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ACUTE MYELOID LEUKEMIAS (H ERBA, SECTION EDITOR)

Hereditary Myelodysplastic Syndrome and Acute Myeloid Leukemia: Diagnosis, Questions, and Controversies

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Abstract

Purpose of Review To review the diagnosis of individuals with hereditary hematopoietic malignancies (HHMs) that predispose to myelodysplastic syndrome and acute myeloid leukemia, barriers to HHM diagnosis, and unaddressed questions and controversies within the HHM field.

Recent Findings Pathogenic germline mutations in approximately a dozen genes predispose to HHMs, and many more genes are likely to be involved. Many of these HHM genes have only been identified recently. HHM phenotypes are diverse, but may be categorized as "purely" myeloid syndromes, syndromes with abnormal platelet number/function, and HHMs with additional organ system involvement. A number of questions remain unanswered in this emerging field, including the ideal diagnostic approach for patients at risk for HHMs, the optimal surveillance of unaffected carriers, and how to personalize care for individuals with HHMs.

Summary The field of HHMs is evolving rapidly. Ongoing research in this area will eventually inform the care of patients with both somatic and hereditary cancer syndromes, but much work remains to be done.

Keywords Inherited leukemia · Familial leukemia · Hereditary leukemia

Introduction

The first confirmed hereditary hematopoietic malignancy (HHM) was described in 1922, but a molecular understanding of HHMs was not developed until the discovery of pathogenic germline *RUNX1* mutations in 1999 [1, 2]. Pathogenic germline mutations that predispose to HHMs have now been described in many additional genes [3••]. The prevalence of HHMs is not yet known, but HHMs are suspected to affect at least 4–13% of pediatric patients and 5% of adult patients with myelodysplastic syndrome or acute myeloid leukemia (MDS/AML). These proportions will almost certainly increase as the full spectrum of genes involved in HHMs is elucidated [4].

Guidelines from the National Comprehensive Cancer Network, European Leukemia Network, and World Health Organization now reinforce the importance of evaluating all patients with MDS/AML for an HHM [5••, 6••, 7••]. This review highlights the known HHMs that predispose to MDS/AML, recommendations for the evaluation and diagnosis of patients at risk for HHMs, and questions and controversies in the field.

Myriad Molecular Aberrations Predispose to Familial MDS/AML

Germline mutations that predispose to MDS/AML affect proteins involved in myriad cellular processes. These proteins perform functions that include transcription (CEBPA, ETV6, GATA2, RUNX1, p53), telomere maintenance (ACD, TERT, TERC), DNA repair (BRCA1, BRCA2, MBD4), RNA processing (DDX41), cell trafficking (SRP54, SRP72), inflammation (DDX41, SAMD9, SAMD9L), and other unknown functions (ANKRD26) [3••, 8, 9•, 10, 11]. In the following sections, we review HHMs that predispose to MDS/AML.

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HHMs With Preexisting Platelet Disorders

Germline mutations in *ANKRD26*, *ETV6*, or *RUNX1* predispose to MDS/AML with preexisting platelet disorders. These disorders have been reviewed elsewhere, but some points bear repeating for the practicing clinician [12]. First, these disorders are notable for normal or reduced platelet sizes and easy bleeding/bruising [12]. These patients may present for an evaluation of immune thrombocytopenic purpura (ITP) and may have been treated for ITP. Suggestion of an HHM may come from the peripheral blood smear where dysplasia may be detected, an informative family history, or a lack of response to ITP treatments.

Second, although these disorders are associated with thrombocytopenia, affected patients and families also possess an elevated risk of hematopoietic and solid malignancies. Therefore, an HHM with platelet disorder should remain on the differential diagnosis even for pedigrees lacking a "pure" thrombocytopenia pattern. For example, individuals with germline *ETV6* mutations are affected by both lymphoid and myeloid malignancies, and *ETV6* carriers have been diagnosed with colorectal cancer, multiple myeloma, and skin cancer [13•, 14, 15].

