Towards European Standard Clinical Practice (ESCP) guidance for individuals with familial leukemia

This document has been developed by:

Alisa Förster[1], Claudia Davenport[1], Nicolas Duployez[2], Miriam Erlacher[3], Alina Ferster[4], Jude Fitzgibbon[5], Gudrun Göhring[1], Henrik Hasle[6], Marjolijn C Jongmans[7], Alexandra Kolenova[8], Geertruijte Kronnie[9], Tim Lammens[10,11,12], Cristina Mecucci[13], Wojciech Mlynarski[14], Charlotte M Niemeyer[15], Francesc Sole[16], Tomasz Szczepanski[17], Esmé Waanders[7,18], Andrea Biondi[19], Marcin Wlodarski[15,20], Brigitte Schlegelberger[1], Tim Ripperger[1]

[1]Department of Human Genetics, Hannover Medical School, Hannover, Germany;

[2]Department of Hematology, CHU Lille, INSERM, University Lille, Lille, France;

[3]Division of Pediatric Hematology-Oncology, Department of Pediatric and Adolescent Medicine, University of Freiburg, Freiburg, Germany;

[4]Department of Pediatric Rheumatology, Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium;

[5]Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK;

[6]Department of Paediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark;

[7]Department of Genetics, University Medical Center Utrecht, Utrecht, The Netherlands;

[8]Department of Pediatric Hematology and Oncology, Comenius University Medical School and University Children's Hospital, Bratislava, Slovak Republic;

[9]Department of Women's and Children's Health, University of Padova, Italy;

[10]Department of Pediatric Hematology-Oncology and Stem Cell Transplantation, Ghent University Hospital, Ghent, Belgium;

[11]Cancer Research Institute Ghent (CRIG), Ghent, Belgium;

[12]Department of Internal Medicine and Pediatrics, Ghent University, Ghent, Belgium;

[13]Institute of Hematology and Center for Hemato-Oncology Research, University and Hospital of Perugia, Perugia, Italy;

[14]Department of Pediatrics, Oncology and Hematology, Medical University of Lodz, Lodz, Poland;

[15]Division of Pediatric Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany;

[16]Josep Carreras Leukemia Research Institute (IJC), Campus ICO-Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain;

[17]Polish Pediatric Leukemia/Lymphoma Study Group, Zabrze, Medical University of Silesia, Katowice, Poland;

[18]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands;

[19]Clinica Pediatrica and Centro Ricerca Tettamanti, Università di Milano-Bicocca, Monza, Italy

[20]Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN, USA

Correspondence: Tim Ripperger, MD, PhD, Department of Human Genetics OE 6300, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany, E-mail: ripperger.tim@mh-hannover.de

Document version and date: Version 1, 25th August 2022

Planned review date: 25th August 2024

DISCLAIMER:

These ESCP guidance documents were produced by the relevant tumour group or specialist committee as recommendations on current best practice. The ESCP guidance documents are not clinical trial protocols.

The interpretation and responsibility of the use of ESCP guidance documents lies fully with the user who retains full responsibility for the use of these guidance documents and his actions and (treatment) decisions based thereon, such as, but without limitation thereto: checking and prescribing certain doses, checking prescriptions, etc. A user should never base its decision solely on the content of these guidance documents and should always check any other relevant medical information that is available and make appropriate use of all relevant medical information.

These guidance documents have been made publicly available by SIOP Europe – the European Society of Paediatric Oncology and the European Reference Network for Paediatric Oncology (ERN PaedCan). It is the responsibility of the user who downloads these documents to make sure that:

- their use within the Paediatric Clinical Unit / Hospital is approved according to the local clinical governance procedures.
- appropriate document control measures are in place to ensure that the most up to date locally approved versions are considered.
- any anomalies or discrepancies within the documents are immediately brought to the attention of the relevant special interest group chair and the European Clinical Study Group who has developed the ESCP guidance document.

Every care has been taken whilst preparing these documents to ensure that they are free of errors. Nonetheless, SIOP Europe and ERN PaedCan cannot be held liable for possible errors or mistakes in these guidance documents, nor can SIOP Europe and ERN PaedCan be held liable for any kind of damage resulting out of the use of these guidance documents.

Table of contents

1. BACKGROUND AND RATIONALE

1.1 Background

In 2020, there was an estimated 474,519 newly diagnosed leukemia cases and 311,594 leukemia-related cancer deaths worldwide (Sung et al., 2021). Although hematologic malignancies (HM) are usually sporadic, familial aggregation is increasingly recognized (Nickels et al., 2013). The discovery of underlying germline mutations (e.g., in the *RUNX1* gene in 1999 (Song et al., 1999)), has supported the notion of hereditary HM. Fostered by the increasing application of next-generation sequencing (NGS), additional genes predisposing to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) have been established (e.g., *DDX41*, *ETV6*, *GATA1*, *GATA2*, *MBD4*, *POT1*, *SAMD9*, and *SAMD9L* (Hasle et al., 2021; Lewinsohn et al., 2016; Narumi et al., 2016; Polprasert et al., 2015; Michler et al., 2021; Sahoo et al., 2021; Sanders et al., 2018; Tesi et al., 2017; Wlodarski et al., 2016; Zhang et al., 2015)). Up to 19% of individuals with MDS or AML carry pathogenic germline variants in known cancer susceptibility genes (Drazer et al., 2018; Feurstein et al., 2021; Huang et al., 2018; Lu et al., 2015). For MDS, this high proportion of pathogenic germline variants is observed particularly in patients under 40 years of age (Feurstein et al., 2021) and, in case of GATA2 deficiency, even amounts to 72% of adolescents with MDS and monosomy 7 (Wlodarski et al., 2016). However, the actual number of HM cases may be higher as (i) novel loci continue to be reported (e.g., *ADA*, *DNMT3A*, *GP6*, *IL17RA*, *MECOM*, and *PRF1* (DiNardo et al., 2021; Rio-Machin et al., 2020; Ripperger et al., 2018)), and (ii) the germline origin of a pathogenic variant is not always recognized when they are identified within the context of analyzing somatic alterations. Moreover, myeloid and/or lymphoid neoplasms can arise in the context of constitutional chromosomal aberrations (e.g., trisomy 21, rob(15;21), trisomy 8 mosaicism), and monogenic hereditary (cancer predisposition) syndromes (e.g., ataxia telangiectasia (MIM 208900), constitutional mismatch repair deficiency (MIM 276300, 619096, 619097, 619101), Fanconi anemia (MIM 227645, 227650, 600901, 605724), Li-Fraumeni syndrome (MIM

151623), and Shwachman-Diamond syndrome (MIM 260400, 617941)). Hereditary syndromes with increased risk for HM can follow autosomal dominant, recessive, and X-linked recessive inheritance. *De novo* mutations are frequently observed, for instance in *TP53* causing Li-Fraumeni syndrome (Renaux-Petel et al., 2018). Notably, incomplete penetrance and variable expressivity may disguise familial aggregation (Maciejewski et al., 2017) and indicate that additionally acquired somatic alterations are required for leukemic transformation, and that additional constitutional genetic alterations can influence the course of disease.

Since 2016, myeloid neoplasms with germline predisposition have been recognized in the revised World Health Organization classification of myeloid neoplasms and acute leukemia (Arber et al., 2016). Presently, three subgroups are defined; group 1 includes syndromes resulting from germline alterations without preexisting disorders (e.g., in *CEBPA* or *DDX41*), whereas group 2 includes predisposition syndromes with preexisting thrombocytopenia due to alterations in *ANKRD26*, *ETV6*, or *RUNX1* (Arber et al., 2016). Group 3 describes syndromes with multi-organ dysfunction (e.g., GATA2 deficiency or trisomy 21) (Arber et al., 2016).

Increasing awareness of familial leukemia raises questions concerning the identification, genetic testing, and treatment of patients with underlying genetic predispositions (Babushok and Bessler, 2015; Churpek et al., 2013; Drazer et al., 2016). Regarding genetic testing, gene variants can be classified as pathogenic (p), likely pathogenic (lp), of uncertain significance, likely benign, or benign according to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines (Richards et al., 2015). Some disease-causing genes require additional specifications, such as the ClinGen variant curation expert panel statements regarding *RUNX1* (Luo et al., 2019) or *TP53* (Fortuno et al., 2021). Previously, Nordic and Spanish expert groups have introduced regional/national guidelines for the genetic diagnosis of germline predisposition in adults with myeloid neoplasms (Baliakas et al., 2019; Palomo et al., 2020). Porter and colleagues have summarized clinical recommendations for children with leukemia predisposition (Porter et al., 2017). Recommendations and guidelines for specific disorders (e.g., Shwachman-Diamond

syndrome and Diamond Blackfan anemia (Dror et al., 2011; Vlachos et al., 2008)), or heterogenic disease groups (e.g., Fanconi anemia (Behrens et al., 2021; Chao et al., 2015; Ebens et al., 2017) and telomeropathies (van Os et al., 2017; Walsh et al., 2017)), already exist and are not within the focus of the present guidelines. A European consensus covering familial leukemia, however, does not yet exist.

