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Review

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Pathophysiology of Acute Myeloid Leukemia

Franziska Wachter Yana Pikman

Department of Pediatric Oncology, Dana-Farber Cancer Institute and Division of Hematology/Oncology, Boston Children's Hospital, Boston, MA, USA

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Abstract
Background: Acute myeloid leukemia (AML) is a biologically heterogenous disease arising in clonally proliferating hematopoietic stem cells. Sequential acquisition of mutations leads to expanded proliferation of clonal myeloid progenitors and failure of differentiation, leading to fulminant AML. ***Summary:*** Here, we review the pathophysiology of AML with a focus on factors predisposing to AML development, including prior chemo- and radiation therapy, environmental factors, and germline predisposition. ***Key Message:*** Increasing genomic characterization of AML and insight into mechanisms of its development will be critical to improvement in AML prognostication and therapy.

Introduction

Clonal expansion and maturation blockade of hematopoietic stem cell (HSC) and progenitor cell are the hallmarks of acute myeloid leukemia (AML). Although overall rare, accounting for 1% of all cancer cases, AML is the most common leukemia in adults. Most cases of AML occur in individuals over the age of 60, and it is characterized by an underlying heterogeneous disease biology. Increased appreciation of the genetic drivers of AML and improved understanding of AML biology have improved the characterization and treatment of this disease [1]. Various risk factors, such as myelodysplastic syndrome (MDS) or myeloproliferative disease, environmental exposures, previous chemo- or radiation therapy, and genetic predispositions, contribute to the development of AML. Pediatric AML, including infant cases, has distinct clinical and genetic features compared to AML in older adults. In this review, we discuss AML pathogenesis, biology and characterization, and differences in adult versus pediatric AML. With increased knowledge of genomics of AML, and the importance of molecular characterization for treatment decisions and prognosis, we highlight some of the key AML genetic features, the importance of next-generation sequencing (NGS) as part of AML diagnostic workup, and the critical need for germline evaluation for every patient with AML.

AML Pathogenesis

AML biology is heterogenous and overall characterized by abnormal proliferation and differentiation of myeloid precursors in the bone marrow. AML is a clonal process that develops from a transformed HSC resulting in a clonal proliferation, which occurs in otherwise healthy

karger@karger.com
www.karger.com/aha

Correspondence to:
Yana Pikman, yana_pikman@dfci.harvard.edu

Karger

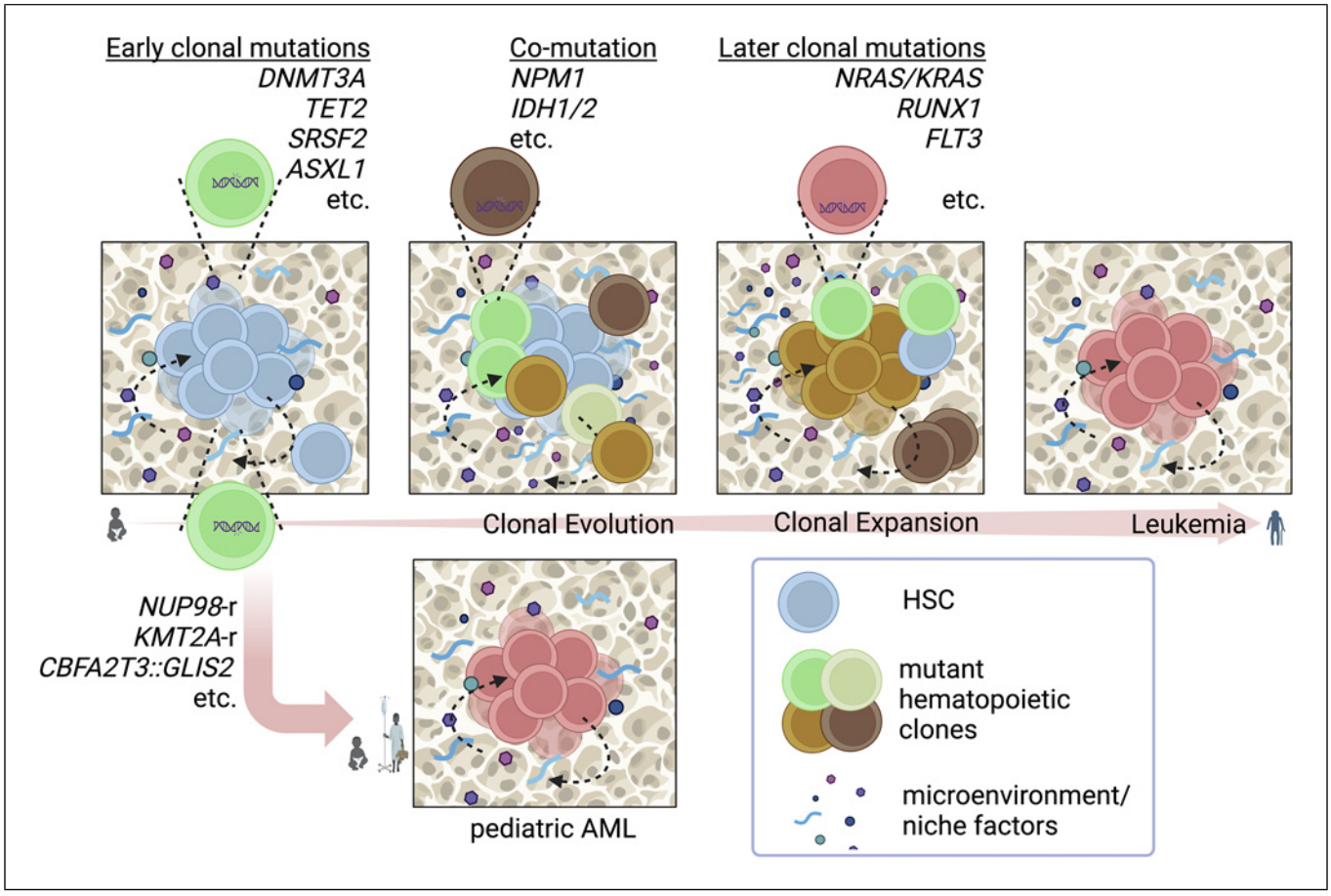

Fig. 1. Illustration showing development of AML. Figure created using biorender.com.