Third, individuals with HHMs and preexisting platelet disorders may respond to ITP treatments, so physicians should continue to consider an HHM even for patients treated successfully with ITP therapies. For example, the oral thrombopoietin receptor agonist (TRA) eltrombopag has been utilized successfully to treat a patient with a germline mutation in the 5′ UTR of *ANKRD26* [16]. The long-term effects of TRAs on leukemogenic risk are unknown, but in theory, may be increased. Therefore, we advocate utilizing TRAs only in urgent situations and then discontinuing these agents when appropriate.

HHMs With Myeloid Malignancies

Some HHMs manifest primarily as myeloid malignancies that segregate in an autosomal dominant fashion. These HHMs stem from germline mutations in *CEBPA, DDX41*, *ATG2B/GSKIP*, or *RBBP6* [17].

Germline *CEBPA* mutations predispose to myeloid malignancies driven by acquisition of a somatic mutation in the non-mutated *CEBPA* allele [18]. Overall, 10% of patients affected by an AML with biallelic *CEBPA* mutations possess a germline mutation in *CEBPA* [19, 20]. Therefore, any patient affected by AML with biallelic *CEBPA* mutations should be offered germline tissue sequencing. The prognostic implications of germline *CEBPA* mutations are not clear, as affected patients treated with standard induction and consolidation therapy appear to have chemosensitive AML, but remain at risk for subsequent primary myeloid malignancies, generally referred to as "relapses." However, examination of the acquired, secondary *CEBPA* mutations has shown those to be distinct, arguing that they are in fact independent leukemias toxicities [21•]. These subsequent primary malignancies are frequently also chemosensitive. The timing of a SCT has been controversial, with some arguing for SCT at the time of first remission to prevent the development of subsequent leukemias, whereas others argue for SCT at the time of second remission given the overall chemosensitivity of *CEBPA*-mutant leukemias. Most agree though that the risk of a second primary malignancy must be balanced against SCT-related toxicities [21•, 22]. This issue that has not been addressed in a prospective, randomized fashion.

DEAD-box RNA helicase DDX41, encoded by *DDX41*, is involved in RNA processing and STING signaling, but its function is otherwise not well understood. Germline *DDX41* mutations affect approximately 1% of all AML cases [23•, 24], but the average age of MDS/AML diagnosis is similar to that of sporadic tumors (62 years) [23•]. Germline mutations in *DDX41* primarily predispose to myeloid malignancies, but there is also evidence that affected carriers may develop lymphoid malignancies and colorectal carcinomas at elevated rates [24, 25]. We have described the case of a patient with a personal history of gastric cancer followed by a therapy-related myeloid neoplasm at the age of 72 years who unexpectedly had a germline *DDX41* mutation detected via tumor-only molecular profiling. This case demonstrates the importance of considering HHMs even in patients who are older and who have a personal or family history of solid tumors [26]. Lenalidomide may be especially effective in patients with germline mutations in *DDX41*, but this finding needs to be validated prospectively [23•].

In 2015, a 700-kb duplication that involved *ATG2B* and *GSKIP* was identified in 30 patients from four families in the French West Indies with HHMs [27]. These mutations increase the risk of myeloid malignancies by heightening hematopoietic stem and progenitor cells (HSPCs) sensitivity to thrombopoietin, driving platelet production, essential thrombocythemia, and leukemogenesis. Cooperating leukemogenic mutations frequently occur in *JAK2*, *MPL*, and *CALR* [27].

HHMs With Additional Organ Systems Affected

Some HHMs present in a syndromic fashion and involve multiple organ systems. These syndromes have classically been associated with germline mutations in telomerase-related genes as well as genes involved in the immune system response. We describe some of these syndromes in the ensuing sections.