1.2 Objectives

Since clinical care and surveillance of rare diseases should be provided based on expert recommendations if evidence-based guidelines are not available, the subnetwork Familial Leukemia within the European Reference Network (ERN)/PaedCan group was formed in 2017 by recruiting experts from eight different countries (i.e., Belgium, Denmark, Germany, Italy, Poland, Slovak Republic, The Netherlands, and UK) including oncologists, hematologists, and human geneticists experienced in HM predisposition. The initiative towards European Standard Clinical Practice (ESCP) guidance for individuals with familial leukemia has been supported by members of MyPred, the German network for rare diseases focusing on young individuals with syndromes predisposing to myeloid malignancies (https://www.research4rare.de/en/research_networks/mypred/), the Host Genome Working Group of the European Society for Pediatric Oncology (https://siope.eu/siope-host-genome-working-group/), as well as the COST action *leukemia gene discovery by data sharing, mining and collaboration* (LEGEND, https://www.legend-cost.eu/). In the following sections, we describe key issues for the medical care of individuals and families with familial leukemia that shall pave the way for consensus recommendations: (i) identification of individuals suggestive of familial leukemia, (ii) genetic analysis and variant interpretation, (iii) genetic counseling and patient education, and (iv) surveillance within or guided by registries/studies as well as interaction with patient and parent associations as well as patient representatives. These recommendations cover both, index patients as well as their family members at risk.

2. PATIENT GROUP

2.1 Patients with familial leukemia

If and when germline genetic testing is offered to individuals with either cancer, HM, or potential donors for hematopoietic stem cell transplantation (HSCT) strongly depends on their current location (i.e., their country) or even the treating medical center. We propose to offer genetic testing to all these individuals who meet the criteria for familial leukemia. In the guidelines at hand, the term “familial leukemia” refers to all individuals with constitutional genetic variants including chromosomal aberrations that predispose to HM. Besides a confirmed pathogenic variant, familial leukemia should be suspected in individuals with HM showing signposts for genetic predisposition based on (i) personal medical history, (ii) specific somatic findings, and/or (iii) family history (Figure 1). More precisely, individual signposts include multiple cancers including ≥1 HM, congenital malformations, adult-type HM in minors, and non-malignant symptoms such as multiple café-au-lait macules, pre-existing cytopenia, recurrent infections, or increased toxicity after chemotherapy. Specific somatic findings indicative of a germline predisposition are low hypodiploidy in children with acute lymphoblastic leukemia, chromothripsis, or monosomy 7 in adolescents with MDS, among others. As some lp/p variants in HM-predisposing genes initially identified by panel sequencing of tumor samples might be of germline origin, variants with a variant allele fraction (VAF) of about or larger than 40% (near heterozygous) should be verified in non-malignant tissues (Baliakas et al., 2019; Yannakou et al., 2018). Beyond this, additional cases of HM or other types of cancer in first- and/or second-degree relatives <45th birthday, and also possible consanguinity of index patients’ parents should be considered when assessing the family history. Apps (https://app.mipogg.com/), algorithms (Baliakas et al., 2019; DiNardo et al., 2018) or questionnaires (Jongmans et al., 2016; Ripperger et al., 2017) can be used to systematically address these clinical and somatic signposts in a structured manner (Schwermer et al., 2021). We summarized key signposts as a scheme (Figure 1) and highly recommend the implementation of appropriate tools when taking care of individuals in question.

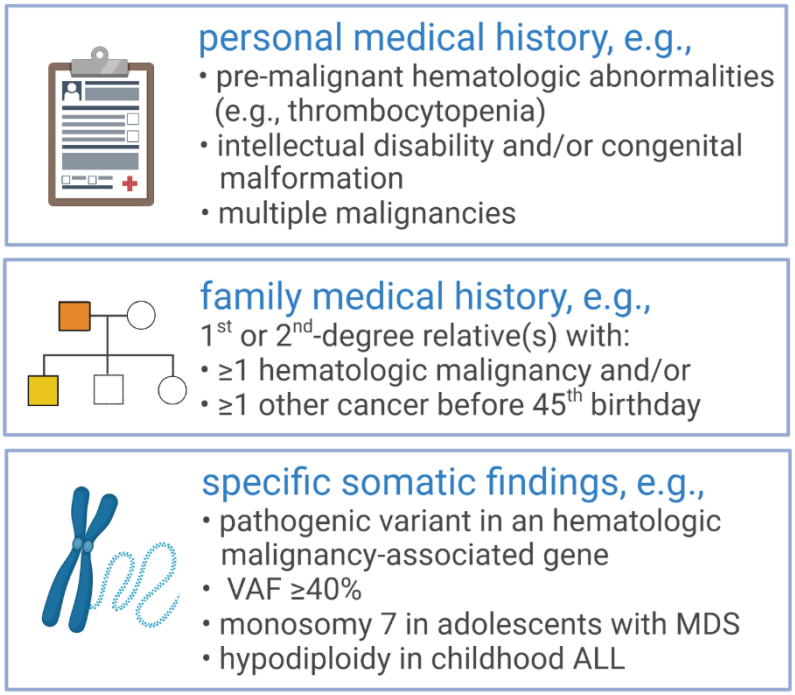

Figure 1: Familial leukemia signposts. The illustration summarizes signposts in the personal and family medical history as well as specific somatic findings that are indicative of a genetic predisposition to hematologic malignancies. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HM, hematologic malignancy; ID, intellectual disability; MDS, myelodysplastic syndrome; VAF, variant allele fraction. Created with BioRender.com.

3. DIAGNOSTICS

3.1 Interdisciplinary management

To address the question on how to proceed with individuals suggestive of or at risk of familial leukemia, we developed an algorithm covering four different, partially linked clinical scenarios (Figure 2 and 3, Förster et al., European Journal of Medical Genetics, unpublished). The first scenario refers to individuals with a HM and a possible lp/p germline variant in a known HM-predisposing gene primarily detected in malignant cells. The second scenario describes individuals suggestive of familial leukemia based on their signposts who have not undergone genetic testing, whereas scenario three includes individuals with HM who have had genetic testing with no lp/p variants detected. The fourth scenario addresses healthy relatives at risk of familial leukemia due to a lp/p germline variant detected in a relative. Individuals from all

four scenarios should be offered comprehensive genetic germline analyses, following pre-test genetic counseling, where appropriate. We emphasize that all steps should be performed under the umbrella of an interdisciplinary team of experts including hematologists/oncologists, human geneticists, and scientists. In our opinion, individuals shall either be referred to expert centers or, if not locally available, get connected with specialized centers elsewhere to secure expert center-guided local care that can be supplemented by telephone/virtual counseling meetings.

3.2 Scheduling of genetic counseling and/or genetic testing

To determine the most appropriate time for genetic testing, clinicians and/or geneticists must consider several parameters, particularly whether the result is therapy-relevant. In addition, it is imperative to assess and acknowledge individual situations, attitudes, and wishes of potentially affected individuals. Above all, counseling and testing should be offered non-directively. In general, patients can be treated irrespective of a confirmed lp/p germline variant when its presence or absence has no impact on treatment decisions. In the absence of sufficient evidence for the necessity of treatment adaptations, chemotherapy in patients with predisposition for HM should be treated according to the disease-specific study protocol. Notably, determining the presence of a genetic predisposition may not be of importance to the present disease for all patients, but it may provide relevant information for possible future cancers associated with the germline alteration and also for relatives at risk. However, in other patients, early identification of a possible lp/p germline variant is pivotal. For example, it is key for children with a diagnosis of juvenile myelomonocytic leukemia and *PTPN11* lp/p variants in tumor samples to immediately ascertain the germline or somatic origin of the variant. Children with somatically acquired variants usually require early HSCT, while children with *PTPN11* germline variants associated with Noonan syndrome do not (Locatelli and Niemeyer, 2015). The latter often show spontaneous regression, thus, a “watch and wait” strategy is

appropriate (Locatelli and Niemeyer, 2015). Another example is *TP53*. Here, early identification of lp/p variants may be relevant for the adaption of treatment protocols, including radiotherapy and chemotherapy (Frebourg et al., 2020; Kratz et al., 2021). In the context of (suspected) familial leukemia, genetic analysis of related donors should be considered prior to allogeneic HSCT so that carriers of known familial lp/p variants can be excluded. If familial leukemia is suspected but genetic analysis cannot be completed prior to HSCT, the use of related donors for HSCT requires critical evaluation. Taken together, genetic testing for potential germline variants needs to be implemented in a way that supports clinical decision-making but at the same time does not interfere with current best practice procedures and treatment protocols.