individuals and precedes the development of leukemia. Recurrent AML-related mutations can accumulate within hematopoietic progenitor cells with age in healthy individuals, leading to clonal growth but without development of leukemia, a phenomenon known as clonal hematopoiesis of indeterminate potential (CHIP) [2]. These cells have a proliferative advantage, allowing them to expand while maintaining normal hematopoiesis. With time, progression to AML from clonal hematopoiesis is estimated at 0.5–1% per year [3]. Factors that distinguish age-related clonal hematopoiesis from pre-AML include number of mutations per sample, higher variant allele frequency, and mutations in specific genes, such as *DNMT3A, TET2, SRSF2, ASXL1* [4] (Fig. 1).

Initiating leukemic mutations occur in early HSCs and result in alterations in self-renewal. The acquired self-renewal capacity of mutant HSCs allows for acquisition of additional mutations over time, development of leukemia stem cell (LSC), and potential transformation to leukemia. The LSC is defined similarly to HSC, with ability for self-renewal, and having multipotent and highly proliferative properties, and originally defined with the functional ability to cause leukemia when transferred to a NOD/SCID mouse [5]. Acquisition of additional mutations may impair differentiation, thus implicating the historical "two-hit hypothesis" of AML development, where class 1 mutations affect cell proliferation and class 2 mutations affect differentiation [6]. The specific combinations of mutations that ultimately lead to leukemogenesis are influenced by the biological cooperation and mutual exclusivity among certain mutated genes which has been more clearly defined with more extensive NGS over the last 10 years.

The sequencing of AML genomes has revealed complex patterns of mutation and clonal evolution and has transformed AML risk stratification as well as expanded beyond the initial "two-hit hypothesis" [7, 8]. The AML TCGA report found AML genomes to have an average of 13 mutations with nearly all samples having at least 1 non-synonymous mutation thought to be relevant for

leukemogenesis, including transcription factor fusions (18%), nucleophosmin (NPM1) (27%), tumor suppressor (16%), DNA-methylation-related (44%), signaling (59%), chromatin-modifying (30%), myeloid transcription factor (22%), cohesin complex (13%), and spliceosome complex genes (14%) [8]. Characterization of 1,540 patients with AML identified 5,234 driver mutations across 76 genes or genomic regions, with 2 or more drivers identified in 86% of the evaluated patients. This characterized AML into 11 classes with distinct features which have influenced the more recent AML classifications based on molecular features. The prognostic significance of individual mutations was influenced by the presence, absence, and possible cooperation of other driver mutations [9]. Early mutations may increase stem cell fitness, leading to subsequent acquisition of other, AML-specific mutations and development of AML. The number of mutated genes and cooperation patterns are extensive, and we highlight more frequent/common patterns below.

The stem cell niche contributes to transformation from the clonal population to development of additional mutations and ultimately AML. There are numerous factors that add to a permissive microenvironment for leukemia development. This is characterized by aberrant cell adhesion, immunosuppression, and changes in cytokine signaling. Age-dependent vascular development with increase in perivascular capillaries, increase in PDGFRB-positive perivascular cells, arteriole formation, and a surge in cellular stem cell factor may all contribute to this niche development [10], altering stem cell interaction within the bone marrow microenvironment. Additional interactions of AML with the vascular niche, such as via E-selectin, VEGF/VEGFR, Notch signaling, and secretion of GM-CSF, also influence LSC development [11, 12]. LSC interactions with the mesenchymal stromal cells, osteoblasts, and osteoclasts are also critical to AML development, and AML cells themselves can also differentiate mesenchymal stromal cells to further support a permissive niche [13].

The inflammatory microenvironment has also been implicated in AML development. For example, patients with CHIP and *TET2* mutations have an increase in interleukin-8, and this has been linked to a number of diseases including atherosclerosis and cardiac disease [14, 15]. *Tet2* deletion was found to have a pro-inflammatory phenotype in mice, with an associated increase in IL-6, IL-1B, and interleukin-8, and accelerated atherosclerosis in mice [16]. Aging itself has been associated with chronic inflammation [17]. Patients with vacuoles, E1 enzyme, X-linked autoinflammatory, somatic (VEXAS) syndrome, a systemic inflammatory condition characterized by somatic mutations in *UBA1*, have an increase in MDS and high rates of CHIP with *TET2* and *DNMT3A* mutations [18, 19]. Clonal cells with *TET2* or *DNMT3A* mutations may have a proliferative advantage in or contribute to the inflammatory microenvironment, to influence development of AML though this connection is unclear [20]. Cell intrinsic inflammatory signals can modulate proliferation of myeloid cells, and repression of inflammation in AML may contribute to survival [21]. The complex biological processes contributing to AML pathogenesis are summarized in Figure 2.

Age-Related Differences in AML

The incidence of AML increases with age, and the median age at diagnosis is around 68 years [22]. In adults 60 years and older, the incidence is approximately 3–4 cases per 100,000 individuals per year [22]. The incidence of AML in young adults, between the ages of 15 and 39, is lower compared to older adults and is estimated to be around 0.7 to 2.0 cases per 100,000 individuals per year. Pediatric AML accounts for approximately 15–20% of all childhood leukemia cases, with incidence of AML in children being highest in infancy and the first few years of life. For infants, the incidence of AML is approximately 1.5 cases per 100,000 individuals per year.

Both pediatric and adult AMLs have a relatively low overall mutation burden compared to other cancers, yet there are clear age-related differences for the type of mutations present [23]. In adults, accumulation of mutations within HSCs over many years leads to development of AML. Pediatric AML occurs much earlier in life and is characterized by a high prevalence of cytogenetic abnormalities, like structural alterations, fusions, and focal copy number (CN) changes [8, 23–25].

