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# Clinical guideline variability in the diagnosis of hereditary hematopoietic malignancy syndromes

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**ABSTRACT**

A growing understanding of the complexities of hematopoietic malignancies necessitates the existence of clinical recommendations that are sufficiently comprehensive. Although hereditary hematopoietic malignancies (HHMs) are increasingly recognized for conferring risk of myeloid malignancy, frequently utilized clinical recommendations have never been appraised for the ability to reliably guide HHM evaluation. We assessed established society-level clinical guidelines for inclusion of critical HHM genes and graded the strength of testing recommendations. We uncovered a substantial lack of consistency of recommendations guiding HHM evaluation. Such heterogeneity in guidelines likely contributes to refusal by payers to support HHM testing, leading to underdiagnoses and lost opportunities for clinical surveillance.

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## Introduction

A substantial proportion of blood cancers are now known to be hereditary hematopoietic malignancies (HHMs) driven by germline variants that adhere to Mendelian inheritance patterns. HHMs are much more common than previously recognized, and approximately 14% of older patients with acute myeloid leukemia (AML) carry HHM-associated germline variants [1]. Similarly, at least 7% of patients undergoing stem cell transplant for myelodysplastic syndrome (MDS) carry germline variants associated with hereditary hematopoietic disorders [2]. The prevalence of HHMs (7–14%) in relatively unselected groups of patients is similar to the prevalence of other biologically relevant subgroups of MDS/AML, such as *FLT3*-mutated AML (approximately 30%), *IDH1*-mutated MDS/AML (10%), and *IDH2*-mutated MDS/AML (10%) [3]. The clinical recognition of patients with HHMs is crucial so as to avoid donor-derived cancer, to counsel family members regarding genetic testing, and to identify potential treatment options [4]. Given the common prevalence of HHMs, there is an urgent need to develop consistent standards for the diagnosis and care of patients at risk for HHMs. For example, we previously showed next generation sequencing-based HHM assays are technically inadequate to diagnose many HHMs [5,6]. In our experience, diagnostic germline testing for HHMs is also frequently denied by third-party payers. Frequent insurance denials also occur in other hereditary cancer syndromes [7]. Guidelines from organizations such as the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and similar groups are used to support decisions regarding third party reimbursement of diagnostic assays. The degree to which current clinical guidelines support the evaluation of patients with possible HHMs, however, has not been evaluated. Heterogeneity in these guidelines could inadvertently lead payers to deny coverage for medically indicated HHM evaluations. To address this knowledge gap, we analyzed clinical guidelines from all groups with published recommendations for MDS and/or AML. We then determined the heterogeneity in HHM-related recommendations from these groups.

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## Methods

Nine sets of clinical guidelines for MDS or AML were analyzed. We excluded publications focused solely on pathologic classifications, such as those from the World Health Organization, as these are rarely used to justify third party payment decisions. We included any articles that made clinical recommendations for germline testing of newly diagnosed patients with MDS or AML, or recommendations regarding the evaluation of adult patients at risk for HHMs, and then analyzed the recommended genes in those manuscripts. For guidelines that discussed HHMs, we then determined which genes, if any, were recommended for germline sequencing. The strength of each recommendation was determined using a scale: 'Not Addressed' (no mention of HHMs), 'Consider Testing' (HHMs discussed, but without clear testing criteria), or 'Firm Recommendation' (clear criteria for HHM testing provided). We used R version 4.2.2 to generate heat maps of genes in each publication and the strength of recommendation from each group.

## Results

The most up-to-date clinical guidelines for MDS were from the NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes v.1.2023 [8], the European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up [9], the British Society of Hematology guidelines for the diagnosis and evaluation of prognosis of adult myelodysplastic syndromes [10], and the UK Cancer Genetics Group (and collaborators) (UKCGG) best practice guidelines for germline predisposition to haematological malignancies [11]. NCCN guidelines discussed the largest number of HHM-related genes ($n = 45$) and made clear clinical recommendations in terms of eligibility criteria for HHM testing. ESMO suggested that clinicians 'consider testing' eight HHM-related genes. The BSH suggested that clinicians consider testing three genes (Figure 1). UKCGG focuses on $n = 6$ genes and provides management recommendations in an accompanying guideline [12].

