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Preemptive hematopoietic stem cell transplantation in *RUNX1* familial platelet disorder: a shared decision-making framework

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Abstract

RUNX1 familial platelet disorder (*RUNX1*-FPD) is associated with a 35% to 50% lifetime risk of hematologic malignancy (HM), and like all germline HM predisposition syndromes, can only be cured with allogeneic hematopoietic stem cell transplantation (HSCT). Current genetic screening techniques allow for early detection of germline predisposition, and consequently, the opportunity for HSCT before overt development of HM (ie, preemptive HSCT). However, there is not yet a consensus on the use of preemptive HSCT for *RUNX1*-FPD. Described here is the case of an individual with *RUNX1*-FPD and a family history of HM who underwent preemptive HSCT. We introduce a shared decision-making framework designed to support individuals with *RUNX1*-FPD, their families, and their multidisciplinary clinical teams in evaluating whether and when to pursue preemptive HSCT versus continued surveillance. The framework reviews key medical factors that influence HSCT timing decisions, including germline and somatic variants, clonal changes over time, familial history of HM, early morphologic or hematologic features, bleeding-related quality of life impacts, and donor availability. The framework also summarizes the major risks and uncertainties potentially associated with preemptive HSCT while highlighting the associated ethical challenges. Together, the case and framework provide a structured, patient-centered approach for navigating the complex clinical decision of preemptive HSCT. Ongoing collaborative efforts to define cytogenetic and clonal changes preceding malignant transformation in *RUNX1*-FPD will refine the framework and bolster individualized treatment strategies aimed at preventing HM and improving the quality of life of individuals with *RUNX1*-FPD.

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Introduction

Recognition of germline variants as important contributors to the risk of hematologic malignancy (HM) is increasing. It is estimated that 5% to 14% of all myeloid malignancies occur in individuals with an underlying germline predisposition.[1-4] Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapeutic option for HM with deleterious germline mutations. Genetic screening allows for early detection of germline predisposition, and consequently, earlier intervention, which raises critical questions regarding the timing and appropriateness of a HSCT.

RUNX1 familial platelet disorder (*RUNX1*-FPD) is a rare disorder, affecting up to 20,000 individuals in the United States, and was one of the earliest germline HM predisposition syndromes identified.[5-7] Individuals with *RUNX1*-FPD commonly exhibit mild to moderate thrombocytopenia and impaired platelet function, and thus, a tendency toward easy bruising and prolonged bleeding.[8-13] *RUNX1*-FPD is also associated with a high burden of atopic disease (eg, allergic rhinitis, eczema, and asthma) and a variety of inflammatory symptoms suggestive of broader immune dysregulation.[9, 10, 14-16] Notably, individuals with *RUNX1*-FPD have a 35%−50% lifetime risk of developing HM, including both myeloid and lymphoid malignancies, with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) being the most frequently reported.[12, 13, 17-20] The age of HM onset in *RUNX1*-FPD varies, ranging from months to 70 years or more. A review of *RUNX1*-FPD families reported that childhood-onset HM is observed in approximately 50% of families with an HM diagnosis.[18] For these reasons, preemptive HSCT–defined as HSCT before the development of MDS or overt HM–could become a therapeutic option for individuals with *RUNX1*-FPD in whom the potential benefits outweigh the potential harms. However, because there is not yet a consensus on how to identify the

appropriate candidates for, or the optimal timing of, preemptive HSCT, there is a significant unmet need for the *RUNX1*-FPD community.

We present a case report of an individual with *RUNX1*-FPD who elected to undergo preemptive HSCT and provide a shared decision-making framework to guide individuals with *RUNX1*-FPD, their families, and their multidisciplinary healthcare teams in considering preemptive HSCT.