In pediatric AML, fusions are identified in as many as 80% of cases (110/137) and significantly higher than 53% (212/402) of adult AML cases [26]. Pediatric patients with *KMT2A*, *NUP98*, or *CBFA2T3::GLIS2* fusions have few other somatic mutations, and these rearrangements are rare in adult AML. Core-binding factor AML (CBF-AML), defined by *RUNX1::RUNX1T1* and *CBFB::MYH11,* accounts for a higher proportion of AML in pediatrics and young adults (up to age 40) compared to the proportion of CBF-AML in older adults [25]. Experiments to model pediatric-specific rearrangements, like *KMT2A*, *NUP98*, and *CBFA2T3::GLIS2,* have revealed that the age of the cell of origin may determine the latency period of the disease as well as the lineage [27]. For example, expression of *CBFA2T3::GLIS2* in fetal liver

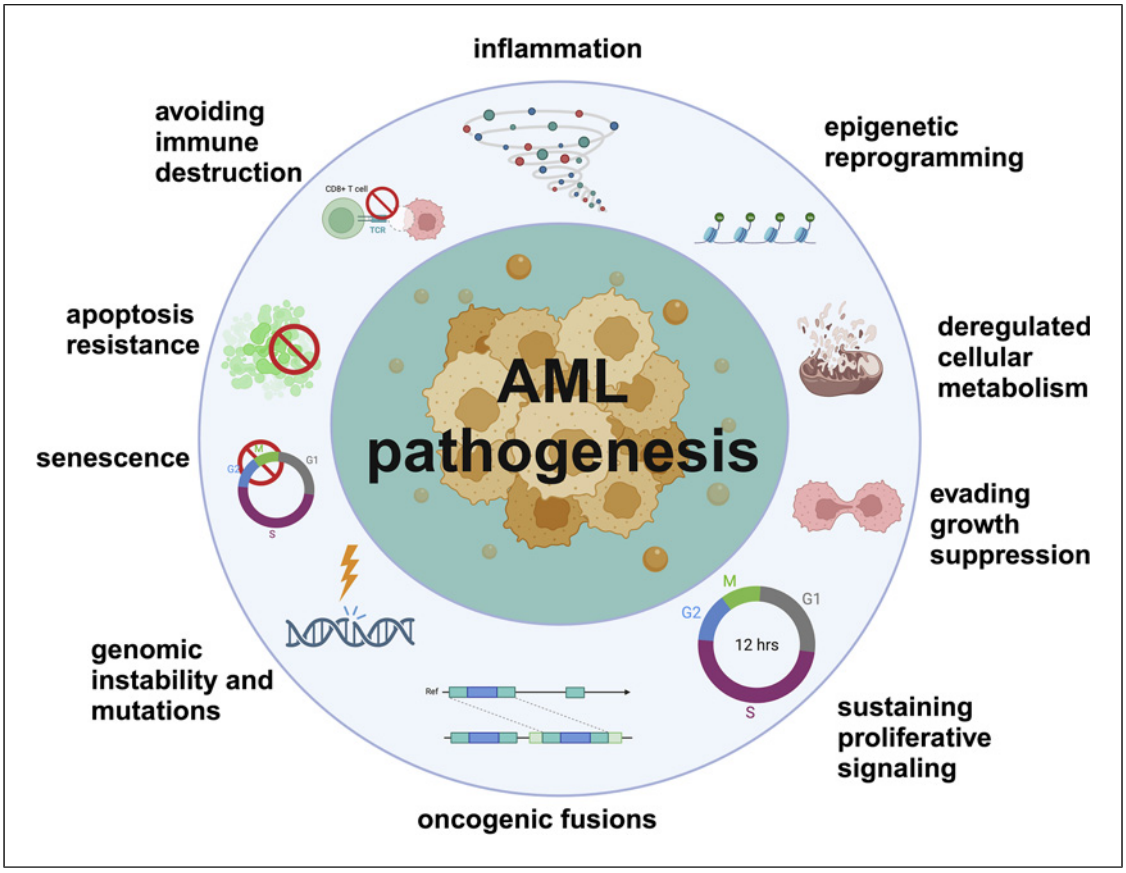

Fig. 2. Biological mechanisms contributing to AML pathogenesis. Figure created using biorender.com.

cells favored a megakaryoblastic AML development with a median latency of 39 days, while expression of this fusion in adult mice led to a mixed phenotype, with 20% of mice developing megakaryoblastic disease with a latency of 164 days, while the rest, a myeloid disease with a latency of 251 days [28]. The expression signature obtained from fetal liver-transformed cells more closely resembled that of patients with *CBFA2T3::GLIS2 AML* [28]. Modeling of translocation t(7;12)(q36;p13), which occurs exclusively in infant AML and is associated with poor prognosis [29], also suggests that the developmental stage of the transformed cell may affect the transforming ability of the fusion [30]. Differences in pediatric and adult hematopoiesis, degree of progenitor lineage commitment, and the type of cell that is targeted by the specific fusion likely all influence the type of leukemia that develops, its aggressiveness, and response to therapy.

The landscape of somatic mutations in pediatric AML is also different, with a higher prevalence of signaling mutations involving the RAS signaling pathway and *KIT*, and low rate of *DNMT3A, NPM1, IDH1/2, TET2* compared to adult AML. The specific mutations within a known AML-associated gene can also vary, e.g., as with novel pathogenic mutations in *FLT3* in pediatric AML [25].

