Summary pages of Nordic guidelines

Germline predisposition to myeloid neoplasms in children and adults
Recommendations for genetic diagnosis, clinical management and follow-up
Version 2.0, June 2021

Background

Myeloid neoplasms (MNs) with germline predisposition are a group of rare diseases recently recognized as novel entities in the latest World Health Organization (WHO) classification for MNs. They are important to recognise as a correct diagnosis may tailor therapy, dictate the selection of donor for allogeneic hematopoietic stem cell transplantation (allo-HSCT), determine the conditioning regimen, may enable prophylactic measures, early intervention or contribute to avoid unnecessary or even harmful medication. Finally, it allows for genetic counselling and follow-up of at-risk family members.

This document presents the summary of the second version of Nordic recommendations for a diagnostic algorithm, surveillance, and considerations for allo-HSCT for patients and carriers of a germline mutation predisposing to myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The detailed main document can be accessed at NMDSG.org, but requires membership login. Please contact a NMDSG member for full access.

Whom to test

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 or 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/der(1;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

monosomy 7 or der(1;7), 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. Functional testing may be available in selected disorders (Table 2).

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/pediatric center with expertise in hereditary malignancies to ensure adequate monitoring and tailored treatment. The haematological/pediatric 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. It should be 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.

Table 1. Overview of germline conditions predisposing for myeloid neoplasms (adapted from WHO 2016 book chapter and NCCN MDS v1.0. 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 *CEBPA* mutation	*CEPBA*	AD	AML	>80%	-	DNA sequencing including del/dup analysis
Myeloid neoplasms with germline *DDX41* mutation	*DDX41*	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 *RUNX1* mutation (Familial platelet disorder with associated myeloid malignancy)	*RUNX1*	AD	MDS, AML	~45%	Thrombocytopenia and abnormal platelet function; clonal hematopoiesis; ALL	DNA sequencing including del/dup analysis
Myeloid neoplasms with germline *ANKRD26* mutation	*ANKRD26*	AD	AML, MDS, CML	8%	Moderate thrombocytopenia with mild bleeding manifestations	DNA sequencing of 5'UTR
Myeloid neoplasms with germline *ETV6* mutation	*EVT6*	AD	ALL, AML, MDS	Unknown	Thrombocytopenia and mild bleeding manifestation	DNA sequencing
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

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
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
Bone marrow failure syndrome 1 (BFMS1/SRP72)	*SRP72*	AD	MDS	Unknown	Congenital sensorineural deafness	DNA sequenicng
Fanconi anaemia	*FANCA*	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
	FANCB, FANCC, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCM, PALB2, RAD51C, SLX4	AR				
Severe congenital neutropenia	*ELANE, CSF3R, GFI1, SRP54*	AD	MDS, AML	21-40%	Severe neutropenia	DNA sequencing including del/dup analysis
	HAX1, G6PC3, JAGN1, VPS45	AR				
	WAS	XLR				
Shwachman-Diamond syndrome	*SBDS*	AR	MDS, AML, ALL	5-24%	Neutropenia, pancreatic insufficiency, short stature, skeletal abnormalities	DNA sequencing including del/dup analysis
Diamond-Blackfan anaemia	*RPS19, RPS17, RPS24, RPL35A, RPL5, RPL11, RPL15, RPL26, RPS7, RPS26, RPS10, RPS29*	AD	MDS, AML, ALL	~5%	Anemia and marrow erythroid hypoplasia. Small stature, congenital anomalies (e.g. craniofacial, cardiac, skeletal, genitourinary)	DNA sequencing including del/dup analysis Elevated erythrocyte adenosine deaminase
	GATA1	XLR				

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
Telomere biology disorders	*DKC1*	XLR	MDS, AML	2-30%	Bone marrow failure, immunodeficiency, 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
	TERT, TERC, TINF2, RTEL1, PARN, ACD	AD				
	NOP10, NHP2, WRAP53, RTEL1, TERT, CTC1,PARN, ACD	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	*CBL, KRAS, NF1, PTPN11*	AD	JMML, AML	~10%	Short stature, facial features, cardio-thoracic defects, coagulopathy	DNA sequencing
Constitutional mismatch repair deficiency	*MLH1, MSH2, MSH6, PMS2, EPCAM*	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
Bloom syndrome	*BLM*	AR	ALL, AML/MDS, lymphoma	20%	Growth deficiency, photosensitive skin changes, immunodeficiency, early-onset diabetes, microcephaly, high-pitched voice, hypogonadism, risk for other cancers	DNA sequencing including del/dup analysis
LIG4 syndrome	LIG4	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	*TP53*	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

