Beyond somatic mutations: the role of next-generation sequencing in identifying germline predisposition in patients with acute myeloid leukemia

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In their study published in this issue of *Haematologica*, Ahn *et al.*[1] highlight the critical role of serial next-generation sequencing (NGS) in detecting germline predisposition in acute myeloid leukemia (AML). By analyzing paired samples from 343 patients with AML from 17 institutions, at diagnosis and at complete remission (CR), the authors identified germline mutations in 5.5% of patients, with *DDX41* being the most commonly mutated gene. This work highlights the potential of NGS in identifying inherited pathogenic genetic variants, with significant implications for clinical management, genetic counseling, and therapeutic decision-making in patients with AML (Figure 1).

AML is a heterogeneous hematopoietic stem cell neoplasm, commonly driven by a complex interplay of somatic genetic alterations; however, a subset of patients carry germline pathogenic mutations that predispose them to myeloid neoplasms.[2,3] While somatic mutations have long guided risk stratification and treatment, the recognition of germline predisposition has reshaped our understanding of AML etiology and prognosis.[4] These germline variants not only increase the risk of AML but also influence treatment outcomes, particularly in the context of allogeneic hematopoietic stem cell transplantation (HSCT).[4,5] In this study, Ahn *et al.*[1] demonstrate that serial NGS, leveraging paired diagnostic and CR samples, can reliably distinguish germline from somatic variants, a distinction critical for the management of these patients.

The study's methodology is robust, targeting 83 genes associated with myeloid malignancies and focusing on 15 genes linked to germline predisposition.[6] By employing a variant allele frequency (VAF) threshold of 40-60% to flag potential germline mutations and their persistence in CR samples, the authors identified pathogenic germline variants in 5.5% of the study cohort with *DDX41* mutations in 58% of patients with pathogenic germline variants, followed by *DNAH5*, *CEBPA*, *TP53*, *MPL*, and *GATA2*. The predominance of *DDX41* mutations aligns with prior reports linking this variant to familial cases of AML.[7,8] Notably, the study reclassified certain mutations, annotated initially as variants of uncertain significance (VUS) in *DDX41* and *CEBPA*, as causal germline mutations when accompanied by somatic mutations, highlighting the nuanced interpretation required in genetic analysis. Table 1 summarizes key germline mutations identified in the study, emphasizing their prevalence and clinical significance.

Clinically, patients with germline mutations exhibited distinct features, including lower bone marrow blast percentages and hypoplastic marrow, suggesting a unique disease phenotype. Although these patients showed a trend toward reduced overall survival (OS), multivariate analysis revealed that age, European LeukemiaNet (ELN) risk, and HSCT were stronger prognostic determinants. Importantly, germline mutation status did not adversely affect post-HSCT outcomes, affirming the role of HSCT as a therapeutic option for this group of patients. This finding is particularly reassuring, as pathogenic germline variants in genes such as *TP53* have historically raised concerns about treatment-related toxicities.[9]

The study's implications extend beyond diagnostics to genetic counseling and donor selection for HSCT. Identifying germline mutations in AML patients enables cascade testing of family members, facilitating early intervention and informed donor choices.[6] For instance, confirming a germline *DDX41* mutation in a patient should prompt screening of related donors to avoid selecting a donor with the same pathogenic mutation when possible. However, in some cases, the only possible donor for a patient might be a relative who also carries the same pathogenic germ-