GATA2 Deficiency Syndrome

GATA2 deficiency syndrome classically presents in syndromic fashion. *GATA2* encodes for a transcription factor that is required for hematopoiesis and vascular development [28]. GATA2 deficiency is notable for lymphedema, sensorineural hearing loss, and a chronic deficiency in various cell lineages (natural killer, dendritic, monocytic). These deficiencies predispose patients to a variety of atypical infections [29], including unexplained disseminated mycobacterial infections, generalized warts related to human papilloma virus, fungal infections, viral infections, and bacterial infections. These patients are also at risk for pulmonary complications [30]. The most common karyotypes in familial MDS resulting from germline *GATA2* are monosomy 7, der(1;7), and trisomy 8 [30]. Because of the high prevalence of *GATA2* mutations in children with MDS and monosomy 7, children with MDS and monosomy 7 should be offered genetic counseling and germline *GATA2* sequencing [31•]. Syndromic manifestations of *GATA2* deficiency often require a multidisciplinary team to address the infections, lymphedema, pulmonary disease, and hearing loss that affect carriers. Hematopoietic SCT remains an important therapeutic modality for patients with germline mutations in *GATA2* who have developed MDS, chronic myelomonocytic leukemia (CMML), or AML, and this approach also improves infection-related symptoms stemming from the syndrome [32–34].

Inherited Bone Marrow Failure Syndromes

Inherited bone marrow failure syndromes (IBMFs) represent a group of HHMs that may present in a syndromic fashion. The IBMFs include congenital amegakaryocytic thrombocytopenia (CAMT), Diamond-Blackfan anemia (DBA), dyskeratosis congenita (DC), Fanconi anemia, severe congenital neutropenia (SCN), Shwachman-Diamond Syndrome (SDS), and thrombocytopenia absent radii (TAR) [35, 36]. IBMFs increase the risk of myeloid malignancies to various degrees. Although IBMFs have classically been considered primarily pediatric disorders, this view has shifted in the era of contemporary genomics. Now, it is increasingly recognized that many individuals with IBMFs present in adulthood, a proportion of whom may be initially diagnosed with apparently sporadic disorders, such as aplastic anemia or MDS. These patients may lack syndromic features that are classically associated with IBMFs, but present instead with varying degrees of cytopenia(s). These individuals are at risk for excess SCT-related toxicity [36, 37] so it is important to identify patients with subtle presentations of IBMFs prior to SCT.

The IBMFs reinforce the importance of considering HHMs in patients with a family history of solid tumors or other syndromic findings. Families with IBMFs may have individuals affected by solid tumors, including squamous cell cancer of the head and neck, skin cancer, and other solid malignancies. Importantly, these syndromes follow autosomal recessive inheritance patterns and tumors may "skip" generations [37, 38].

Familial Aplastic Anemia/MDS Due to Germline *SRP54* or *SRP72* Mutation

Autosomal dominant pancytopenia with sensorineural hearing loss stems from germline mutations in *SRP72*. The germline mutations in this hereditary syndrome disrupt proper localization of a signal recognition particle (SRP) that is involved in protein trafficking to the endoplasmic reticulum [39]. No other patients with germline *SRP72* mutations have been described, but germline mutations in a related gene *SRP54* have been observed in three additional families who presented with neutropenia and exocrine pancreatic insufficiency [11]. This protein is involved in a similar cellular trafficking pathway.

Ataxia-Pancytopenia Syndrome (*SAMD9L* Mutation) and MIRAGE Syndrome (*SAMD9* Mutation)

SAMD9 and *SAMD9L* are located in tandem on chromosome 7. Germline mutations in these genes predispose to MIRAGE and ataxia-pancytopenia syndromes, respectively, through gain of function mutations that exacerbate the normal anti-proliferative functions of SAMD9 and SAMD9L [9•, 40•, 41•]. Intriguingly, hematopoietic stressors, such as viral infection, may result in reversion events, such as uniparental disomy, loss of function, or monosomy, in the hematopoietic tissue. These reversions predispose affected individuals to clonal hematopoiesis and/or MDS/AML with loss of chromosome 7 that occurs as an escape mechanism from the germline gain of function mutation [9•, 40•, 42]. These disorders reinforce the importance of sequencing germline tissue when evaluating patients with a suspected HHM, as the germline mutation is lost during the reversion event in involved tissue. Therefore, peripheral blood will lack the mutation of interest [43].