3.3 Comprehensive genetic analysis

Comprehensive genetic analysis seeking germline variants associated with HM have contributed to a better understanding of the disease as well as risk stratification. Along with the identification of HM-predisposing gene variants, the international community needs to address the issues of incorporating testing for hereditary HM into patient care and how to address incidental findings (Tawana et al., 2018). Specific diagnostic algorithms on how to proceed with individuals to detect lp/p germline variants, including single nucleotide variants and copy number variations, have been previously proposed by the Nordic MDS study group (Baliakas et al., 2019), the Spanish MDS Group (Palomo et al., 2020), and DiNardo and colleagues (DiNardo et al., 2018). Where possible, genetic testing for germline variants should be performed in accredited diagnostic laboratories. A challenge in performing germline DNA analysis in patients with HM is the source of non-hematopoietic tissue. Currently, the gold standard is cultured skin-derived fibroblasts, as buccal swabs, saliva samples or even fingernails may contain hematologic cells. When it comes to genetic analysis, not only the choice of material but also the method is crucial in order to detect possible lp/p variants. We summarized the main HM-associated variant types with applicable methods in Table 1. Despite

this, somatic genetic rescue (e.g., in *SAMD9*, *SAMD9L* or *GATA2* (Buonocore et al., 2017; Catto et el, 2020; Narumi et al., 2016; Sahoo et al., 2021)), has to be kept in mind. Detailed genetic analyses, especially in the context of large sequencing panels or even whole exomes or genomes, increase the number of identified variants per analysis, and certainly raise the handling time for variant interpretation, clinical impact evaluation and genetic counseling. In general, we recommend to clearly distinguish between genetic testing in clinical (i.e., focused testing of known causal genes) and research (i.e., designed to expand knowledge) settings (Ripperger et al., 2021).

Table 1: Overview of the most common variant types associated with HM predisposition and possible methods to detect them in a diagnostic setting.

variant type	affected genes, e.g.,	applicable method, e.g.,
point mutations and small indels in coding and flanking intronic regions	*GATA2* (Kozyra et al., 2020)	sequencing (Sanger or NGS panel sequencing, WES/WGS)*
non-coding alterations in untranslated regions	*ANKRD26* (Pippucci et al., 2011)	sequencing (Sanger or NGS panel sequencing, WGS)
non-coding, deep-intronic, regulatory variants	*GATA2* (Hsu et al., 2013)	sequencing (Sanger or NGS panel sequencing, WGS)*
copy number alterations ranging from partial exon up to microdeletions	*RUNX1* (Duployez et al., 2019; Rio-Machin et al., 2020; Ripperger et al., 2011; Ripperger et al., 2013)	MLPA, aCGH, SNP-array, FISH, WES, WGS
copy number alterations encompassing gene promoters/regulatory elements	*RUNX1* (Rio-Machin et al., 2020)	MLPA, aCGH, SNP-array, FISH, WGS

*, if applicable, additional RNA-based analyses are needed to address potential splicing effects. aCGH, microarray-based comparative genomic hybridisation; FISH, fluorescence *in situ* hybridization; MLPA, multiplex ligation-dependent probe amplification; NGS, next generation sequencing; SNP, single nucleotide polymorphism; WES, whole exome sequencing, WGS, whole genome sequencing.

3.4 Variant interpretation

Genetic analyses have to follow established quality criteria, including the classification of pathogenicity of variants (Fortuno et al., 2021; Luo et al., 2019; Richards et al., 2015). Their proper clinical reporting needs to follow the current guidelines by the International System for Human Cytogenetic Nomenclature (ISCN, (McGowan-Jordan and GmbH 2016)) or Human Genome Variation Society (HGVS, https://www.hgvs.org/). We recommend data sharing of genetic variants with associated phenotypes among diagnostic laboratories and the scientific community, preferably within general or gene-specific publicly available curated databases (e.g., ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/)) or the RUNX1 Database (https://runx1db.runx1-fpd.org/). Especially in case of rare variants of uncertain significance (VUS), sharing of specific phenotypes, family history, and segregation is helpful to accelerate knowledge on clinical impact and possibly guide re-classification.

In case of likely pathogenic and pathogenic variants

Detection of lp/p germline variants might influence diagnosis, treatment decision, donor choice for HSCT with related donors, and future surveillance. It is important to clarify whether lp/p germline variants are *de novo*. In case of *de novo* germline variants, no increased risks for parents exists and the risk for siblings to disease is dramatically reduced. Germline mosaicism and somatic genetic rescue in parents needs to be considered in apparent *de novo* scenarios, although there is no available data regarding its frequency. However, the offspring of index patients with heterozygous *de novo* autosomal germline variants have a 50% possibility to inherit the mutated allele.

In case of variants of uncertain significance, likely benign and benign variants

Particular care needs to be taken when dealing with VUS, which in general allow no clinical translation. We highly recommend to implement interdisciplinary teams of experts for the

decision-making process. Variant-specific functional data, validation cohorts and/or familial segregation might be helpful to better classify VUS, as has been illustrated with functional data for RUNX1 variants (Decker et al., 2021; Decker et al., 2022). Unremarkable genetic results (i.e., no lp/p variants) raise the question if a genetic cause can be ruled out or if a causative genetic alteration is being missed. Here, we recommend follow-up diagnostic genetic analyses after three to five years or earlier in case of novel relevant findings to (i) reanalyze genetic data, and to reclassify previously identified variants, (ii) incorporate the current state of methodology (i.e., additional analyses if appropriate), and (iii) consider novel knowledge regarding associated genes (Figure 2, Förster et al., European Journal of Medical Genetics, unpublished). Besides future diagnostic tests, further scientific investigations should be considered. Controversies regarding the best care of individuals/families without proven causative germline variants but with a familial background suggestive of a HM predisposition need to be resolved. Patients who are clinically conspicuous due to their own and/or family history of disease but do not carry lp/p variants at established loci, may remain with an increased (familial) risk of developing HM. Hence, without causing unnecessary anxiety, this needs to be clearly communicated and follow-up appointments and germline genetic re-evaluation should be offered.

4. PATIENT CARE

4.1 Genetic counseling and patient education

The aim of identifying individuals at-risk is to inform them about (i) their own disease risk, (ii) the probability of additional affected relatives and the risk to their offspring, (iii) if applicable, available surveillance strategies to detect disease onset at an early stage, (iv) the need to prevent HSCT with familial donors also carrying the risk allele, (v) if applicable, the need of specific treatment protocols, (vi) ongoing studies, registries, and/or trials, and (vii) coping strategies and patient support groups. Most of the informative and educational tasks can be covered during genetic counseling following non-directive principles. It is important to not

only offer genetic counseling to already affected patients but also to family members at risk. Moreover, proper education forms the basis of the informed consent process for genetic testing and ensures that patients understand risks and benefits of genetic testing, possible testing outcomes, and the potential impact of test results for themselves as well as for their relatives (Nickels et al., 2013). Shared decision-making considering (i) whether and when to undergo genetic testing, (ii) whether, how and when to inform relatives, (iii) communication about clinical consequences, and (iv) effects on family planning must be performed within the scope of genetic counseling. We recommend tailored information adapted to the individual's situation.

General topics of genetic counseling are:

- evaluation of the family history, at least three generations with documentation of malignant diseases including the age of onset,
- clinical features indicative of inherited HM,
- medical indication of genetic testing and the personal right *to-know* or *not-to-know*,
- potential results of genetic testing, including VUS, and their potential impact on future care,
- possible reactions to the disclosure of genetic test results,
- shared decision-making regarding genetic testing, including pre-implantation genetic diagnosis and prenatal diagnosis, and risk assessment,
- interdisciplinary care, particularly for the implementation of adequate surveillance programs and education about signs and symptoms of HM and associated non-malignant and malignant diseases also including solid tumors (e.g., in Li-Fraumeni syndrome),
- if applicable, the limited knowledge about the natural course of the disease and currently missing evidenced-based surveillance guidelines, and
- contact information regarding general or specific registries, ongoing trials if applicable, as well as patient support groups.

Every individual should be educated about (self-recognizable) symptoms of HM, the pros and cons of regular surveillance, and the option of re-testing after three to five years if initial investigations did not identify causative genetic alterations. Re-testing of index patients' germline tissue should include novel diagnostic knowledge and methodology. We advise to involve hematologists/oncologists that are familiar with genetic predisposition in the education of patients and families. Besides, responsible primary care physicians (e.g., general practitioner or pediatricians) also need to be informed. The ERN Paedcan Subnetwork on Familial Leukemia, but also ERN GENTURIS, which focuses on genetic tumor risk syndromes, can serve as European hubs, offering information, local services or advice to get in contact with experts in the field. Moreover, they provide current ESCP protocols for each common childhood cancer (https://paedcan.ern-net.eu/the-escp-project/), which is particularly helpful in countries without standard care. Established data sharing systems can be used to discuss patients and review primary medical reports. In addition to the clinical care, these networks are also connected with research initiatives (e.g., COST action LEGEND or national networks such as MyPred) that can be of help or interest especially if clinical genetic testing did not identify causative variants or when additional functional investigations are required to classify variants.