Importance of Molecular Testing in AML

AML diagnosis traditionally relies on morphology and cytogenetics. Numerous transcription factors, such as *RUNX1* and *CBFB*, are targeted for translocations involved in AML, and these translocations have been characterized by cytogenetic analysis (i.e., *RUNX1::RUNX1T1* and *CBFB::MYH11*). Additionally, recurrent cytogenetic aberrations, such as loss of chromosomes −5/5q, −7/7q, gain of chromosome +8, or deletion of 17p, can have diagnostic, prognostic, and treatment implications. Fluorescence in situ hybridization (FISH) can identify these cytogenetic findings even when metaphases are

insufficient for routine cytogenetic analysis or when cryptic rearrangements are present. Implementation of NGS panels is increasingly routine for AML diagnosis and provides information on the presence of class-defining, prognostic, and clinically actionable mutations with available targeted therapies (i.e., *IDH1*, *IDH2*, and *FLT3*). Fusion partner agnostic sequencing (RNA sequencing or anchored NGS, e.g., Archer FusionPlex) is increasingly used to identify cytogenetically cryptic fusions and specific fusion partners.

Somatic mutations are now routinely used for AML classification and diagnosis, prognosis and risk stratification, as well as informing treatment, highlighting the need for availability of molecular profiling [9]. Clinically, various methods can be employed to detect somatic mutations, such as targeted sequencing of an individual gene, quantitative polymerase chain reaction assays based on RNA or DNA, NGS gene panel assays, or comprehensive sequencing of the entire exome or genome. *NPM1, FLT3*, and *CEBPA* genes have the potential to impact diagnostic subtyping and offer valuable prognostic insights specifically in patients with a normal karyotype (NK) leukemia. The 2022 European LeukemiaNet (ELN) classification includes mutations in ten genes (*BCOR, EZH2, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2, ASXL1, RUNX1,* and *TP53*) as criteria for adverse group assignment, unless they co-exist with "favorable-risk" AML subtypes [31]. Clinical genomic sequencing, such as with a panel assay, may also be an informative test for evaluation of patients with cytopenia and at risk for myeloid malignancy [32]. Sensitivity of the assay as well as the type of mutations detected (and their relation to the AML clonal evolution) can determine if these can be used for measuring measurable residual disease (MRD) though this is under active investigation [31].

Subtypes of AML Based on Genetic Alterations

Molecular features are increasingly considered for diagnostic purposes, as AML is either defined as >20% myeloid blasts in the bone marrow or peripheral blood or by distinct genetic mutations even if less blasts are present [33–36]. If no AML-defining genetic abnormalities can be identified, AML is classified by the degree of differentiation and increasingly fewer cases are characterized this way [34, 37]. The classification of AML has recently been updated by the World Health Organization (WHO) and the International Consensus Classification (ICC) [33, 34]. Recommendations for prognostic stratification, response assessment, and MRD determination have also been updated by the European LeukemiaNet (ELN) [31].

Genomic alterations, both mutations and translocations, in AML can be characterized as involving epigenetic modifiers (such as *DNMT3A, TET2, ASXL1, IDH*, etc.), signaling pathways (*FLT3*, RAS pathway, *JAK*, *KIT*, etc.), transcription factors (*RUNX1, CEBPA, GATA2*), cohesin complex (*STAG2, RAD21, SMC3, SMC1A*), RNA splicing factors (*SF3B1, SRSF2, U2AF1, ZRSR2*), *TP53*, and *NPM1.* We highlight some of the more prevalent mutated genes here.

Epigenetic Modifiers

Mutations in epigenetic modifiers play a critical role in essential cellular processes including transcriptional repression and genomic imprinting. Common mutations in epigenetic genes, such as *DNMT3A*, *TET2*, and *ASXL1*, are early events in AML development and may be associated with CHIP in older adults. *DNMT3A* is a DNA methyltransferase and mutated in ~20% of adult AML [38, 39]. In AML, 65% of *DNMT3A* mutations are heterozygous missense mutations affecting codon R882 resulting in down-regulation of genes involved in promoting hematopoietic differentiation [40]. *DNMT3A* tetramers have substantially more active enzymatic function. The mutant protein can dimerize with wildtype DNMT3A but is not able to form tetramers. Therefore, a heterozygous mutation reduces available wildtype DNMT3A for trimer formation and this dominant negative effect causes genome-wide hypomethylation [41, 42]. Non-R882 mutations are heterogeneous and encompass a variety of mutations, and further studies are needed to characterize these mutations. *DNMT3A* mutations frequently co-occur with *NPM1* (*NPM1c*) and *FLT3* mutations, with 60–80% of *DNMT3A* cases having *NPM1c* and 30% displaying both *NPM1c* and *FLT3* mutations [38]. *DNMT3A* mutations detected post-treatment likely indicate the persistence of preleukemic clones rather than leukemic cells, discouraging the use of *DNMT3A* as marker for MRD monitoring [43].

ASXL1 is a chromatin modifier gene with the protein interacting with the polycomb repressor complex 2 (PRC2) [44]. *ASXL1* mutations occur in about 10% of patients with AML, typically in exon 12, cause truncation with loss of the plant homeodomain (PHD) domain of the protein, and result in a loss of H3K27me3 and increased expression of leukemogenic genes [45–47]. *ASXL1* mutations are mutually exclusive with NPM1 mutations and inversely associated with *FLT3* internal

tandem duplications. In a study of 882 patients with AML, *ASXL1* mutations were identified as an unfavorable prognostic factor [48].

TET2 modulates DNA hydroxy-methylation. *TET2* mutations occur in ~15% of AML patients, causing protein inactivation and epigenetic deregulation [49]. A meta-analysis containing 2,552 adult patients with AML identified *TET2* as a marker with poor prognostic impact [50]. *TET2* mutations can be observed with *NPM1, FLT3, JAK2, RUNX1, CEBPA, CBL,* and *KRAS* mutations but are mutually exclusive with *IDH1/2* mutations.

IDH catalyzes the oxidative decarboxylation of isocitrate to alpha-ketoglutarate, though recurrent mutations in *IDH1* and *IDH2* result in the formation of an oncometabolite 2-hydroxyglutarate, which can impede alpha-ketoglutarate-dependent reactions, affecting DNA methylation, mitochondrial respiration among others. Mutations in *IDH1/2* are frequently associated with older age and concurrent *NPM1* mutations [51].