Germline *MBD4* Deficiency

A recent study of two sisters and a third patient from another family revealed a mutation in *MBD4*, a DNA glycosylase that removes thymines produced by the spontaneous deamination of 5-methylcytosine [44•]. All three patients were young (ages 30, 31, and 33) at the time of AML diagnosis, and two of the patients also developed colonic polyps, consistent with a defective DNA repair pathway (dMMR). Each patient developed a leukemia that was negative for *NPM1*, *FLT3*, and *CEBPA* mutations but that possessed a profound 33-fold increase in somatic mutations, the majority (> 95%) of which were CG>TG, consistent with defective removal of mispaired thymines. Intriguingly, leukemogenesis in all three patients followed a shared path: a second hit in *MBD4*, biallelic *DNMT3A* mutations, and mutations in hotspots in *IDH1* or

IDH2 [44•]. Intriguingly, pembrolizumab is approved for dMMR solid tumors regardless of site of origin [45]. HHMs driven by germline mutations in *MBD4* possess syndromic characteristics typical for a disrupted mismatch repair pathway and, in theory, may also demonstrate increased sensitivity to treatment with PD-1 inhibitors. This theory will need to be investigated prospectively in clinical trials.

Identifying a Patient With Suspected Hereditary MDS/AML

History and Physical Exam

Health care providers must be aware of HHMs in order to diagnose these syndromes. We encourage every hematologist/oncologist involved in patient care to keep a hereditary cancer syndrome on the differential diagnosis for every patient. Identifying individuals with HHMs begins with a thorough personal and family history aimed at eliciting symptoms and patterns associated with hereditary syndromes. The following details in the history should elicit suspicion for an HHM: multiple malignancies in one individual, a family member with a hematopoietic malignancy within two generations of the index patient (or proband), other family members with cytopenias or macrocytosis, and/or the presence of syndromic findings associated with HHMs.

Regarding extra-hematopoietic syndromic presentations, HHMs may manifest with syndromic phenotypes, and these symptoms are often misattributed to other disease processes instead of the underlying HHM. Some of these phenotypes include unexplained disseminated mycobacterial infections (*GATA2*); warts (*GATA2*); a personal or family history of premature gray hair (IBMFs); repeated fungal, viral, or bacterial infections (*GATA2*); nail dystrophy (IBMFs); pulmonary disease (*GATA2*, IBMFs); unexplained lymphedema (*GATA2*); hearing loss (*GATA2*, *SRP72*); and idiopathic hepatic cirrhosis (IBMFs) [3••]. Of note, these syndromic findings may precede MDS/AML development.

Basic Laboratory Evaluation

The laboratory evaluation of a patient or relatives with a suspected HHM may also raise suspicion for a hereditary process. Some laboratory findings seen in individuals with HHMs include lymphopenia with a low CD4/CD8 ratio (*GATA2*) [29]; chronic neutropenia (*GATA2*, IBMFs); chronic monocytosis (*GATA2*); chronic cytopenias (*GATA2*, IBMFs) [30]; and thrombocytopenia (*ANKRD26*, *ETV6*, *RUNX1*) [7••]. These laboratory findings may precede an MDS/AML diagnosis and may also be present in family members. Therefore, every patient should be asked if they or a family member have a personal history of abnormal blood counts, blood diseases, solid tumors, or any other syndromic findings. We take a minimum of a three-generation pedigree as some HHMs are notable for a recessive inheritance pattern that may "skip" generations. Some patients may also recall additional medical problems among family members that may not strike the patient as significant [3••].