4.2 Support and surveillance

Recently, the discovery of germline HM predisposition syndromes has been found to have a positive impact on 91% of patients (e.g., by cancer-specific screening measures, donor selection for allogenic HSCT, modification of treatment, and genetic counseling) (Martin et al., 2021). Germline predisposition variants causing HM can be associated with a significantly earlier age of onset (Feurstein et al., 2021; Kim et al., 2020). Regarding surveillance, apart from leukemia-associated tumor risk syndromes such as Li-Fraumeni syndrome (Frebourg et al., 2020) or constitutional mismatch repair deficiency syndrome (Durno et al., 2021), prospective clinical trials generating evidence-based measures for mainly leukemia-

predisposing diseases are not available. Different strategies have been reported in the literature and are based on expert opinions (Baliakas et al., 2019; DiNardo et al., 2018; Drazer et al., 2016; Godley and Shimamura, 2017; Porter et al., 2017). There is an urgent need for natural history studies (e.g., the NIH RUNX1-FPD Clinical research study (NCT03854318, https://www.genome.gov/Current-NHGRI-Clinical-Studies/hematologic-and-premalignant-conditions-associated-with-RUNX1-mutation)), to better understand the clinical course of HM-predisposing diseases and to do this as objectively as possible, since data extracted from previous reports might be biased by severe cases raising our attention. In general, strategies should be guided by local or if unavailable regional/national experts. Besides missing evidence for their effectiveness, surveillance measures for HM need to be discussed in the light of cancer risk, type of associated HM (i.e., acute versus non-acute HM), age of onset, and the presence of non-malignant hematological findings that may influence surveillance intervals (e.g., thrombocytopenia). If the associated risk for HM in a cancer predisposing syndrome is considered to be relatively low (i.e., below 5%), no general surveillance measure is currently recommended (Brodeur et al., 2017). However, if desired, these patients can also be referred to support groups and offered the prospect of re-consultation to re-assess their situation. The usefulness of such a procedure should be adapted individually to a patient's situation and be discussed within an interdisciplinary team. Regular surveillance is ineffective if hereditary diseases predispose to acute leukemia or lymphoma only (e.g., *CEBPA*-, *ETV6*-, *PAX5*-associated predisposition) (Porter et al., 2017), since acute leukemia becomes symptomatic immediately and no prior action can be taken. In contrast, in predisposing diseases associated with myelodysplastic syndrome (MDS), which can transform to AML, individuals may benefit from MDS detection prior to AML transformation. Age of onset often spans from early childhood to late adulthood even within families. Thus, continued surveillance is necessary for these diseases. In case of non-malignant findings (e.g., severe thrombocytopenia), surveillance intervals can be adapted as needed.

We recommend referring patients to clinical studies, working groups, and/or appropriate registries that also include healthy relatives (e.g., FIT – facts, investigation, therapy, a general cancer predisposition registry, http://www.krebs-praedisposition.de/en/). To ensure a systematic assessment and documentation of clinical characteristics, respective tools (e.g., the Pediatric Cancer Predisposition Documentation Tool (Hoyer et al., 2021)) should be used. If available, patients should be motivated to participate in longitudinal natural history studies such as the aforementioned NIH RUNX1-FPD Clinical research study, prospectively allowing documentations of clinical, genetic, and outcome data. Moreover, registries can provide information regarding co-morbidities and post- and pretreatment factors of transformation and/or relapse risk (e.g., age and specific genetic alterations) (Ravandi et al., 2018; Schuurhuis et al., 2018). As known for genetic cancer predisposition in general, the psychosocial impact of genetic predisposition to HM cannot be overlooked (Cameron and Muller, 2009; Vetsch et al., 2018). While psycho-oncological support is routinely offered to patients, professional support should also be offered to individuals at risk of HM. In addition, individuals with genetic predisposition can benefit from patient support groups and should connect with patient representatives (e.g., *RUNX1* research program, https://www.runx1-fpd.org/).

5. REFERENCE LIST

Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May 19;127(20):2391-405. doi: 10.1182/blood-2016-03-643544. Epub 2016 Apr 11. PMID: 27069254.

Babushok DV, Bessler M. Genetic predisposition syndromes: when should they be considered in the work-up of MDS? Best Pract Res Clin Haematol. 2015 Mar;28(1):55-68. doi: 10.1016/j.beha.2014.11.004. Epub 2014 Nov 12. PMID: 25659730; PMCID: PMC4323616.

Baliakas P, Tesi B, Wartiovaara-Kautto U, Stray-Pedersen A, Friis LS, Dybedal I, Hovland R, Jahnukainen K, Raaschou-Jensen K, Ljungman P, Rustad CF, Lautrup CK, Kilpivaara O, Kittang AO, Grønbæk K, Cammenga J, Hellström-Lindberg E, Andersen MK. Nordic Guidelines for Germline Predisposition to Myeloid Neoplasms in Adults: Recommendations for Genetic Diagnosis, Clinical Management and Follow-up. Hemasphere. 2019 Nov 4;3(6):e321. doi: 10.1097/HS9.0000000000000321. PMID: 31976490; PMCID: PMC6924562.

Behrens YL, Göhring G, Bawadi R, Cöktü S, Reimer C, Hoffmann B, Sänger B, Käfer S, Thol F, Erlacher M, Niemeyer CM, Baumann I, Kalb R, Schindler D, Kratz CP. A novel classification of hematologic conditions in patients with Fanconi anemia. Haematologica. 2021 Nov 1;106(11):3000-3003. doi: 10.3324/haematol.2021.279332. PMID: 34196171; PMCID: PMC8561275.

Brodeur GM, Nichols KE, Plon SE, Schiffman JD, Malkin D. Pediatric Cancer Predisposition and Surveillance: An Overview, and a Tribute to Alfred G. Knudson Jr. Clin Cancer Res. 2017 Jun 1;23(11):e1-e5. doi: 10.1158/1078-0432.CCR-17-0702. PMID: 28572261; PMCID: PMC5553563.

Buonocore F, Kühnen P, Suntharalingham JP, Del Valle I, Digweed M, Stachelscheid H, Khajavi N, Didi M, Brady AF, Blankenstein O, Procter AM, Dimitri P, Wales JKH, Ghirri P, Knöbl D, Strahm B, Erlacher M, Wlodarski MW, Chen W, Kokai GK, Anderson G, Morrogh D, Moulding DA, McKee SA, Niemeyer CM, Grüters A, Achermann JC. Somatic mutations and progressive monosomy modify SAMD9-related phenotypes in humans. J Clin Invest. 2017 May 1;127(5):1700-1713. doi: 10.1172/JCI91913. Epub 2017 Mar 27. PMID: 28346228; PMCID: PMC5409795.

Cameron LD, Muller C. Psychosocial aspects of genetic testing. Curr Opin Psychiatry. 2009 Mar;22(2):218-23. doi: 10.1097/YCO.0b013e3283252d80. PMID: 19553879.

Catto LFB, Borges G, Pinto AL, Clé DV, Chahud F, Santana BA, Donaires FS, Calado RT. Somatic genetic rescue in hematopoietic cells in GATA2 deficiency. Blood. 2020 Aug 20;136(8):1002-1005. doi: 10.1182/blood.2020005538. PMID: 32556109.

Chao MM, Ebell W, Bader P, Beier R, Burkhardt B, Feuchtinger T, Handgretinger R, Hanenberg H, Koehl U, Kratz C, Kremens B, Lang P, Meisel R, Mueller I, Roessig C, Sauer M, Schlegel PG, Schulz A, Strahm B, Thol F, Sykora KW. Consensus of German transplant centers on hematopoietic stem cell transplantation in Fanconi anemia. Klin Padiatr. 2015 May;227(3):157-65. doi: 10.1055/s-0035-1548841. Epub 2015 May 18. PMID: 25985449.

Churpek JE, Lorenz R, Nedumgottil S, Onel K, Olopade OI, Sorrell A, Owen CJ, Bertuch AA, Godley LA. Proposal for the clinical detection and management of patients and their family members with familial myelodysplastic syndrome/acute leukemia predisposition syndromes. Leuk Lymphoma. 2013 Jan;54(1):28-35. doi: 10.3109/10428194.2012.701738. Epub 2012 Jul 9. PMID: 22691122.

Decker M, Lammens T, Ferster A, Erlacher M, Yoshimi A, Niemeyer CM, Ernst MPT, Raaijmakers MHGP, Duployez N, Flaum A, Steinemann D, Schlegelberger B, Illig T, Ripperger T. Functional classification of RUNX1 variants in familial platelet disorder with associated myeloid malignancies. Leukemia. 2021 Nov;35(11):3304-3308. doi: 10.1038/s41375-021-01200-w. Epub 2021 Mar 10. PMID: 33692461; PMCID: PMC8550979.