Several other epigenetic alterations have been implicated in AML pathogenesis including oncogenic fusions. For example, Lysine [K]-specific Methyl Transferase 2A (KMT2A) encodes a nuclear protein with methyltransferase activity that is part of a large multifunctional complex. Leukemia-associated translocations involving the N-terminus of the *KMT2A* gene and over 100 *KMT2A* fusion partners have been documented in pediatric and adult de novo AML, therapy-related AML, and other acute leukemias [52]. *MLLT3, AFDN, ELL*, and *MLLT10* are the most prevalent fusion partners in adult AML, and the prevalence of fusion partners varies with age and type of leukemia [52].

Signaling Pathway Mutations

Multiple signaling pathways are implicated in AML pathogenesis and alter normal hematopoietic growth and differentiation, resulting in an accumulation of abnormal, immature myeloid cells in the bone marrow and peripheral blood. These mutations are often sub-clonal and may develop later in the AML development trajectory. Given the sub-clonal nature, signaling pathway mutations may develop at the time of relapse or be present at diagnosis and absent at relapse. Mutations in the tyrosine kinase FLT3 gene are commonly observed, which can occur through either an internal tandem duplication in the juxta-membrane domain (*FLT3-ITD*; approximately 25% of all AML cases) or activating point mutations in the tyrosine kinase domain [53]. Availability and proven efficacy of FLT3 inhibitors make identification of these mutations and integration of targeted therapy particularly critical [54–59].

Activating mutations in the Ras signaling pathway, involving the genes *NRAS, KRAS, PTPN11,* and *NF1*, are present in about 10–15% of adult and up to 30% of pediatric AML [25]. Prognostic significance of these mutations has been debated [60, 61]. The development of drugs to inhibit the Ras/mitogen-activated protein kinase (MAPK) signaling pathway in other cancers, such as melanoma, pancreatic, and colon cancers, has maintained interest in the utility of inhibiting this activating signaling in AML [62]. However, the utility of this approach has been hindered by activation of other signaling pathways that become upregulated with inhibition of the Ras/MAPK signaling pathway. Interestingly, mutations in the Ras signaling pathway arise as a resistance mechanism in patients who receive FLT3 inhibitors, possibly from selective survival advantage of a pre-existing clone, highlighting cooperativity among parallel signaling pathways [63–65].

Transcription Factors

Mutations in myeloid transcription factors, mainly *RUNX1* and *CEBPA*, are each present in about 10% of adult AML [8]. Transcription factor fusions, *CBFB::MYH11* and *RUNX1::RUNX1T1*, define CBF-AML, typically associated with better response to treatment and prognosis. These translocations result in disruption of the CBF complex, which regulates hematopoietic differentiation, and have traditionally been called the type 2 translocations in the "two-hit hypothesis" of AML [6]. In the current genomic classification, these fusions are AML-defining, and patients are considered to have AML in the presence of these irrespective of the blast percentage [34]. *CBFB::MYH11* and *RUNX1::RUNX1T1* alone are insufficient to cause AML, and cooperating mutations are needed, involving signaling pathways, epigenetic regulators, or cohesion complex mutations most commonly [66, 67].

Cohesin Mutations

The cohesin complex is composed of 4 subunits, SMC1A, SMC3, RAD21, and either STAG1 or STAG2, and is critical for mediating DNA looping, regulating chromatin accessibility, and thus regulating gene expression [68]. Mutations within the complex have been identified in approximately 10–20% of patients with AML/MDS [69]. Mutations in the cohesin subunits tend to be mutually exclusive, typically result in loss of function [8], and may be associated with poor outcomes [69]. Mutations in the cohesin complex subunits alone are insufficient to cause leukemia, and these mutations tend to cooperate with others, with *NPM1, RUNX1, FLT3,* and

ASXL1 being the most common [69]. Mutations affecting the regulatory subunits of cohesin complex (*NIPBL, WAPL, PDS5,* and *ESCO2*) are rare and have been reported in less than 0.5% of AML [70]. However, these mutations are more commonly observed in specific rare hereditary disorders of the cohesin complex, such as Cornelia de Lange and Roberts syndromes [70].

Nucleophosmin

NPM1 encodes a chaperone protein that is mostly localized to the nucleus but shuttles between the nucleus and the cytoplasm. *NPM1* mutation (*NPM1c*) occurs in one-third of adult AML and results in a mislocalized NPM1 to the cytoplasm [71]. Around 10% of the protein remains nuclear and is responsible for altered chromatin interactions that contributes to AML [72]. Here, *NPM1c* drives a distinct gene expression signature, characterized by expression of HOX genes and MEIS1, as well as other self-renewal programs. Recent studies show that NPM1c directly binds to specific chromatin targets, which are co-occupied by the histone methyltransferase KMT2A, thus possibly explaining its sensitivity to menin inhibition [72]. NPM1 mutations serve as excellent targets for MRD monitoring due to their specificity to AML (lack of presence in CHIP or antecedent MDS), high frequency, and remarkable stability during relapse. An increase in NPM1 transcripts in bone marrow and/or peripheral blood has been shown to reliably predict hematological relapse within a short period of time [73, 74].

TP53

TP53 is a tumor suppressor implicated in MDS, de novo AML, and therapy-related AML, as well as germline predisposition to cancer as in Li-Fraumeni syndrome. *TP53* abnormalities occur in nearly 5–10% of patients with de novo AML [75], and the frequency in AML/MDS goes up to 20–40% in older patients or those with therapy-related myeloid malignancies [76]. In the analysis of 500 *TP53*-mutant AML cases, 75% harbored a missense variant, most commonly R248, R273, and Y220, with over 70% of patients also harboring CN loss of *TP53* [77]. TP53 expression by immunohistochemistry provides a robust readout for TP53 expression and may thus effectively integrate both mutation status and CN alterations for improved prognostication [77]. *TP53* mutations are consistently associated with adverse prognostic factors, indicative of increased disease progression, treatment resistance, and reduced overall survival [78].