Patient and Tumor Characteristics

The age of the patient and characteristics of the MDS/AML may also offer insights into a potential HHM diagnosis. For example, 13% of patients under the age of 45 with MDS at one center were diagnosed with a hereditary form of MDS or BMF [46]. The authors utilized a next generation sequencing (NGS) panel that was up to date at the time of the study but did not contain all genes that are now known to cause HHMs. Therefore, the prevalence of HHMs among individuals with MDS under the age of 45 is almost certainly in excess of 13%. Germline *GATA2* mutations are especially prevalent in children with MDS and monosomy 7 (37%), therefore any child with MDS and monosomy 7 should be offered genetic testing [31•]. As a whole, these findings suggest that the age of MDS/BMF diagnosis, as well as tumor characteristics, may raise suspicion for an HHM. We anticipate that similar high-risk groups of patients with MDS/AML will be identified.

Screening of Matched Related Donors for Allogeneic Stem Cell Transplant

For patients with MDS/AML who are offered a matched related allogeneic SCT, it is vital that the physician directing the care of the related donor carefully considers the donor's medical history. For example, related donors with macrocytosis, cytopenia, or difficulty mobilizing HSPCs should be carefully evaluated by a physician with experience diagnosing HHMs and an alternative donor should be strongly considered. Members of our group have demonstrated that macrocytosis and thrombocytopenia are risk factors for HHMs [47], and 7% of poor mobilizers carry germline mutations [48].

Next Generation Sequencing of Leukemia May Inadvertently Identify Patients at Risk for HHMs

Multiple organizations emphasize the molecular profiling of leukemia cells at diagnosis [6••, 49]. Molecular profiling identifies presumably somatic mutations in order to inform disease prognostication and guide treatment decisions. Many NGS panels now sequence hundreds of genes. These panels, however, are generally sent as "tumor-only" assays without paired germline tissue. For example, the FoundationOneHeme® panel sequences *BRCA1*, *BRCA2*, *CEBPA*, *ETV6*, *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCL*, *GATA2*, *MLH1*, *MSH2*, *MSH6*, *RUNX1*, and other genes that

contribute to HHMs. This assay utilizes formalin-fixed paraffin-embedded tissue, peripheral whole blood, or bone marrow aspirate but does not require matched germline tissue [50].

Members of our group have demonstrated that tumor-only NGS panels frequently detect variants that are associated with HHMs when inherited in germline tissue. For example, 21% of tumor-only NGS panels at our institution identified potentially damaging mutations in *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, or *TP53* that could cause an HHM if the variant in question was inherited in the germline. We located germline samples for these patients and discovered that approximately a quarter (24%) of patients with high-risk variants identified on tumor-only testing were eventually found to possess the same variant in their germline tissue, thereby diagnosing these individuals with an HHM [26]. Our approach was insensitive to larger structural rearrangements that are known to contribute to HHMs but that are missed by most contemporary NGS-based approaches [51]. We suspect that the proportion of patients inadvertently diagnosed with HHMs via tumor-only NGS will increase as novel HHM genes are identified and included on these panels.

Patients, therefore, should be informed that tumor-only NGS may identify an HHM despite not being designed for this purpose. Tumor-only profiling, however, must not substitute germline sequencing for patients with a suspected HHM, as tumor-only panels frequently omit HHM-related genes. For example, germline *DDX41* mutations affect 1% of individuals with AML [23•], but the FoundationOneHeme® panel does not currently sequence *DDX41* [50]. Furthermore, tumor-only NGS profiling based on short read sequencing is only capable of detecting smaller structural rearrangements (~ 50 bp), but approximately 10% of HHMs stem from larger structural rearrangements that are only detectable via array comparative genomic hybridization [51, 52]. Finally, some HHMs, such as MIRAGE syndrome (*SAMD9*), ataxia-pancytopenia syndrome (*SAMD9L*), and Fanconi anemia (numerous genes) are notable for somatic reversion events, reverse mosaicism, or chromosomal loss that results in the germline mutation being undetectable in the blood or present at unexpected variant allele frequencies (VAFs) that are typically not associated with germline variants [9•, 40•, 53]. These reversion events suggest that germline tissue, not involved tissue, should be sequenced and tumor-based VAFs should not be used as a proxy for germline sequencing. We detail our algorithm for screening and evaluating patients with a potential HHM in Fig. 1 and detail barriers to diagnosis in Table 1.