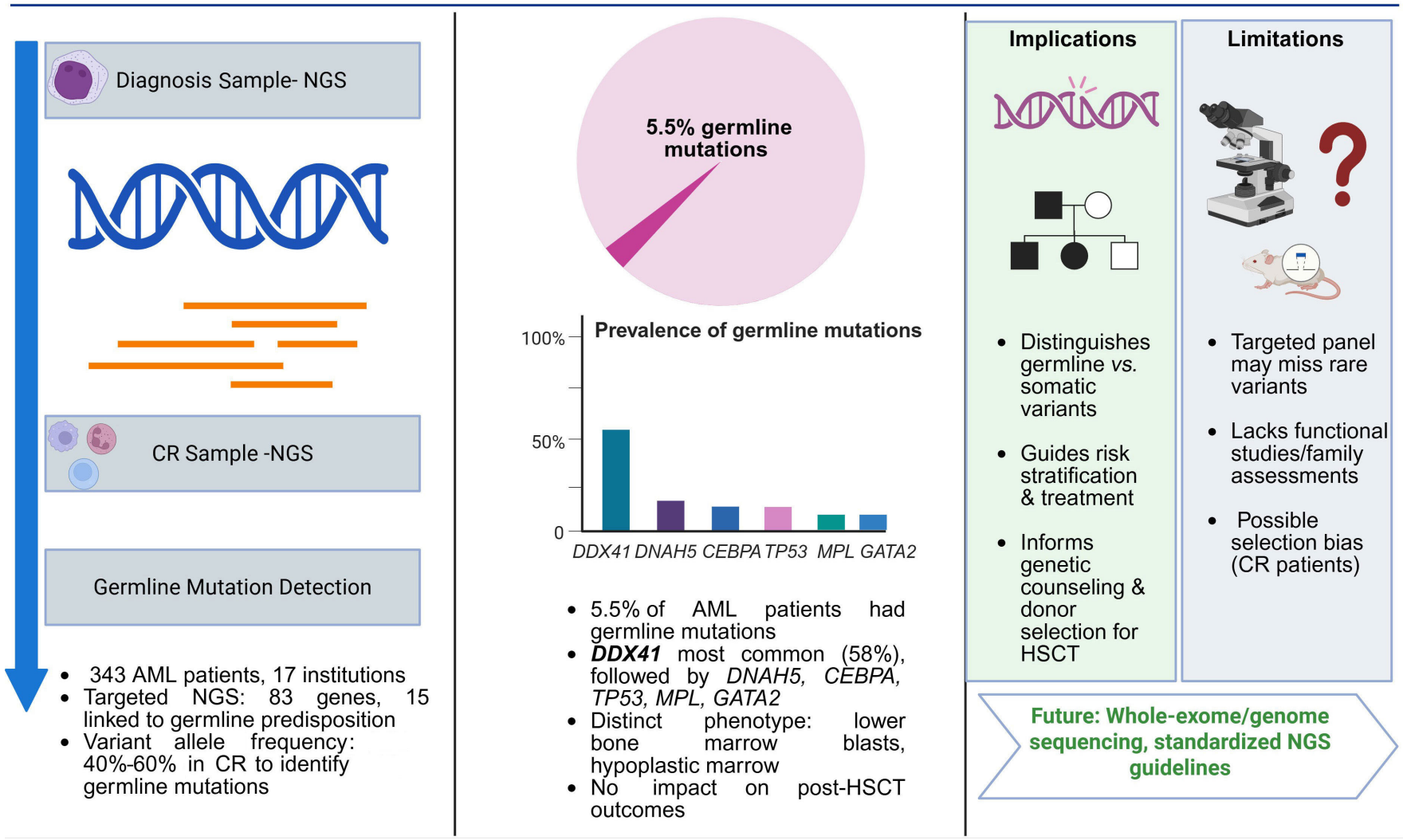

Figure 1. Serial next-generation sequencing identifies germline predisposition in acute myeloid leukemia: clinical therapeutic implications. Schematic representation of the workflow of serial next-generation sequencing (NGS) utilized in the study by Ahn *et al.*[1] to identify germline predisposition to myeloid neoplasms. The study findings, clinical implications, and limitations are summarized in this schematic. (Created in BioRender. Loghavi, S. (2025) https://BioRender.com/0s30l8r). AML: acute myeloid leukemia; CR: complete remission; HSCT: hematopoietic stem cell transplantation.

line mutation. In such situations, the risks and benefits of selecting that donor must be carefully weighed, and the final decision should be made on a case-by-case basis, taking into account the risk-benefit balance.

Moreover, the persistence of germline variants during CR, as detected by serial NGS, underscores the need for ongoing monitoring to guide therapeutic adjustments, as these germline variants should not be interpreted as persistence of AML-associated mutations and molecular evidence of measurable residual disease (MRD).[6,10]

Despite its strengths, the study has limitations. The targeted NGS panel, while focused, may miss rare germline variants outside the 15 prioritized genes. Whole-exome or whole-genome sequencing could enhance detection rates. Additionally, the absence of functional studies or family genetic assessments limits insights into variant pathogenicity. Selection bias, stemming from the inclusion of only patients achieving CR, may also skew prevalence estimates.

Ahn *et al.*'s[1] findings further highlight the need to integrate serial NGS into routine AML care. By identifying germline predisposition, clinicians can tailor risk stratification, refine treatment strategies, and provide more effective genetic counseling. The study also calls for broader adoption of NGS panels in clinical practice, supported by standardized guidelines for variant interpretation.[11] We are optimistic that broader use of NGS in clinical care for surveillance of patients with AML will be more routinely adopted as NGS

Table 1. Key germline mutations in acute myeloid leukemia identified by serial next-generation sequencing in this study.

Gene	Prevalence, % of germline cases	Common variants	Clinical implications
DDX41	58	p.A500fs, p.A550fs	Associated with familial AML, older age at onset
DNAH5	16	p.R1883*, p.S914*	Rare, linked to hypoplastic marrow
CEBPA	11	Biallelic mutations	Often accompanied by somatic mutations
TP53	11	p.R248Q, p.G44S	Potential for treatment-related toxicities
MPL	5	p.R357*	Rare, pathogenic
GATA2	5	p.G200fs	Linked to myeloid malignancies

AML: acute myeloid leukemia.

technology evolves, becoming more cost-effective and more readily accessible.

In conclusion, Ahn *et al.*'s study[1] represents an important step toward precision oncology in AML. By harnessing serial NGS, the authors reveal the prevalence and clinical significance of germline predisposition, paving the way for personalized treatment and improved outcomes in patients with AML.

Disclosures

No conflicts of interest to disclose.

Contributions

SL and FR have written the editorial and created the figure. Both authors have read and approved the final copy submitted for publication.

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