Risk Factors for AML Development

Prior Disease: MDS and Bone Marrow Failure

Secondary AML (s-AML) or more recently defined AML, myelodysplasia related (AML-MR) develops from an antecedent myeloid malignancy, often MDS. AML-MR is defined by a combination of 20% blasts and harboring mutations in specific genes [34], though the mutations may be enriched but not necessarily specific to AML-MR, and can be present in de novo AML [79]. AML-MR is associated with multilineage dysplasia, often evolving in the elderly and in the context of clonal hematopoiesis and accumulation of DNA damage [80]. In a cohort of patients with AML, the presence of mutations in 8 genes (*SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR*, or *STAG2*) was >95% specific for diagnosis of s-AML [81]. The complex mutation pattern, indicative of numerous subclones, results in disease with variable sensitivity to chemotherapy and chemotherapy resistance and has led to use of alternative chemotherapy regimens, such as implementation of liposomal formulation of cytarabine and daunorubicin (CPX-351) [80, 82].

Environmental Factors Contributing to AML

Patient intrinsic risk factors for development of AML, such as patient age, sex, or germline predisposition, have been identified, but patient extrinsic factors remain potentially modifiable. Tobacco exposure is one of the strongest leukemogens, and smoking has been associated with worse AML overall survival [83]. Environmental exposure to benzene and dioxins has also been linked to AML [84]. Benzene and dioxin exposure has been associated with genomic abnormalities, such as acquisition of monosomy 7 and deletion of 5q in in vitro models, as well as alterations in DNA methylation [85].

Treatment-Related Myeloid Neoplasms

Potentially curative chemo- and radiation therapy is unavoidable in the treatment of many malignancies and is also associated with development of therapy-related myeloid neoplasm (t-MN). t-MN typically develops after cytotoxic chemo- or radiotherapy as a treatment for malignant disease but can also be associated with immunosuppression for solid organ transplant or autoimmune disease [86]. Treatment for breast cancer, sarcomas, and hematological malignancies, specifically non-Hodgkin lymphoma, Hodgkin lymphoma, and multiple myeloma, are the primary malignancies associated with an elevated risk of development of t-MN [87, 88]. t-MN on average occurs within 7 years after treatment. Patients with t-MN, despite receiving conventional induction

chemotherapy, have lower rates of complete remission and overall survival, partially due to an increased incidence of high-risk features including complex karyotype and *TP53* mutations [89]. The small subset of patients with t-MN with NK and lack of TP53 mutations have improved outcome compared to patients with t-MN with abnormal karyotype [90], though this outcome is still likely worse than patients with NK AML and is associated with increased death in remission [91]. This may be related to poor tolerance of chemotherapy in patients with t-MN. Comorbidities related to initial cancer therapy, prior to t-MN, may influence both therapy selection and ability to tolerate intensive chemotherapy in patients with t-MN.

Overall, t-MN has an increased rate of mutations compared to de novo AML due to chemotherapy-induced mutagenesis [92]. There is an increase in CN and structural variants, likely associated with chemotherapy-induced chromothripsis [92]. Antecedent CH, as has been seen in pre-therapy samples, may contribute to t-MN [92]. This has been demonstrated for patients undergoing treatment for lymphoma [93] or other non-myeloid disease using autologous stem cell transplant [94] and multiple myeloma [95]. In contrast, in pediatrics, t-MN was not associated with pre-existing CHIP mutations, though 15% of pediatric patients had germline alterations [96]. Mutations in familial cancer predisposition genes have been found in about 20% of patients with t-MN and a previous breast cancer or lymphoproliferative disease [97].

Novel molecular characterization and NGS separate t-MN into 3 groups that vary in prevalence across age groups based on distinct mutational patterns: among 101 adults with clinically defined t-MN, 33% (34/101) harbored secondary-type mutations in *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR*, or *STAG2*; 23% (23/101) of patients had TP53 mutations; 47% (47/101) had only de novo or pan-AML alterations. The latter group included all other mutations identified not specific to either AML subtype and were thus labeled "pan-AML" mutations [81].

Translocations involving *KMT2A* at 11q23 and *RUNX1* at 21q22 are the most frequent translocations in t-MN and are associated with prior exposure to topoisomerase II inhibitors [98]. Topoisomerase-induced t-MN classically is notable for a truncated latency period, typically ranging from 1 to 2 years post-drug exposure. It presents as overt leukemia and exhibits a distinct association with a more favorable response to intensive induction therapy. Alkylating agent or radiotherapy-induced t-MN is more common (70% of all t-MN) and historically characterized by monosomy for chromosome 5 or 7 or loss of 5q or 7q chromosome arms [99]. This t-MN subtype has a long latency period (on average 5 years), presents as MDS, often transforming rapidly to AML, and is associated with a poor prognosis (median survival: 8 months).

Germline Predisposition to AML

Pathogenic germline mutations that predispose to AML have been described in a growing number of genes [100, 101] (Table 1). The 2016 classification identifies myeloid malignancies with germline predisposition as a distinct subgroup, and this was further characterized in the 2022 WHO update [102]. The suspicion of an inherited cancer syndrome arises in patients with a personal history marked by long-standing cytopenia, frequent atypical infections, immunodeficiency, previous malignancies, or various congenital abnormalities. Advancements in and increased use of germline testing identify around 10–15% of AML to be linked to a genetic susceptibility [102, 103]. Whole-exome sequencing data of paired leukemia and skin biopsy samples of 391 adult patients with AML showed that 13.6% of the evaluated patients harbor pathogenic/likely pathogenic germline variants, including 6.4% of patients with variants in clinically actionable genes, supporting the routine screening for germline variants. No strong correlation was found between the germline mutational rate and age of AML onset [103]. From a research perspective, three-dimensional protein modeling using AlphaFold multimer and deposited protein structures can be effective methodologies to prioritize variants of unknown significance for functional studies [104]. The WHO defines types of myeloid neoplasms associated with germline predisposition in three categories: (1) myeloid neoplasms with germline predisposition without pre-existing platelet disorders or organ dysfunction, (2) myeloid neoplasms with germline predisposition with pre-existing platelet disorder, (3) or with potential organ dysfunction [34].