Six clinical guidelines for AML were identified: the NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia v.3.2023 [13], the ESMO 2020 Clinical Practice Guidelines for diagnosis, treatment and follow-up [14], the ASCO initial diagnostic workup of acute leukemia [15], the European LeukemiaNet (ELN) 2022 update [16], the Nordic recommendations for the genetic diagnosis, clinical management, and follow-up of germline predisposition to myeloid neoplasms [17] and the UKCGG [12]. A total of 64 genes were included across these guidelines. The Nordic guidelines included the largest number of genes (41) with clear testing criteria. The NCCN provided clear criteria for thirteen genes. Both the ELN and ESMO guidelines suggested testing for select HHM-related genes without clear criteria. While mentioning the importance of HHMs, ASCO did not discuss testing criteria and did not include specific HHM-related genes (Figure 2). We generated a Venn diagram to determine which HHM-related genes were included in clinical guidelines for MDS and/or AML (Figure 3).

## Discussion

Rapid advances in the biological understanding of blood cancers and the clinical care of people with these diseases have necessitated the development of updated clinical guidelines. HHMs, many of which have been discovered in the past decade, are a 'case study' in the rapid pace of the scientific understanding of the genetic origins of MDS and AML. These advances necessitate the development of up-to-date guidelines that reflect the most contemporary developments in the clinical care of people with MDS and AML.

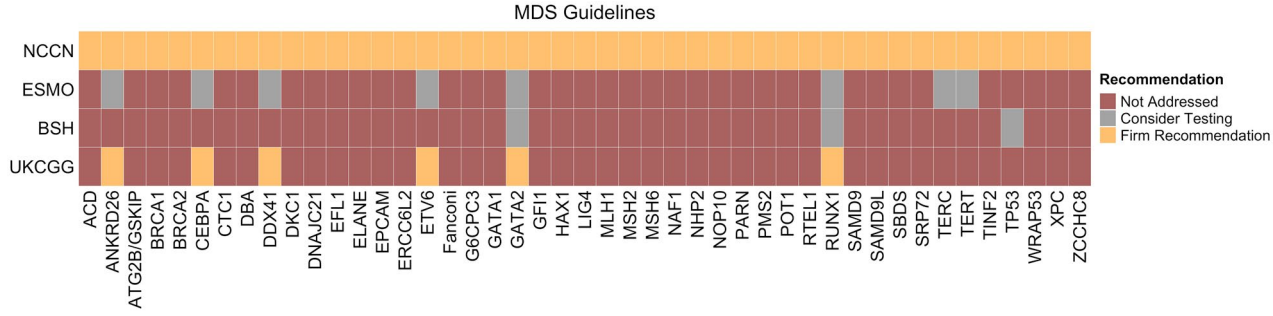


**Figure 1.** Recommendations for HHM-focused evaluation of patients with MDS across clinical guidelines. Genes included for HHM evaluation are on the horizontal axis. Recommendations were scaled based on the strength of the language used. 'Fanconi' refers to the full spectrum of Fanconi anemia genes. 'DBA' refers to the full spectrum of Diamond Blackfan anemia genes.

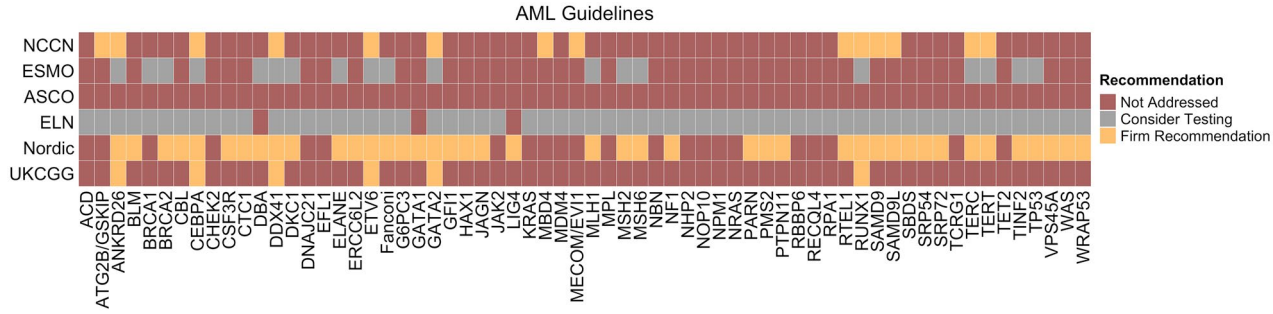


**Figure 2.** Recommendations for HHM-focused evaluation of patients with AML across clinical guidelines. Genes included for HHM evaluation are on the horizontal axis. Recommendations were scaled based on the strength of the language used. 'Fanconi' refers to the full spectrum of Fanconi anemia genes. 'DBA' refers to the full spectrum of Diamond Blackfan anemia genes.