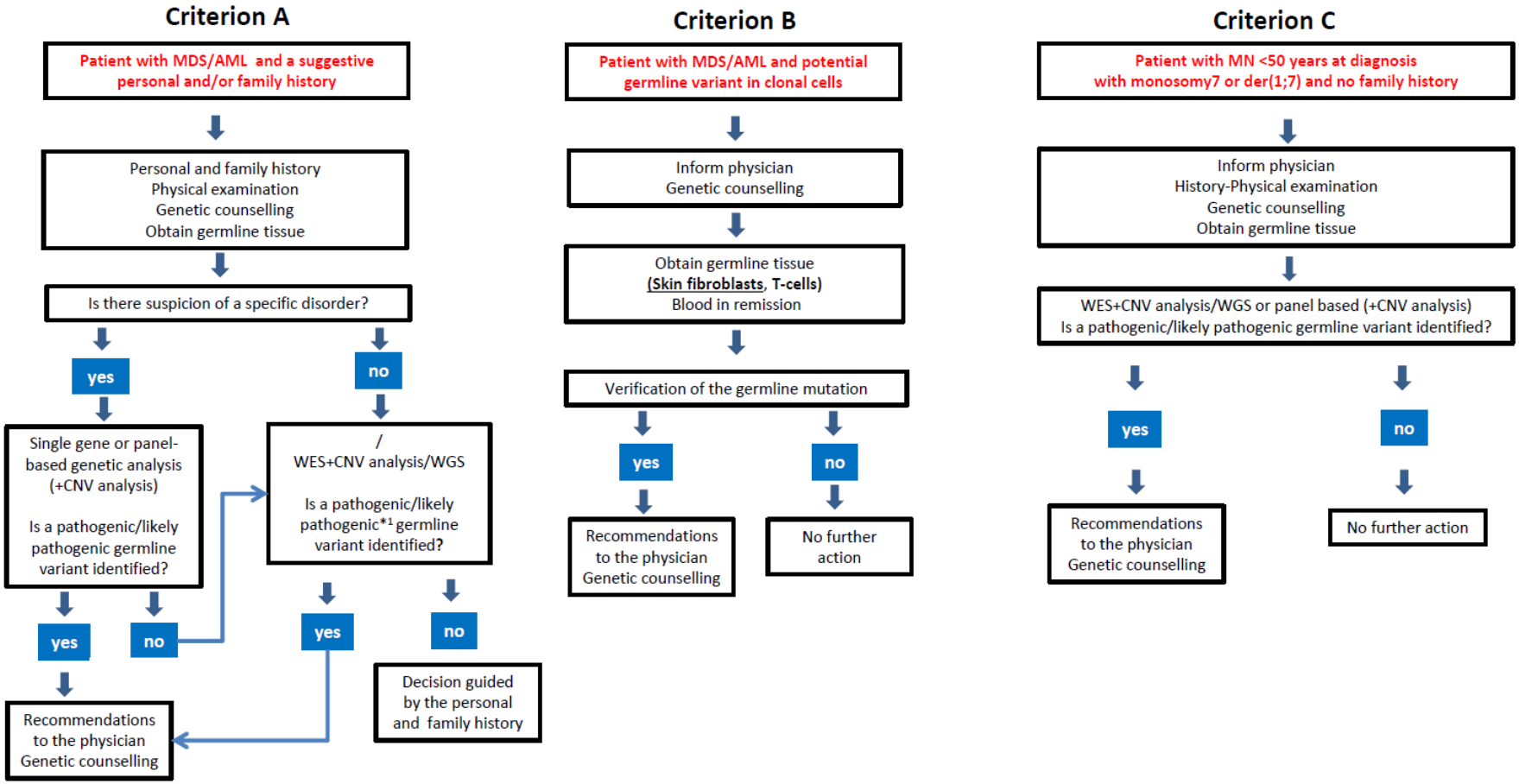
Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic haematological malignancies	Lifetime risk for myeloid malignancies	Other phenotypes and clinical features	Diagnostic testing
Other bone marrow failure syndromes	*MECOM* *ERCC6L2*	AD AR	MDS, AML For ERCC6L2: MDS, AML (M6), MDS-F	Unknown	Skeletal/cardiac abnormalities, neurological defects Abnormalities or neurol defects not sure in ERCC6L2 (perhaps not included at all); instead strong tendency to form somatic TP53 hematopoietic clones	DNA sequencing

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 Tel: +45 2974 5169
	Chromosome breakage analysis (FA) with mitomycin Cell cycle-specific by flow cytometry	Institut für Humangenetik, Labor für Genomische Instabilität Biozentrum, Am Hubland 97074 Würzburg Germany	Prof. Dr. Med. Detlev Schindler schindler@biozentrum.uni-wuerzburg.de
	DNA damage assessment after mitomycin by flow cytometry	Department of Clinical Chemistry Sahlgrenska University Hospital 413 45 Göteborg Sweden	https://www.sahlgrenska.se/for-dig-som-ar/vardgivare/laboratoriemedicin/analyslista/mitomycin-c-kanslighet/ Tel: +46 31-3421051
	Chromosome breakage assessment with diepoxybutane	Genetics centre 5th floor, Tower Wing Guy's Hospital Great Maze Pond London SE1 9RT United Kingdom	http://www.viapath.co.uk/our-tests/chromosome-breakage-studies gst-tr.geneticsreferrals@nhs.net Tel: +44 20 7188 1364
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
	Erythrocyte adenosine deaminase activity (eADA)	Department of Clinical Chemistry Sahlgrenska University Hospital 413 45 Göteborg Sweden	https://www.sahlgrenska.se/for-dig-som-ar/vardgivare/laboratoriemedicin/analyslista/adenosindeaminas-ec-3.5.4.4/1285.html Tel: +46 31-3422425

Figure 1



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