Case report of preemptive HSCT for *RUNX1*-FPD

A 17-year-old female with lifelong easy bruising, menorrhagia, and borderline thrombocytopenia (platelets, 147 × 10^3/μL; mean platelet volume, 10.1 fL) was referred for evaluation of familial *RUNX1*-FPD. Genetic testing confirmed a heterozygous pathogenic splice-site variant *RUNX1* c.271-1G>T. The patient's bone marrow was normocellular with subtle megakaryocytic hypolobation, normal cytogenetics, without any identified acquired somatic mutations. The patient's father, who had the same variant, died in his 40s due to treatment-related complications after HSCT for AML that progressed from *SF3B1*-mutant MDS. The patient's paternal grandfather was diagnosed with leukemia at 27 years of age and died of relapsed AML in his mid 30s. Her great aunt (her paternal grandfather's sister) had also died of leukemia, and her father's nephew was also diagnosed with leukemia.

Given the paternal history of early-onset leukemia in affected relatives and the availability of several 10/10 matched unrelated donors, the patient, her parent, and her multidisciplinary team discussed preemptive HSCT versus continued surveillance. The potential advantages of preemptive HSCT discussed included (1) elimination of *RUNX1*-associated leukemia risk before clonal evolution; (2) avoidance of pre-transplant cytoreductive chemotherapy should she develop MDS with excess blasts or AML while in serial surveillance; (3) use of a T cell–depleted graft to prevent graft-versus-host

disease (GVHD) in a setting where the competing risk of relapse is absent; (4) resolution of bleeding symptoms; and (5) the opportunity for fertility preservation. The potential risks of preemptive HSCT that were discussed included transplant-related morbidity and mortality, GVHD, premature gonadal failure, and the possibility of future, less-toxic curative options becoming available. Multiple family members supported the patient's decision to receive preemptive intervention to prevent the development of leukemia.

At the age of 18 years, the patient chose to undergo preemptive HSCT. After ovarian tissue cryopreservation, she received conditioning with rabbit anti-thymocyte globulin (rATG; day −9 to −7 total dose, 9 mg/kg), busulfan (day 4 cumulative AUC, 86.0 mg×h/L), fludarabine (day −6 to −2 total dose, 150 mg/m^2), and thiotepa (day −3 to −2 total dose, 10 mg/kg), followed by a partially T cell–depleted peripheral blood stem cell graft from a matched unrelated donor. The patient's immediate post-transplant course was generally uncomplicated, with mild mucositis and transient fevers. She was discharged on day +26 without subsequent readmissions. She achieved stable, 100% donor chimerism and has not developed acute or chronic GVHD. More than five years later, the patient remains healthy with full donor chimerism and no bleeding symptoms. She has completed college and begun her career.

A shared decision-making framework for preemptive HSCT

Although the case report illustrates a positive outcome with preemptive HSCT for *RUNX1*-FPD, it is not without caveats. Each patient, caregiver, and multidisciplinary care team must carefully weigh the potential risks and benefits to determine whether to undergo preemptive HSCT versus continued surveillance. Shared decision-making frameworks are designed to assist patients with making the difficult decisions in the treatment or prevention of cancer.[21, 22] The framework presented here is intended to support individuals with *RUNX1*-FPD and their healthcare team with this complex

decision (**Figure 1**). The framework (1) describes the genetic and clinical factors that inform the timing and appropriateness of preemptive HSCT; (2) addresses the risks, benefits, and uncertainties associated with preemptive HSCT; and (3) summarizes the key ethical and psychosocial variables potentially encountered by individuals with *RUNX1*-FPD contemplating preemptive HSCT.

Medical considerations for preemptive HSCT

Germline variants and clonal hematopoiesis and the influence of age

Identifying individuals with *RUNX1*-FPD as candidates for, and determining the optimal timing of, preemptive HSCT relies upon the ability to detect events preceding malignant transformation. A large effort has been directed at assessing the risk of HM in *RUNX1*-FPD based on specific germline mutations. In the first two years of a prospective natural history study conducted at the National Institutes of Health (NIH), 19 of 111 (17.1%) individuals with *RUNX1*-FPD had a prior or current diagnosis of HM, 18 of whom were refractory to first-line therapy.[12] The risk of HM in these families did not directly correlate with the type of germline *RUNX1* mutation they carried. In a retrospective analysis of a large European *RUNX1*-FPD cohort, 60 of 134 (44.8%) evaluable individuals had a prior or current diagnosis of HM.[13] The widespread heterogeneity of malignant penetrance among individuals with *RUNX1*-FPD indicates that germline mutations alone are insufficient for malignant transformation and that additional somatic mutations are also needed.[20, 23-25]

