlf.: +45 2974 5169
	Chromosome breakage analysis (FA) with mitomycin Cell cycle-specific by flow	Institut für Humangenetik, Labor für Genomische Instabilität Biozentrum, Am Hubland 97074 Würzburg Germany	Prof. Dr. Med. Detlev Schindler schindler@biozentrum.uni-wuerzburg.de
	Chromosome breakage analysis (FA) with mitomycin C and diepoxybutane (B –KromFA)	Fimlab Laboratoriot Oy Tampere Shipping address: Fimlab Laboratoriot Oy 5009400 31006 VASTAUSLÄHETYS Finland	genetiikka@fimlab.fi Tlf: +358-3-3117 5424
Telomere biology disorder	Measurement of telomere lengths	Department of Clinical Genetics, Laboratoriecentrum Byggnad 6M, 1tr Norrlands University Hospital 901 85 Umeå Sweden	Dr. Anna Norberg Anna.norberg@vll.se
Diamond-Blackfan anemia	Erythrocyte adenosine deaminase activity (eADA)	Department of Clinical Genetics 4062 The Metabolic Laboratory Rigshospitalet Blegdamsvej 9 2100 Copenhagen Denmark	Dr.Sci. Flemming Wibrand Flemming.wibrand@regionh.dk

Table 3. Follow-up of individuals with a germline predisposition to MDS/AML

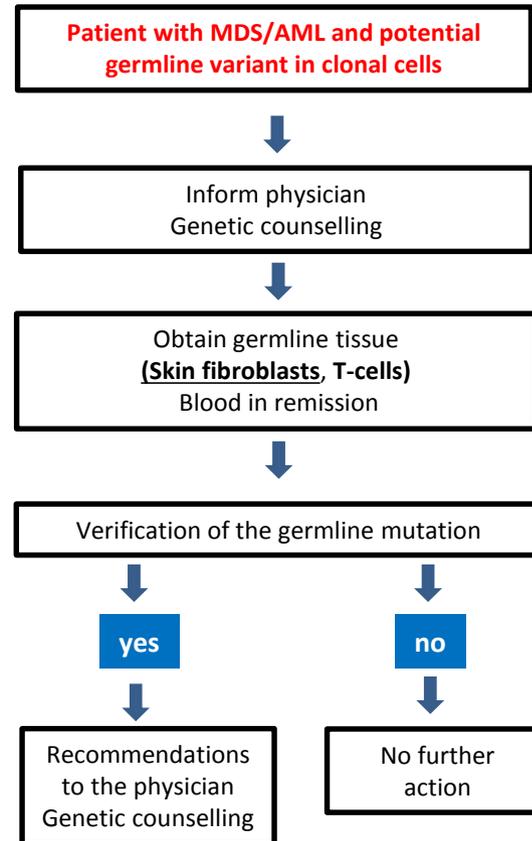
	Baseline	Follow-up
Complete blood count (CBC)	YES	Every six months
Bone marrow aspirate/biopsy	YES	Only in case of change in CBC
NGS-myeloid gene panel	YES (bone marrow)	Once a year* (blood)
Control of other relevant organs	As indicated depending on the underlying condition	As indicated depending on the underlying condition

*The emergence of a clone should not solely be an indication for action. The gene, the variant allele frequency (VAF), the number of pathogenic variants as well as the dynamics over time should be taken into account.

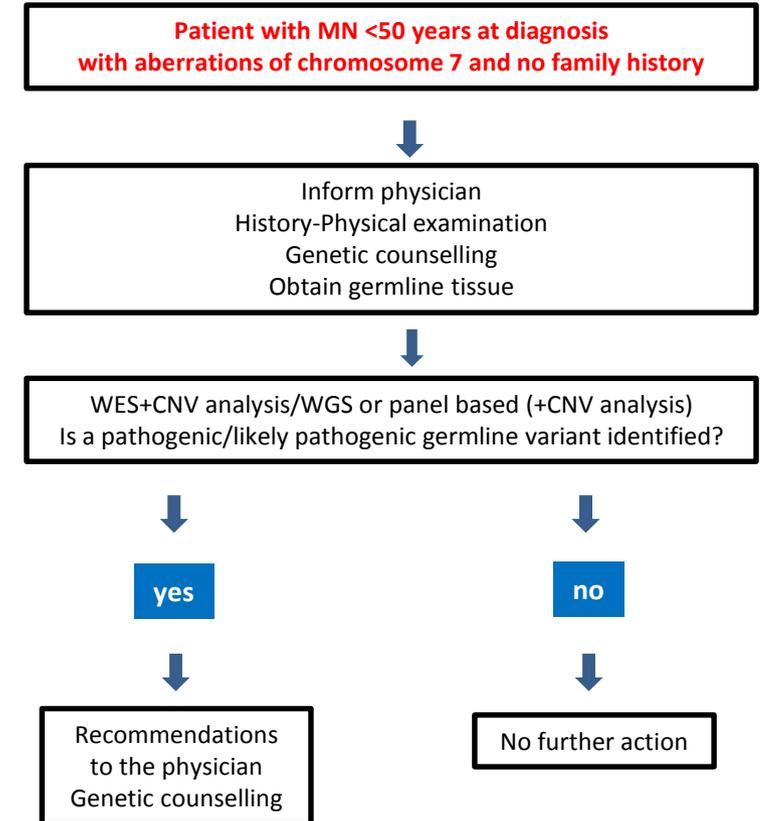
Criterion A



Criterion B



Criterion C



*1: If no pathogenic/likely pathogenic variant is detected consider functional studies such as measurement of telomere length, chromosomal breakage analysis etc. In case of variants of unknown significance (VUS) perform segregation analysis