Myeloid Neoplasms with Germline Predisposition without Pre-Existing Platelet Disorders or Organ Dysfunction

Mutations in CCAAT/enhancer binding protein alpha (CEBPA), DEAD-box helicase 41 gene (DDX41), and TP53 predispose to AML but are not typically associated with pre-existing platelet disorders. CEBPA is a transcription factor primarily involved in myeloid cell regulation. Germline CEBPA mutations cluster within the

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Table 1. Myeloid neoplasms with germline predisposition

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic hematological malignancies	Lifetime risk malignancies	Other phenotypes and features	Diagnostic testing	Resources
Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction							
AML with germline *CEBPA* mutation	*CEPBA*	AD	AML	>80%		DNA sequencing 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 AD 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	*RUNX1*	AD	MDS, AML	45%	Thrombocytopenia and abnormal platelet function; clonal hematopoiesis; ALL	DNA sequencing including del/dup analysis	https://www.runx1-fpd.org/
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	*ETV6*	AD	ALL, AML, MDS		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	https://rarediseases.org/gard-rare-disease/gata2-deficiency/

Table 1 (continued)

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic hematological malignancies	Lifetime risk malignancies	Other phenotypes and features	Diagnostic testing	Resources
MIRAGE syndrome	*SAMD9*	AD	MDS, AML	High, spontaneous resolution through revertant mosaicism possible	Cytopenias and marrow failure; growth restriction, infection susceptibility, adrenal hypoplasia, genital phenotypes, and enteropathy	DNA sequencing	https://www.stjude.org/samd9
Ataxia-pancytopenia syndrome	*SAMD9L*	AD	MDS, AML	High, spontaneous resolution through revertant mosaicism possible	Cytopenias and marrow failure; gait disturbance, nystagmus, cerebellar atrophy and white matter hyperintensities; immunodeficiency	DNA sequencing	https://www.stjude.org/samd9
Bone marrow failure syndrome 1 (BFMS1/SRP72)	*SRP72*	AD	MDS	Unknown	Congenital sensorineural deafness	DNA sequencing	
Fanconi anemia	*FANCA FANCB, FANCC, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCM, PALB2, RAD51C, SLX4*	XLR AR	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	https://www.fanconi.org/
SCN	*ELANE, CSF3R, GFI1, SRP54 HAX1, G6PC3, JAGN1, VPS45 WAS*	AD AR XLR	MDS, AML	21–40%	Severe neutropenia	DNA sequencing including del/dup analysis, chromosomal breakage analysis	https://neutropenianet.org/
SDS	*SBDS*	AR	MDS, AML, ALL	5–24%	Neutropenia, pancreatic insufficiency, short stature, skeletal abnormalities	DNA sequencing including del/dup analysis	https://sdsregistry.org/

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Table 1 (continued)

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic hematological malignancies	Lifetime risk malignancies	Other phenotypes and features	Diagnostic testing	Resources
Diamond-Blackfan anemia	*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	https://dbafoundation.org/, https://www.dbar.org/
Telomere biology disorders	*DKC1* *TERT, TERC, TINF2, RTEL1, PARN, ACD* *NOP10, NHP2, WRAP53, RTEL1, TERT, CTC1, PARN, ACD*	XLR AD AR	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	https://teamtelomere.org/
Down syndrome	*Trisomy 21*	95% de novo, 5% translocation	TAM/AML, acute megakaryoblastic leukemia, ALL	10% (transient myelopoiesis), 2–3% AML, ALL	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	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	
LIG4 syndrome	*LIG4*	AR	MDS	Rare	Short stature, microcephaly, immunodeficiency combined; pancytopenia and myelodysplastic syndrome	DNA sequencing including del/dup analysis	

Table 1 (continued)

Genetic syndrome	Gene(s)	Inheritance pattern(s)	Characteristic hematological malignancies	Lifetime risk malignancies	Other phenotypes and features	Diagnostic testing	Resources
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	
Bone marrow failure syndrome, MECOM	*MECOM*	AD	MDS, AML	Unknown	Skeletal/cardiac abnormalities, neurological defects	DNA sequencing	https://www.pdsa.org/inherited-thrombocytopenia.html
Bone marrow failure syndrome, ERCC6L2	*ERCCL6*	AR	MDS, AML	Unknown	Skeletal/cardiac abnormalities, neurological defects	DNA sequencing	

Adapted from WHO 2016 book chapter, NCCN MDS v1.2019, The Nordic MDS Group (NMDSG) guidelines, Narla A. When to worry about inherited bone marrow failure and myeloid malignancy predisposition syndromes in the setting of a hypocellular marrow. Hematology Am Soc Hematol Educ Program. 2021 Dec 10; 2021(1):153–156. doi: 10.1182/hematology.2021000246. PMID: 34889379; PMCID: PMC8791095. SCN, severe congenital neutropenia; FA, Fanconi anemia; JMML, juvenile myelomonocytic leukemia; TAM, transient abnormal myelopoiesis; SDS, Shwachman-Diamond syndrome; MPN, myeloproliferative disease.