Decker M, Agarwal A, Benneche A, Churpek JE, Duployez N, DuVall A, Ernst MPT, Förster A, Høberg Vetti H, Nash M, Raaijmakers MHGP, Tvedt THA, Vlachos A, Schlegelberger B, Illig T, Ripperger T. Validation and clinical application of transactivation assays for RUNX1 variant classification. Blood Adv. 2022 Jan 13:bloodadvances.2021006161. doi: 10.1182/bloodadvances.2021006161. Epub ahead of print. PMID: 35026845.

DiNardo CD, Beird HC, Estecio M, Hardikar S, Takahashi K, Bannon SA, Borthakur G, Jabbour E, Gumbs C, Khoury JD, Routbort M, Gong T, Kondo K, Kantarjian H, Garcia-Manero G, Chen T, Futreal PA. Germline DNMT3A mutation in familial acute myeloid leukaemia. Epigenetics. 2021 May;16(5):567-576. doi: 10.1080/15592294.2020.1809871. Epub 2020 Aug 28. PMID: 32856987; PMCID: PMC8078744.

DiNardo CD, Routbort MJ, Bannon SA, Benton CB, Takahashi K, Kornblau SM, Luthra R, Kanagal-Shamanna R, Medeiros LJ, Garcia-Manero G, M Kantarjian H, Futreal PA, Meric-

Bernstam F, Patel KP. Improving the detection of patients with inherited predispositions to hematologic malignancies using next-generation sequencing-based leukemia prognostication panels. Cancer. 2018 Jul 1;124(13):2704-2713. doi: 10.1002/cncr.31331. Epub 2018 Apr 6. PMID: 29682723.

Drazer MW, Feurstein S, West AH, Jones MF, Churpek JE, Godley LA. How I diagnose and manage individuals at risk for inherited myeloid malignancies. Blood. 2016 Oct 6;128(14):1800-1813. doi: 10.1182/blood-2016-05-670240. Epub 2016 Jul 28. PMID: 27471235; PMCID: PMC5813725.

Drazer MW, Kadri S, Sukhanova M, Patil SA, West AH, Feurstein S, Calderon DA, Jones MF, Weipert CM, Daugherty CK, Ceballos-López AA, Raca G, Lingen MW, Li Z, Segal JP, Churpek JE, Godley LA. Prognostic tumor sequencing panels frequently identify germ line variants associated with hereditary hematopoietic malignancies. Blood Adv. 2018 Jan 23;2(2):146-150. doi: 10.1182/bloodadvances.2017013037. PMID: 29365323; PMCID: PMC5787862.

Dror Y, Donadieu J, Koglmeier J, Dodge J, Toiviainen-Salo S, Makitie O, Kerr E, Zeidler C, Shimamura A, Shah N, Cipolli M, Kuijpers T, Durie P, Rommens J, Siderius L, Liu JM. Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. Ann N Y Acad Sci. 2011 Dec;1242:40-55. doi: 10.1111/j.1749-6632.2011.06349.x. PMID: 22191555.

Duployez N, Martin JE, Khalife-Hachem S, Benkhelil R, Saada V, Marzac C, Auger N, Marceau-Renaut A, Favier R, Ballerini P, Caron O, Baruchel A, de Botton S, Preudhomme C, Micol JB, Raslova H, Antony-Debré I. Germline RUNX1 Intragenic Deletion: Implications for Accurate Diagnosis of FPD/AML. Hemasphere. 2019 Jun 4;3(3):e203. doi: 10.1097/HS9.0000000000000203. PMID: 31723833; PMCID: PMC6746022.

Durno C, Ercan AB, Bianchi V, Edwards M, Aronson M, Galati M, Atenafu EG, Abebe-Campino G, Al-Battashi A, Alharbi M, Azad VF, Baris HN, Basel D, Bedgood R, Bendel A, Ben-Shachar S, Blumenthal DT, Blundell M, Bornhorst M, Bronsema A, Cairney E, Rhode S, Caspi S, Chamdin A, Chiaravalli S, Constantini S, Crooks B, Das A, Dvir R, Farah R, Foulkes WD, Frenkel Z, Gallinger B, Gardner S, Gass D, Ghalibafian M, Gilpin C, Goldberg Y, Goudie C,

Hamid SA, Hampel H, Hansford JR, Harlos C, Hijiya N, Hsu S, Kamihara J, Kebudi R, Knipstein J, Koschmann C, Kratz C, Larouche V, Lassaletta A, Lindhorst S, Ling SC, Link MP, Loret De Mola R, Luiten R, Lurye M, Maciaszek JL, MagimairajanIssai V, Maher OM, Massimino M, McGee RB, Mushtaq N, Mason G, Newmark M, Nicholas G, Nichols KE, Nicolaides T, Opocher E, Osborn M, Oshrine B, Pearlman R, Pettee D, Rapp J, Rashid M, Reddy A, Reichman L, Remke M, Robbins G, Roy S, Sabel M, Samuel D, Scheers I, Schneider KW, Sen S, Stearns D, Sumerauer D, Swallow C, Taylor L, Thomas G, Toledano H, Tomboc P, Van Damme A, Winer I, Yalon M, Yen LY, Zapotocky M, Zelcer S, Ziegler DS, Zimmermann S, Hawkins C, Malkin D, Bouffet E, Villani A, Tabori U. Survival Benefit for Individuals With Constitutional Mismatch Repair Deficiency Undergoing Surveillance. J Clin Oncol. 2021 Sep 1;39(25):2779-2790. doi: 10.1200/JCO.20.02636. Epub 2021 May 4. PMID: 33945292; PMCID: PMC8407605.

Ebens CL, MacMillan ML, Wagner JE. Hematopoietic cell transplantation in Fanconi anemia: current evidence, challenges and recommendations. Expert Rev Hematol. 2017 Jan;10(1):81-97. doi: 10.1080/17474086.2016.1268048. Epub 2016 Dec 21. PMID: 27929686; PMCID: PMC6089510.

Feurstein S, Churpek JE, Walsh T, Keel S, Hakkarainen M, Schroeder T, Germing U, Geyh S, Heuser M, Thol F, Pohlkamp C, Haferlach T, Gao J, Owen C, Goehring G, Schlegelberger B, Verma D, Krause DS, Gao G, Cronin T, Gulsuner S, Lee M, Pritchard CC, Subramanian HP, Del Gaudio D, Li Z, Das S, Kilpivaara O, Wartiovaara-Kautto U, Wang ES, Griffiths EA, Döhner K, Döhner H, King MC, Godley LA. Germline variants drive myelodysplastic syndrome in young adults. Leukemia. 2021 Aug;35(8):2439-2444. doi: 10.1038/s41375-021-01137-0. Epub 2021 Jan 28. PMID: 33510405.

Fortuno C, Lee K, Olivier M, Pesaran T, Mai PL, de Andrade KC, Attardi LD, Crowley S, Evans DG, Feng BJ, Foreman AKM, Frone MN, Huether R, James PA, McGoldrick K, Mester J, Seifert BA, Slavin TP, Witkowski L, Zhang L, Plon SE, Spurdle AB, Savage SA; ClinGen TP53 Variant Curation Expert Panel. Specifications of the ACMG/AMP variant interpretation

guidelines for germline TP53 variants. Hum Mutat. 2021 Mar;42(3):223-236. doi: 10.1002/humu.24152. Epub 2020 Dec 25. PMID: 33300245; PMCID: PMC8374922.

Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, Evans DG; European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. Eur J Hum Genet. 2020 Oct;28(10):1379-1386. doi: 10.1038/s41431-020-0638-4. Epub 2020 May 26. PMID: 32457520; PMCID: PMC7609280.

Godley LA, Shimamura A. Genetic predisposition to hematologic malignancies: management and surveillance. Blood. 2017 Jul 27;130(4):424-432. doi: 10.1182/blood-2017-02-735290. Epub 2017 Jun 9. PMID: 28600339; PMCID: PMC5533201.

Hasle H, Kline RM, Kjeldsen E, Nik-Abdul-Rashid NF, Bhojwani D, Verboon JM, DiTroia SP, Chao KR, Raaschou-Jensen K, Palle J, Zwaan CM, Nyvold CG, Sankaran VG, Cantor AB. Germline GATA1s generating mutations predispose to leukemia with acquired trisomy 21 and Down syndrome-like phenotype. Blood. 2021 Nov 10:blood.2021011463. doi: 10.1182/blood.2021011463. Epub ahead of print. PMID: 34758059.