Controversies in HHM Diagnosis and Management

Given the rapid increase in knowledge regarding HHMs as well as the relatively young nature of the field, a number of issues remain unaddressed, unanswered, and even controversial. A brief list of these issues is provided in Table 2. Most of these topics have not been addressed in a prospective, rigorous fashion.

Questions Regarding Optimal Diagnostic Practices

The optimal evaluation of individuals with hematopoietic malignancies is rapidly changing in the era of less-expensive NGS panels and recent guidelines encourage the use of these assays [6••, 49]. As detailed above, NGS panels may inadvertently identify germline mutations passed into the tumor clone despite not being designed for this purpose [26]. Despite this inadvertent but anticipated finding, patients are not always informed that tumor-only NGS panels also perform a de facto, albeit limited, molecular profile of germline tissue. In theory, this issue may be averted by performing paired tumor/germline sequencing at diagnosis and "subtracting" germline variants for purposes of tumor profiling. Germline variants would not be reported to patients who waive information regarding hereditary processes. Conversely, for patients who prefer knowledge regarding hereditary diseases that may impact the care of the patient or their family members, paired tumor/germline sequencing at diagnosis has many advantages, including a more timely HHM diagnosis that may inform decisions regarding allogeneic SCT and/or donor selection [4]. Universal paired tumor/germline sequencing would likely increase the cost of medical care for patients with MDS/AML and it remains to be seen if third party payers would cover these expenses [4].

The choice of "ideal" germline tissue for hereditary genetic testing and paired tumor/germline sequencing remains unclear. We prefer cultured skin (dermal) fibroblasts [3••], but buccal swabs may also serve as suitable germline controls [55]. Many physicians do not feel comfortable collecting these samples, and some laboratories may not have the capacity to process these samples. Similarly, many molecular diagnostic groups may need to alter their bioinformatics pipelines in order to efficiently process tumor/germline sequencing data. These difficulties suggest that a solution that allows for the shipping of samples to organizations with a laboratory and bioinformatics team capable of processing germline samples will be required in the event that paired tumor/germline tissue sequencing becomes a standard diagnostic practice.

Questions Regarding Clinical Surveillance of Unaffected Carriers

The optimal approach to clinical surveillance for individuals with germline mutations associated with HHMs, but who have not developed syndromic symptoms or MDS/AML (unaffected carriers), is unclear. Germline mutations in HHM-related genes are not fully penetrant, and the majority of carriers will