N-terminus and are heterozygous. Germline CEBPA pathogenic variants exhibit near-complete penetrance for the development of AML [105, 106]. A high occurrence of additional somatic CEBPA mutations as a secondary event in AML cases with germline CEBPA mutations is described [107]. The presumption that familial leukemias present in pediatrics is no longer true. Germline DDX41 mutations have been identified in adult MDS/AML. In a cohort of 1,385 patients with MDS or AML, 28 different germline DDX41 variants were identified in 43 unrelated patients [108]. DDX41-related myeloid malignancies occur more commonly in males and are associated with pre-existing cytopenia, additional somatic DDX41 mutation, and relatively good outcome. Only 9 patients (27%) had a family history of hematological malignancy, and 15 (46%) had a personal history of cytopenia years before MDS/AML diagnosis. TP53 mutations, Li-Fraumeni syndrome, are also associated with an increased lifetime risk of AML in about 4% of the patients [109].

Germline Mutations in RUNX1, ANKRD26, and ETV6 Are All Associated with Thrombocytopenia

Mutations in RUNX1 lead to an autosomal dominant familial platelet disorder, with both quantitative and qualitative platelet defects, with predisposition to myeloid malignancy [110]. The cumulative risk of developing a myeloid disease over lifetime is 44% for patients with a RUNX1 germline mutation [111, 112]. *ANKRD26*-related thrombocytopenia (*ANKRD26*-RT) is a non-syndromic autosomal dominant thrombocytopenic disorder with a predisposition to myeloid leukemia. Multiple causative variants have been shown to be the result of single nucleotide changes in the highly conserved 5′ UTR region of the gene [113, 114]. A case series of 118 subjects with ANKRD26-RT revealed an 8% incidence of myeloid malignancy [113].

Germline Predisposition with Potential for Organ Dysfunction

There are several syndromes associated with germline predisposition to AML/MDS and potential for organ dysfunction. GATA2 deficiency syndrome results in immunodeficiency with monocytosis, B cell, natural killer cell, and dendritic cell deficiencies, and common *Mycobacterium*, fungal, and viral infections, along with myelodysplastic syndrome/AML predisposition. Patients with GATA2 deficiency syndrome may also exhibit lymphedema [115]. AML associated with GATA2 deficiency often harbors monosomy 7 [116–120]. Germline mutations in *SAMD9/SAMD9L* cause multisystem disorders that carry an increased risk of developing myeloid malignancies with somatic monosomy 7 [121, 122]. Monosomy 7 AML should trigger evaluation for germline evaluation especially in a pediatric patient [123].

Bone marrow failure syndromes such as severe congenital neutropenia, Shwachman-Diamond syndrome, Fanconi anemia, and telomeropathies, such as dyskeratosis congenita, have an increased risk of malignant transformation to s-AML. Germline alterations in the RAS signaling pathway, resulting in Noonan's syndrome, also predispose to myeloproliferative syndrome in children (juvenile myelomonocytic leukemia) as well as AML [124]. Biallelic mutations in *BLM* result in Bloom syndrome, an inherited genomic instability disorder which confers a significant cancer predisposition risk, including increased risk for AML. Bloom syndrome is caused by impaired function of the RecQ DNA helicase resulting in DNA damage, with characteristic features including short stature, sun sensitivity, immunodeficiency, and increased risk for malignancy [125, 126]. Recognition of family history and clinical features associated with these syndromes is critical for patient care given possibility of organ dysfunction or altered sensitivity to chemotherapy.

People with Down syndrome (germline trisomy 21) have an increased risk of myeloid disease which is typically characterized by the presence of *GATA1* mutations. In the first 6 months of life, about 20% of children with germline trisomy 21 will develop transient abnormal myelopoiesis, a self-limited myeloproliferative disorder characterized by the presence of *GATA1* mutations [121]. Within the first 5 years of life, children with germline T21 are at an increased risk for development of myeloid leukemia of Down syndrome, typically with a mutation spectrum of *GATA1* mutations plus additional mutations in genes involving the cohesin complex [125, 127]. The prognosis of myeloid leukemia of Down syndrome is better than typical pediatric AML and tends to be treated with alternate protocols to minimize toxicity of chemotherapy [128]. Children with germline T21 are also at an increased risk for developing lymphoid leukemia, though the age distribution for this typically mirrors that of other ALL [129].

Primary Immunodeficiency and Risk of AML

The understanding of the overlap between immunodeficiency and bone marrow failure syndromes, which can lead to AML development, is evolving. Some germline disorders are characterized by the concomitant

impairment of both marrow precursor growth and the immune cell development. The concomitant immunodeficiency, bone marrow failure, and risk of AML development may be due to effect of the mutations on stem cells leading to both myeloid and lymphoid development, as well as a break in immune surveillance due to an underlying immunodeficiency or immune dysregulation. For example, mutations in the transcriptional regulator MYSM1 with defects in B-cell maturation result in MDS due to poor genotoxic stress response [130]. Additional syndromes are associated with mutations in *GATA2* [131] or *ADA2* [132], Shwachman-Diamond syndrome, and chromosomal breakage syndromes [133, 134]. Bloom syndrome, characterized by mutations in BLM helicase involved in DNA repair, can also be associated with mild immunodeficiency, though the risk of AML is likely due to increased DNA damage [135]. Understanding the connections between these conditions is crucial for providing comprehensive care to patients with overlapping symptoms and identifying potential genetic predispositions that may influence disease development, including involvement of other organs or ability to tolerate chemotherapy. Studying the interplay between AML and immunodeficiency and marrow failure syndromes may lead to improved diagnostic strategies, risk assessments, and targeted therapies tailored to individual patient needs [136]. Underlying immunodeficiency may increase risk for infection and ability to tolerate intensive chemotherapy and thus need to be considered as part of decision about treatment options.

Conclusions

AML is a genetically heterogenous disease, arising at every age across the lifespan. Improved diagnostic characterization has informed classification and prognosis based on genetic alterations and is informing development and use of targeted therapies. The importance of genetic classification highlights the need for extensive clinical genetic characterization of AML. With 10–15% of AML occurring in the setting of a cancer/leukemia predisposition syndrome, germline testing is critical especially in younger patients and may guide therapy selection and disease surveillance.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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