Hoyer J, Brecht IB, Ripperger T, Karow A , Borkhardt A , Brozou T, Cazzaniga G, Ebinger M , Farah R, García Obregón S, Hauer J, Kamawal A, Kronnie G, Kuhlen M, Lazic J, Lohi O, Özbek U, Pérez-Martínez A, Rieß O, Schneider DT, Schrappe M, Schroeder C, Zimmermann S, Thiel C, Schroeck E, Reis A, Schlegelberger B, Metzler M. Pediatric Cancer Predisposition Documentation Tool - Standardized Reporting Form for Children and Adolescents with Suspected Cancer Predisposition Syndrome. Clin Oncol. 2021; 6: 1844.

Hsu AP, Johnson KD, Falcone EL, Sanalkumar R, Sanchez L, Hickstein DD, Cuellar-Rodriguez J, Lemieux JE, Zerbe CS, Bresnick EH, Holland SM. GATA2 haploinsufficiency caused by mutations in a conserved intronic element leads to MonoMAC syndrome. Blood. 2013 May 9;121(19):3830-7, S1-7. doi: 10.1182/blood-2012-08-452763. Epub 2013 Mar 15. PMID: 23502222; PMCID: PMC3650705.

Huang KL, Mashl RJ, Wu Y, Ritter DI, Wang J, Oh C, Paczkowska M, Reynolds S, Wyczalkowski MA, Oak N, Scott AD, Krassowski M, Cherniack AD, Houlahan KE, Jayasinghe

R, Wang LB, Zhou DC, Liu D, Cao S, Kim YW, Koire A, McMichael JF, Hucthagowder V, Kim TB, Hahn A, Wang C, McLellan MD, Al-Mulla F, Johnson KJ; Cancer Genome Atlas Research Network, Lichtarge O, Boutros PC, Raphael B, Lazar AJ, Zhang W, Wendl MC, Govindan R, Jain S, Wheeler D, Kulkarni S, Dipersio JF, Reimand J, Meric-Bernstam F, Chen K, Shmulevich I, Plon SE, Chen F, Ding L. Pathogenic Germline Variants in 10,389 Adult Cancers. Cell. 2018 Apr 5;173(2):355-370.e14. doi: 10.1016/j.cell.2018.03.039. PMID: 29625052; PMCID: PMC5949147.

Jongmans MC, Loeffen JL, Waanders E, Hoogerbrugge PM, Ligtenberg MJ, Kuiper RP, Hoogerbrugge N. Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. Eur J Med Genet. 2016 Mar;59(3):116-25. doi: 10.1016/j.ejmg.2016.01.008. Epub 2016 Jan 26. PMID: 26825391.

Kim B, Yun W, Lee ST, Choi JR, Yoo KH, Koo HH, Jung CW, Kim SH. Prevalence and clinical implications of germline predisposition gene mutations in patients with acute myeloid leukemia. Sci Rep. 2020 Aug 31;10(1):14297. doi: 10.1038/s41598-020-71386-z. PMID: 32868804; PMCID: PMC7459095.

Kozyra EJ, Pastor VB, Lefkopoulos S, Sahoo SS, Busch H, Voss RK, Erlacher M, Lebrecht D, Szvetnik EA, Hirabayashi S, Pasaulienė R, Pedace L, Tartaglia M, Klemann C, Metzger P, Boerries M, Catala A, Hasle H, de Haas V, Kállay K, Masetti R, De Moerloose B, Dworzak M, Schmugge M, Smith O, Starý J, Mejstrikova E, Ussowicz M, Morris E, Singh P, Collin M, Derecka M, Göhring G, Flotho C, Strahm B, Locatelli F, Niemeyer CM, Trompouki E, Wlodarski MW; European Working Group of MDS in Childhood (EWOG-MDS). Synonymous GATA2 mutations result in selective loss of mutated RNA and are common in patients with GATA2 deficiency. Leukemia. 2020 Oct;34(10):2673-2687. doi: 10.1038/s41375-020-0899-5. Epub 2020 Jun 18. PMID: 32555368; PMCID: PMC7515837.

Kratz CP, Freycon C, Maxwell KN, Nichols KE, Schiffman JD, Evans DG, Achatz MI, Savage SA, Weitzel JN, Garber JE, Hainaut P, Malkin D. Analysis of the Li-Fraumeni Spectrum Based on an International Germline TP53 Variant Data Set: An International Agency for Research on

Cancer TP53 Database Analysis. JAMA Oncol. 2021 Oct 28:e214398. doi: 10.1001/jamaoncol.2021.4398. Epub ahead of print. PMID: 34709361; PMCID: PMC8554692.

Lewinsohn M, Brown AL, Weinel LM, Phung C, Rafidi G, Lee MK, Schreiber AW, Feng J, Babic M, Chong CE, Lee Y, Yong A, Suthers GK, Poplawski N, Altree M, Phillips K, Jaensch L, Fine M, D'Andrea RJ, Lewis ID, Medeiros BC, Pollyea DA, King MC, Walsh T, Keel S, Shimamura A, Godley LA, Hahn CN, Churpek JE, Scott HS. Novel germ line DDX41 mutations define families with a lower age of MDS/AML onset and lymphoid malignancies. Blood. 2016 Feb 25;127(8):1017-23. doi: 10.1182/blood-2015-10-676098. Epub 2015 Dec 28. PMID: 26712909; PMCID: PMC4968341.

Locatelli F, Niemeyer CM. How I treat juvenile myelomonocytic leukemia. Blood. 2015 Feb 12;125(7):1083-90. doi: 10.1182/blood-2014-08-550483. Epub 2015 Jan 6. PMID: 25564399.

Lu C, Xie M, Wendl MC, Wang J, McLellan MD, Leiserson MD, Huang KL, Wyczalkowski MA, Jayasinghe R, Banerjee T, Ning J, Tripathi P, Zhang Q, Niu B, Ye K, Schmidt HK, Fulton RS, McMichael JF, Batra P, Kandoth C, Bharadwaj M, Koboldt DC, Miller CA, Kanchi KL, Eldred JM, Larson DE, Welch JS, You M, Ozenberger BA, Govindan R, Walter MJ, Ellis MJ, Mardis ER, Graubert TA, Dipersio JF, Ley TJ, Wilson RK, Goodfellow PJ, Raphael BJ, Chen F, Johnson KJ, Parvin JD, Ding L. Patterns and functional implications of rare germline variants across 12 cancer types. Nat Commun. 2015 Dec 22;6:10086. doi: 10.1038/ncomms10086. PMID: 26689913; PMCID: PMC4703835.

Luo X, Feurstein S, Mohan S, Porter CC, Jackson SA, Keel S, Chicka M, Brown AL, Kesserwan C, Agarwal A, Luo M, Li Z, Ross JE, Baliakas P, Pineda-Alvarez D, DiNardo CD, Bertuch AA, Mehta N, Vulliamy T, Wang Y, Nichols KE, Malcovati L, Walsh MF, Rawlings LH, McWeeney SK, Soulier J, Raimbault A, Routbort MJ, Zhang L, Ryan G, Speck NA, Plon SE, Wu D, Godley LA. ClinGen Myeloid Malignancy Variant Curation Expert Panel recommendations for germline RUNX1 variants. Blood Adv. 2019 Oct 22;3(20):2962-2979. doi: 10.1182/bloodadvances.2019000644. PMID: 31648317; PMCID: PMC6849945.

Maciejewski JP, Padgett RA, Brown AL, Müller-Tidow C. DDX41-related myeloid neoplasia. Semin Hematol. 2017 Apr;54(2):94-97. doi: 10.1053/j.seminhematol.2017.04.007. Epub 2017 Apr 21. PMID: 28637623; PMCID: PMC8190973.

Martin ES, Ferrer A, Mangaonkar AA, Khan SP, Kohorst MA, Joshi AY, Hogan WJ, Olteanu H, Moyer AM, Al-Kali A, Tefferi A, Chen D, Wudhikarn K, Go R, Viswanatha D, He R, Ketterling R, Nguyen PL, Oliveira JL, Gangat N, Lasho T, Patnaik MM. Spectrum of hematological malignancies, clonal evolution and outcomes in 144 Mayo Clinic patients with germline predisposition syndromes. Am J Hematol. 2021 Nov 1;96(11):1450-1460. doi: 10.1002/ajh.26321. Epub 2021 Aug 27. PMID: 34390506.

Michler P, Schedel A, Witschas M, Friedrich UA, Wagener R, Mehtonen J, Brozou T, Menzel M, Walter C, Nabi D, Pearce G, Erlacher M, Göhring G, Dugas M, Heinäniemi M, Borkhardt A, Stölzel F, Hauer J, Auer F. Germline POT1 Deregulation Can Predispose to Myeloid Malignancies in Childhood. Int J Mol Sci. 2021 Oct 26;22(21):11572. doi: 10.3390/ijms222111572. PMID: 34769003; PMCID: PMC8583981.