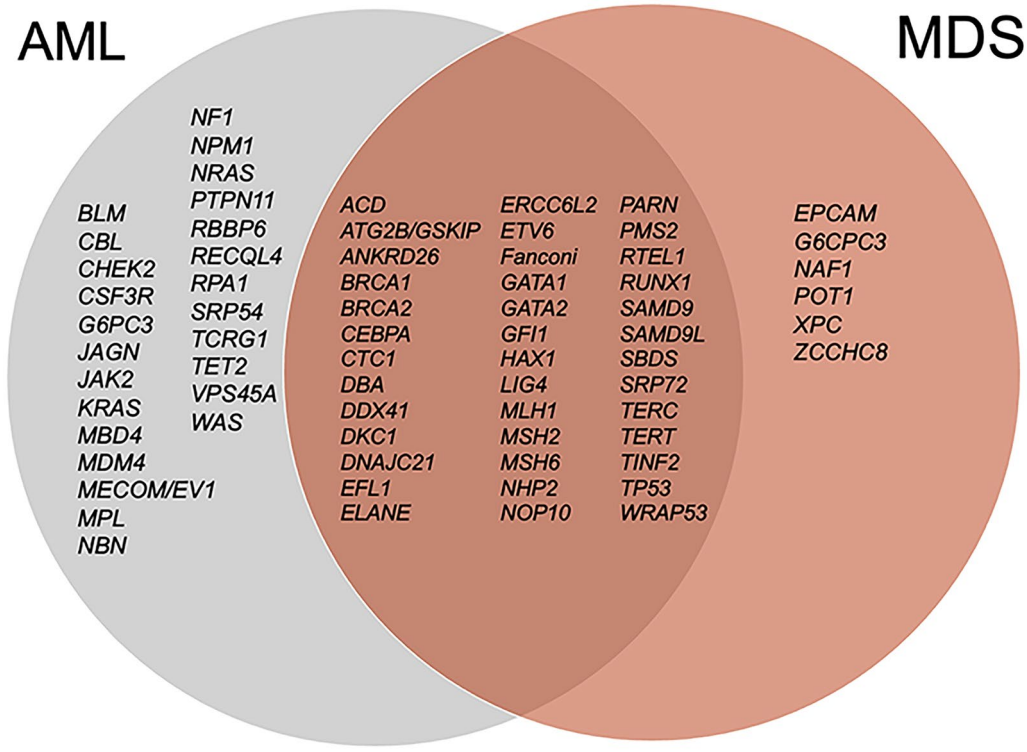


**Figure 3.** Overlap and mutual exclusivity of genes included on clinical guidelines for HHM. Shown in the Venn diagram, genes recommended for evaluation of AML and MDS are depicted to assess overlap or exclusivity. 'Fanconi' refers to the full spectrum of Fanconi anemia genes. 'DBA' refers to the full spectrum of Diamond Blackfan anemia genes.

Here, we performed the first analysis of HHM-specific recommendations within MDS and/or AML clinical guidelines. Our analysis revealed marked heterogeneity and inconsistency in recommendations regarding HHM diagnosis and testing. This heterogeneity may potentially lead to coverage denials by third party payers, which could frustrate clinicians and make them reticent to pursue HHM evaluations. Inconsistent clinical guidelines, therefore, may lead to HHM under-diagnosis and ultimately hinder the quality of care of patients with these syndromes. A 'core' set of genes should be developed by a team of HHM experts and then included in MDS and/or AML clinical guidelines. The team of HHM experts should be multi-institutional so as to provide credence to this effort. This 'minimum' set of genes could form the backbone of panels developed by individual clinical laboratories. These laboratories could tailor their individual test offerings to meet the local needs of their patients and institutions. Ultimately, including a core set of HHM genes in clinical MDS/AML guidelines will improve coverage of HHM diagnostics by third-party payers. This will potentially reduce the risk for HHM under-diagnosis and prevent complications that stem from undiagnosed

HHMs, such as donor-derived malignancies. The increased recognition of HHMs will also accelerate research efforts for these patients. Patients with HHMs represent an underserved and vulnerable population, as no HHM-specific treatments currently exist. Harmonizing clinical MDS/AML guidelines to include the full spectrum of HHM-related variants and providing clear eligibility criteria for HHM testing will ultimately improve the diagnosis and care of patients with these syndromes.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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