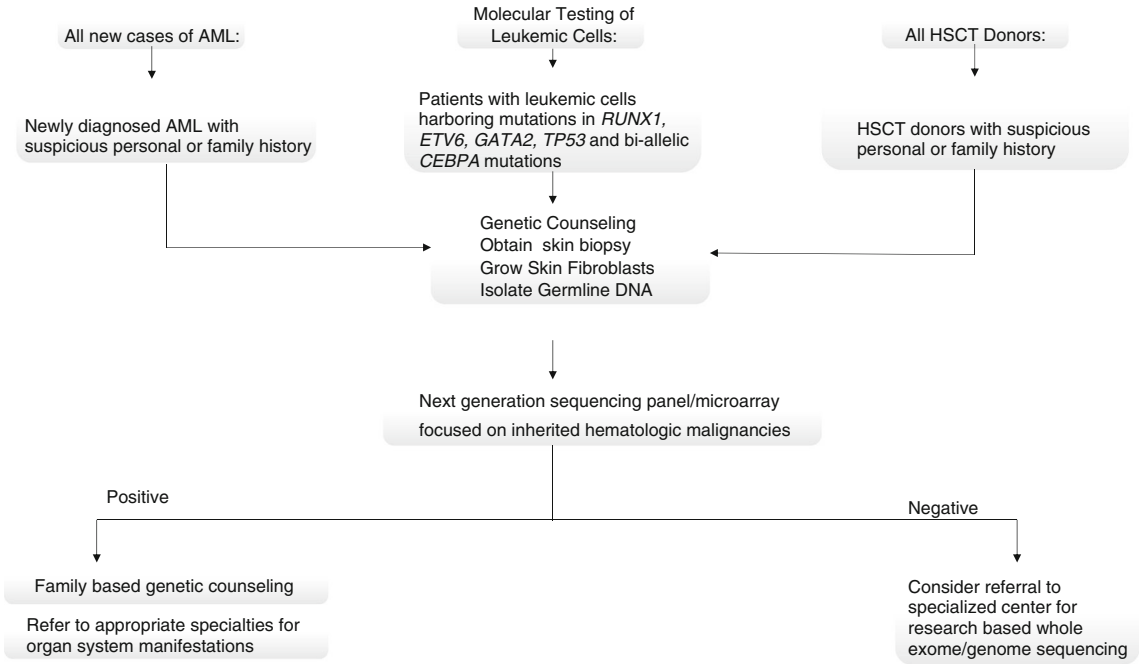

Fig. 1 Algorithm for work up of patient with inherited myeloid leukemia syndrome

not develop MDS/AML [17]. How do we identify patients at increased leukemogenic risk? The answer to this question is currently unknown, but we typically perform a clinical evaluation every 3–6 months with relevant laboratory analyses. We perform bone marrow biopsies for changes in baseline blood counts. This approach is inspired by the care of patients with other hereditary processes, but we acknowledge that there is a lack of prospective evidence to inform these practices [3••].

The role of prophylactic allogeneic stem cell transplant (SCT) for unaffected germline mutation carriers is unclear, and the field lacks a consensus that prophylactic allogeneic stem cell transplantation is a reasonable consideration. A lack

Table 1 Barriers to testing [54]

Lack of appreciation for the existence of HHMs	• Lack of awareness and knowledge of HHMs by physicians contribute to a low index of suspicion for these processes and missed opportunities for diagnosis.
	• Patients are told that "MDS/AML cannot be hereditary."
Lack of testing availability	• Some centers may not be capable of processing germline samples that are used in HHM diagnosis (skin fibroblasts and hair samples).
	• Bioinformatics pipelines are optimized for tumor-only sequencing, not paired tumor/normal testing.
	• Many clinical practices do not have access to genetic counseling.
	• Third party payers may not cover germline genetic testing.
	• Many clinicians may not feel comfortable deciding which germline assay is the most appropriate test to order for their patients.
Incomplete personal/family histories	• Physicians may be reluctant to take family histories in the setting of other issues that may be more pressing initially, such as a newly diagnosed MDS/AML.
	• In the era of "copy and paste" and the increased utilization of electronic medical records, the initial "unremarkable" is propagated and a positive personal or family history is missed.
	• Contemporary family sizes are smaller than in prior generations, which may reduce the likelihood that a hereditary disorder will be apparent to physicians, patients, and family members.
A perception that HHMs only affect pediatric patients	• Hereditary disorders have classically been presented as pediatric disorders.
	• Physicians may have a lower index of suspicion for syndromic presentations in adult patients.