Narumi S, Amano N, Ishii T, Katsumata N, Muroya K, Adachi M, Toyoshima K, Tanaka Y, Fukuzawa R, Miyako K, Kinjo S, Ohga S, Ihara K, Inoue H, Kinjo T, Hara T, Kohno M, Yamada S, Urano H, Kitagawa Y, Tsugawa K, Higa A, Miyawaki M, Okutani T, Kizaki Z, Hamada H, Kihara M, Shiga K, Yamaguchi T, Kenmochi M, Kitajima H, Fukami M, Shimizu A, Kudoh J, Shibata S, Okano H, Miyake N, Matsumoto N, Hasegawa T. SAMD9 mutations cause a novel multisystem disorder, MIRAGE syndrome, and are associated with loss of chromosome 7. Nat Genet. 2016 Jul;48(7):792-7. doi: 10.1038/ng.3569. Epub 2016 May 16. PMID: 27182967.

Nickels EM, Soodalter J, Churpek JE, Godley LA. Recognizing familial myeloid leukemia in adults. Ther Adv Hematol. 2013 Aug;4(4):254-69. doi: 10.1177/2040620713487399. PMID: 23926458; PMCID: PMC3734901.

Palomo L, Ibáñez M, Abáigar M, Vázquez I, Álvarez S, Cabezón M, Tazón-Vega B, Rapado I, Fuster-Tormo F, Cervera J, Benito R, Larrayoz MJ, Cigudosa JC, Zamora L, Valcárcel D, Cedena MT, Acha P, Hernández-Sánchez JM, Fernández-Mercado M, Sanz G, Hernández-

Rivas JM, Calasanz MJ, Solé F, Such E; Spanish Group of MDS (GESMD). Spanish Guidelines for the use of targeted deep sequencing in myelodysplastic syndromes and chronic myelomonocytic leukaemia. Br J Haematol. 2020 Mar;188(5):605-622. doi: 10.1111/bjh.16175. Epub 2019 Oct 16. PMID: 31621063; PMC ID: PMC7064979.

Pippucci T, Savoia A, Perrotta S, Pujol-Moix N, Noris P, Castegnaro G, Pecci A, Gnan C, Punzo F, Marconi C, Gherardi S, Loffredo G, De Rocco D, Scianguetta S, Barozzi S, Magini P, Bozzi V, Dezzani L, Di Stazio M, Ferraro M, Perini G, Seri M, Balduini CL. Mutations in the 5' UTR of ANKRD26, the ankirin repeat domain 26 gene, cause an autosomal-dominant form of inherited thrombocytopenia, THC2. Am J Hum Genet. 2011 Jan 7;88(1):115-20. doi: 10.1016/j.ajhg.2010.12.006. PMID: 21211618; PMCID: PMC3014357.

Polprasert C, Schulze I, Sekeres MA, Makishima H, Przychodzen B, Hosono N, Singh J, Padgett RA, Gu X, Phillips JG, Clemente M, Parker Y, Lindner D, Dienes B, Jankowsky E, Sauntharajah Y, Du Y, Oakley K, Nguyen N, Mukherjee S, Pabst C, Godley LA, Churpek JE, Pollyea DA, Krug U, Berdel WE, Klein HU, Dugas M, Shiraishi Y, Chiba K, Tanaka H, Miyano S, Yoshida K, Ogawa S, Müller-Tidow C, Maciejewski JP. Inherited and Somatic Defects in DDX41 in Myeloid Neoplasms. Cancer Cell. 2015 May 11;27(5):658-70. doi: 10.1016/j.ccell.2015.03.017. Epub 2015 Apr 23. PMID: 25920683.

Porter CC, Druley TE, Erez A, Kuiper RP, Onel K, Schiffman JD, Wolfe Schneider K, Scollon SR, Scott HS, Strong LC, Walsh MF, Nichols KE. Recommendations for Surveillance for Children with Leukemia-Predisposing Conditions. Clin Cancer Res. 2017 Jun 1;23(11):e14-e22. doi: 10.1158/1078-0432.CCR-17-0428. PMID: 28572263.

Ravandi F, Walter RB, Freeman SD. Evaluating measurable residual disease in acute myeloid leukemia. Blood Adv. 2018 Jun 12;2(11):1356-1366. doi: 10.1182/bloodadvances.2018016378. PMID: 29895626; PMCID: PMC5998930.

Renaux-Petel M, Charbonnier F, Théry JC, Fermey P, Lienard G, Bou J, Coutant S, Vezain M, Kasper E, Fourneaux S, Manase S, Blanluet M, Leheup B, Mansuy L, Champigneulle J, Chappé C, Longy M, Sévenet N, Paillerets BB, Guerrini-Rousseau L, Brugières L, Caron O,

Sabourin JC, Tournier I, Baert-Desurmont S, Frébourg T, Bougeard G. Contribution of de novo and mosaic TP53 mutations to Li-Fraumeni syndrome. J Med Genet. 2018 Mar;55(3):173-180. doi: 10.1136/jmedgenet-2017-104976. Epub 2017 Oct 25. PMID: 29070607.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID: 25741868; PMCID: PMC4544753.

Rio-Machin A, Vulliamy T, Hug N, Walne A, Tawana K, Cardoso S, Ellison A, Pontikos N, Wang J, Tummala H, Al Seraihi AFH, Alnajar J, Bewicke-Copley F, Armes H, Barnett M, Bloor A, Bödör C, Bowen D, Fenaux P, Green A, Hallahan A, Hjorth-Hansen H, Hossain U, Killick S, Lawson S, Layton M, Male AM, Marsh J, Mehta P, Mous R, Nomdedéu JF, Owen C, Pavlu J, Payne EM, Protheroe RE, Preudhomme C, Pujol-Moix N, Renneville A, Russell N, Saggar A, Sciuccati G, Taussig D, Toze CL, Uyttebroeck A, Vandenberghe P, Schlegelberger B, Ripperger T, Steinemann D, Wu J, Mason J, Page P, Akiki S, Reay K, Cavenagh JD, Plagnol V, Caceres JF, Fitzgibbon J, Dokal I. The complex genetic landscape of familial MDS and AML reveals pathogenic germline variants. Nat Commun. 2020 Feb 25;11(1):1044. doi: 10.1038/s41467-020-14829-5. PMID: 32098966; PMCID: PMC7042299.

Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, Debatin KM, Deubzer H, Dirksen U, Eckert C, Eggert A, Erlacher M, Fleischhack G, Frühwald MC, Gnekow A, Goehring G, Graf N, Hanenberg H, Hauer J, Hero B, Hettmer S, von Hoff K, Horstmann M, Hoyer J, Illig T, Kaatsch P, Kappler R, Kerl K, Klingebiel T, Kontny U, Kordes U, Körholz D, Koscielniak E, Kramm CM, Kuhlen M, Kulozik AE, Lamottke B, Leuschner I, Lohmann DR, Meinhardt A, Metzler M, Meyer LH, Moser O, Nathrath M, Niemeyer CM, Nustede R, Pajtler KW, Paret C, Rasche M, Reinhardt D, Rieß O, Russo A, Rutkowski S, Schlegelberger B, Schneider D, Schneppenheim R, Schrappe M, Schroeder C, von Schweinitz D, Simon T,

Sparber-Sauer M, Spix C, Stanulla M, Steinemann D, Strahm B, Temming P, Thomay K, von Bueren AO, Vorwerk P, Witt O, Wlodarski M, Wössmann W, Zenker M, Zimmermann S, Pfister SM, Kratz CP. Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A. 2017 Apr;173(4):1017-1037. doi: 10.1002/ajmg.a.38142. Epub 2017 Feb 7. PMID: 28168833.

Ripperger T, Evans DG, Malkin D, Kratz CP. Choose and stay on one out of two paths: distinction between clinical versus research genetic testing to identify cancer predisposition syndromes among patients with cancer. Fam Cancer. 2021 Oct;20(4):289-291. doi: 10.1007/s10689-021-00228-2. Epub 2021 Feb 12. Erratum in: Fam Cancer. 2021 Mar 10;: PMID: 33576909; PMCID: PMC8484144.

Ripperger T, Hofmann W, Koch JC, Shirneshan K, Haase D, Wulf G, Issing PR, Karnebogen M, Schmidt G, Auber B, Schlegelberger B, Illig T, Zirn B, Steinemann D. MDS1 and EVI1 complex locus (MECOM): a novel candidate gene for hereditary hematological malignancies. Haematologica. 2018 Feb;103(2):e55-e58. doi: 10.3324/haematol.2017.178723. Epub 2017 Nov 2. PMID: 29097497; PMCID: PMC5792286.

Ripperger T, Tauscher M, Haase D, Griesinger F, Schlegelberger B, Steinemann D. Managing individuals with propensity to myeloid malignancies due to germline RUNX1 deficiency. Haematologica. 2011 Dec;96(12):1892-4. doi: 10.3324/haematol.2011.053710. Epub 2011 Aug 31. PMID: 21880633; PMCID: PMC3232279.