Table 2 Controversies in hereditary AML syndromes

Controversies at the time of diagnosis
• What is the population prevalence of hereditary AML syndromes?
• Should patients be warned that tumor-only sequencing panels may inadvertently identify pathogenic germline mutations?
• Should somatic tumor panels performed at time of diagnosis uniformly include paired germline tissue samples?
• Should all patients with myeloid malignancies have germline screening performed for HHMs at the time of diagnosis?
• Should third party payers cover expenses for panel-based germline sequencing?
• What is the ideal source of germline tissue?
Controversies regarding the care of unaffected carriers of pathogenic germline mutations
• What is the role of prophylactic allogeneic stem cell transplant for unaffected people with HHM-related mutations?
• What is the role of prophylactic allogeneic stem cell transplant for people with HHM-related mutations who are affected by syndromic manifestations of HHMs?
• Should prophylactic allogeneic stem cell transplant be offered to otherwise unaffected carriers of germline mutations who develop clonal hematopoiesis or cytopenias of undetermined significance?
• Given that HHMs are not fully penetrant, how can we identify patients at highest risk for leukemogenesis?
• What is the ideal method of clinical surveillance for unaffected carriers of germline mutations?
Controversies regarding the care of individuals with pathogenic germline mutations who have developed MDS/AL
• What is the best timing for the use of allogeneic stem cell transplant for individuals with AML with germline *CEBPA* mutations?
• Should all matched related donors be genetically screened for germline mutations prior to stem cell donation?

of knowledge regarding the factors that could inform timing of a prophylactic SCT contribute to the uncertainty is this approach. For example, somatic *ASXL1* mutations in patients with germline *GATA2* mutations appear to be associated with a higher risk for CMML. Patients with hematopoietic clones containing *ASXL1* mutations may benefit from prophylactic SCT, but this has not been rigorously demonstrated in a prospective fashion [56]. Other HHM syndromes may possess similar molecular "triggers" that warrant consideration for a prophylactic SCT, but it will take years and multi-institutional efforts to demonstrate the benefits and utility of prophylactic SCT. We are not aware of ongoing randomized, prospective efforts, but encourage a dialog regarding their development.

Questions Regarding Precision Therapy for Carriers Who Develop MDS/AML

The optimal care of individuals with HHM-related mutations who develop MDS/AML is not clear. For example, one would assume that all patients with an HHM who are eligible for allogeneic SCT and who have a suitable stem cell donor (and a donor who is wild type for the HHM mutation in question in the case of related donors) should undergo a SCT in order to eradicate the underlying hematopoietic clone and reduce the likelihood of a second primary malignancy. This approach, however, may not be suitable for HHMs, such as AML with germline *CEBPA* mutations, that are notable for chemosensitivity and long latency periods between recurrent hematopoietic malignancies [18, 21•]. Some patients with AML stemming from germline *CEBPA* mutations may be able to forego SCT, especially if the patient is a marginal candidate for transplant secondary to comorbidities [22]. Other HHMs may prove to possess similar characteristics in terms of chemosensitivity and risk of second primary malignancies. There are currently no therapies directed specifically against the genetic lesions that underlie HHMs, but work is ongoing to utilize HHM models for developing treatments for use in both HHMs and sporadic tumors.

Conclusions

Despite the previously held notion that HHMs primarily affect children, we now appreciate that HHMs affect patients of all ages. Hematologist/oncologists must keep an HHM on the differential diagnosis for all patients and should have a low threshold for referring patients with a personal or family history of suspicious clinical histories or laboratory findings for genetic counseling and germline genetic analyses. Ideally, these patients should be managed by a multidisciplinary team at a center that specializes in management of MDS/AML patients and HHMs. It is critical that matched related SCT donors be thoroughly evaluated for an HHM so as to avoid the potential for a donor-derived malignancy or the potential to increase the risk of leukemia development in a related donor due to stem cell mobilization. Ideally, future efforts in the field will focus on standardizing diagnostic processes for HHMs, developing scientifically rigorous methods to perform clinical surveillance for unaffected carriers, and developing precision therapies for patients with HHMs and eventually utilizing HHMs to inform therapies for sporadic MDS/AML.

Compliance with Ethical Standards

Conflict of Interest Lucy Godley reports other from UpToDate, Inc., outside of the submitted work. Imo J. Akpan, Afaf Osman, and Michael W. Drazer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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