Ripperger T, Tauscher M, Thomay K, Göhring G, Kraemer D, Schlegelberger B, Steinemann D. No evidence for ITSN1 loss in a patient with mental retardation and complex chromosomal rearrangements of 21q21-21q22. Leuk Res. 2013 Jun;37(6):721-3. doi: 10.1016/j.leukres.2013.02.013. Epub 2013 Mar 14. PMID: 23498976.

Sahoo SS, Pastor VB, Goodings C, Voss RK, Kozyra EJ, Szvetnik A, Noellke P, Dworzak M, Starý J, Locatelli F, Masetti R, Schmugge M, De Moerloose B, Catala A, Kállay K, Turkiewicz D, Hasle H, Buechner J, Jahnukainen K, Ussowicz M, Polychronopoulou S, Smith OP, Fabri

O, Barzilai S, de Haas V, Baumann I, Schwarz-Furlan S; European Working Group of MDS in Children (EWOG-MDS), Niewisch MR, Sauer MG, Burkhardt B, Lang P, Bader P, Beier R, Müller I, Albert MH, Meisel R, Schulz A, Cario G, Panda PK, Wehrle J, Hirabayashi S, Derecka M, Durruthy-Durruthy R, Göhring G, Yoshimi-Noellke A, Ku M, Lebrecht D, Erlacher M, Flotho C, Strahm B, Niemeyer CM, Wlodarski MW. Clinical evolution, genetic landscape and trajectories of clonal hematopoiesis in SAMD9/SAMD9L syndromes. Nat Med. 2021 Oct;27(10):1806-1817. doi: 10.1038/s41591-021-01511-6. Epub 2021 Oct 7. PMID: 34621053.

Sanders MA, Chew E, Flensburg C, Zeilemaker A, Miller SE, Al Hinai AS, Bajel A, Luiken B, Rijken M, Mclennan T, Hoogenboezem RM, Kavelaars FG, Fröhling S, Blewitt ME, Bindels EM, Alexander WS, Löwenberg B, Roberts AW, Valk PJM, Majewski IJ. MBD4 guards against methylation damage and germ line deficiency predisposes to clonal hematopoiesis and early-onset AML. Blood. 2018 Oct 4;132(14):1526-1534. doi: 10.1182/blood-2018-05-852566. Epub 2018 Jul 26. PMID: 30049810; PMCID: PMC6172562.

Schuurhuis GJ, Heuser M, Freeman S, Béné MC, Buccisano F, Cloos J, Grimwade D, Haferlach T, Hills RK, Hourigan CS, Jorgensen JL, Kern W, Lacombe F, Maurillo L, Preudhomme C, van der Reijden BA, Thiede C, Venditti A, Vyas P, Wood BL, Walter RB, Döhner K, Roboz GJ, Ossenkoppele GJ. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018 Mar 22;131(12):1275-1291. doi: 10.1182/blood-2017-09-801498. Epub 2018 Jan 12. PMID: 29330221; PMCID: PMC5865231.

Schwermer M, Behnert A, Dörgeloh B, Ripperger T, Kratz CP. Effective identification of cancer predisposition syndromes in children with cancer employing a questionnaire. Fam Cancer. 2021 Oct;20(4):257-262. doi: 10.1007/s10689-021-00233-5. Epub 2021 Mar 2. PMID: 33651299; PMCID: PMC8484089.

Song WJ, Sullivan MG, Legare RD, Hutchings S, Tan X, Kufrin D, Ratajczak J, Resende IC, Haworth C, Hock R, Loh M, Felix C, Roy DC, Busque L, Kurnit D, Willman C, Gewirtz AM,

Speck NA, Bushweller JH, Li FP, Gardiner K, Poncz M, Maris JM, Gilliland DG. Haploinsufficiency of CBFA2 causes familial thrombocytopenia with propensity to develop acute myelogenous leukaemia. Nat Genet. 1999 Oct;23(2):166-75. doi: 10.1038/13793. PMID: 10508512.

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.

Tawana K, Drazer MW, Churpek JE. Universal genetic testing for inherited susceptibility in children and adults with myelodysplastic syndrome and acute myeloid leukemia: are we there yet? Leukemia. 2018 Jul;32(7):1482-1492. doi: 10.1038/s41375-018-0051-y. Epub 2018 Feb 27. PMID: 29483711.

Tesi B, Davidsson J, Voss M, Rahikkala E, Holmes TD, Chiang SCC, Komulainen-Ebrahim J, Gorcenco S, Rundberg Nilsson A, Ripperger T, Kokkonen H, Bryder D, Fioretos T, Henter JI, Möttönen M, Niinimäki R, Nilsson L, Pronk CJ, Puschmann A, Qian H, Uusimaa J, Moilanen J, Tedgård U, Cammenga J, Bryceson YT. Gain-of-function SAMD9L mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. Blood. 2017 Apr 20;129(16):2266-2279. doi: 10.1182/blood-2016-10-743302. Epub 2017 Feb 15. PMID: 28202457; PMCID: PMC5399482.

van Os NJH, Haaxma CA, van der Flier M, Merkus PJFM, van Deuren M, de Groot IJM, Loeffen J, van de Warrenburg BPC, Willemsen MAAP; A-T Study Group. Ataxia-telangiectasia: recommendations for multidisciplinary treatment. Dev Med Child Neurol. 2017 Jul;59(7):680-689. doi: 10.1111/dmcn.13424. Epub 2017 Mar 20. PMID: 28318010.

Vetsch J, Wakefield CE, Warby M, Tucker K, Patterson P, McGill BC, Metcalfe A, Cohn RJ, Fardell JE. Cancer-Related Genetic Testing and Personalized Medicine for Adolescents: A Narrative Review of Impact and Understanding. J Adolesc Young Adult Oncol. 2018 Jun;7(3):259-262. doi: 10.1089/jayao.2017.0102. Epub 2018 Jan 16. PMID: 29336661.

Vlachos A, Ball S, Dahl N, Alter BP, Sheth S, Ramenghi U, Meerpohl J, Karlsson S, Liu JM, Leblanc T, Paley C, Kang EM, Leder EJ, Atsidaftos E, Shimamura A, Bessler M, Glader B, Lipton JM; Participants of Sixth Annual Daniella Maria Arturi International Consensus Conference. Diagnosing and treating Diamond Blackfan anaemia: results of an international clinical consensus conference. Br J Haematol. 2008 Sep;142(6):859-76. doi: 10.1111/j.1365-2141.2008.07269.x. Epub 2008 Jul 30. PMID: 18671700; PMCID: PMC2654478.

Walsh MF, Chang VY, Kohlmann WK, Scott HS, Cunniff C, Bourdeaut F, Molenaar JJ, Porter CC, Sandlund JT, Plon SE, Wang LL, Savage SA. Recommendations for Childhood Cancer Screening and Surveillance in DNA Repair Disorders. Clin Cancer Res. 2017 Jun 1;23(11):e23-e31. doi: 10.1158/1078-0432.CCR-17-0465. PMID: 28572264; PMCID: PMC5697784.

Wlodarski MW, Hirabayashi S, Pastor V, Starý J, Hasle H, Masetti R, Dworzak M, Schmugge M, van den Heuvel-Eibrink M, Ussowicz M, De Moerloose B, Catala A, Smith OP, Sedlacek P, Lankester AC, Zecca M, Bordon V, Matthes-Martin S, Abrahamsson J, Kühl JS, Sykora KW, Albert MH, Przychodzien B, Maciejewski JP, Schwarz S, Göhring G, Schlegelberger B, Cseh A, Noellke P, Yoshimi A, Locatelli F, Baumann I, Strahm B, Niemeyer CM; EWOG-MDS. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. Blood. 2016 Mar 17;127(11):1387-97; quiz 1518. doi: 10.1182/blood-2015-09-669937. Epub 2015 Dec 23. PMID: 26702063.

Yannakou CK, Jones K, Ryland GL, Thompson ER, Reid G, McBean M, Trainer A, Westerman D, Blombery P. Incidental detection of germline variants of potential clinical significance by massively parallel sequencing in haematological malignancies. J Clin Pathol. 2018 Jan;71(1):84-87. doi: 10.1136/jclinpath-2017-204481. Epub 2017 Aug 11. PMID: 28801348.

Zhang MY, Churpek JE, Keel SB, Walsh T, Lee MK, Loeb KR, Gulsuner S, Pritchard CC, Sanchez-Bonilla M, Delrow JJ, Basom RS, Forouhar M, Gyurkocza B, Schwartz BS, Neistadt B, Marquez R, Mariani CJ, Coats SA, Hofmann I, Lindsley RC, Williams DA, Abkowitz JL, Horwitz MS, King MC, Godley LA, Shimamura A. Germline ETV6 mutations in familial

thrombocytopenia and hematologic malignancy. Nat Genet. 2015 Feb;47(2):180-5. doi: 10.1038/ng.3177. Epub 2015 Jan 12. PMID: 25581430; PMCID: PMC4540357.