Although great strides have been made in identifying somatic mutations in individuals with *RUNX1*-FPD before the development of HM, assigning HM risk to specific germline and somatic variants is not yet been possible due to the rarity of *RUNX1*-FPD. Among individuals with *RUNX1*-FPD without HM, the most frequent somatic mutations identified have been in *BCOR*, *TET2, and DNMT3A*.[26, 27] Interestingly,

among individuals with *RUNX1*-FPD and HM, the most frequently identified somatic mutation has been a second hit in *RUNX1*[13, 26]; other common somatic mutations in individuals with HM include *FLT3-ITD*, *PHF6*, *BCOR*, and *TET2*.[13, 26, 27] Acquired cytogenetic abnormalities are also common at malignant progression. Further prospective investigation is needed to elucidate the relationship between specific germline and somatic mutations with the risk of HM development in *RUNX1*-FPD.

In the general population, the expansion of clones harboring somatic mutations (ie, clonal hematopoiesis [CH]) increases with age and is associated with an increased lifetime risk of HM (**Figure 2**).[28, 29] In a recent analysis of the UKBiobank—a large-scale biomedical database with health records, whole exome sequencing, and lifestyle data from ~500,000 adults—germline variants in specific cancer predisposition genes (eg, *RUNX1*, *ATM*, *ETV6, TP53,* and *DDX41*) were associated with an increased prevalence of CH and significantly elevated risk of HM among individuals with both germline variants and CH.[7] Furthermore, individuals with germline *RUNX1* variants and CH had one of the highest relative risks of HM.[7] Multiple studies have demonstrated that CH is detectable at a much higher rate among individuals with *RUNX1*-FPD than in the general population, occurs as early as adolescence or even early childhood, and generally increases with age.[13, 17, 20, 23, 26, 28-34] Among individuals with *RUNX1*-FPD, the frequency of somatic mutations in HM driver genes increases over time.[26, 27]

Although the ideal time window for preemptive HSCT in *RUNX1*-FPD is before the onset of CH, or after detection of CH but before progression to overt HM, the duration of the time window is unknown and varies between individuals (**Figure 2**). Furthermore, the relative HM risk associated with various secondary somatic mutations is unknown. Therefore, routine monitoring for CH is an essential component of the shared decision-making framework for preemptive HSCT. For example, a sudden expansion in the clone size, acquisition of multiple clonal abnormalities or complex

cytogenetic abnormalities, or the development of clones harboring high-risk mutations within an individual may signal the appropriate time for consideration of preemptive HSCT. Although HM may occur in early childhood, preemptive HSCT in pediatric patients must be considered from ethical and biological perspectives. The NIH natural history study has shown that children with *RUNX1*-FPD have a nearly 50-fold increased risk of developing HM compared with children in the general population, with the highest relative risk occurring before the age of 5 years.[35] The NIH study team also observed a notable biologic difference between children and adults with *RUNX1*-FPD who developed HM. Children more commonly exhibited structural chromosomal abnormalities but not sequence changes, whereas adults more often acquired sequence changes but not chromosomal changes.[35] Importantly, although myeloid malignancies are the most common in children and adults, children may also develop lymphoid malignancies. The mutational spectrum of pediatric MDS and AML are distinct versus that of adult MDS and AML, and more broadly, both MDS and AML are characterized by considerable genetic and phenotypic heterogeneity.[36-39]

Preemptive HSCT during childhood offers several advantages over transplantation in adulthood. Because many children have not yet developed CH, preemptive HSCT could eliminate the need for conditioning to eradicate pathogenic clones and reduce the risk of clonal recurrence after transplant, assuming that full donor engraftment has occurred (residual stem cells exposed to alkylating agents could pose additional concerns). In addition, performing preemptive HSCT during childhood could spare the cumulative physical and emotional burden of repeated bone marrow biopsies long term. Lastly, overall survival and transplant-related complication rates across all indications are generally more favorable in younger individuals than in older individuals. For example, in a retrospective study of 35 children and adolescents with *RUNX1*-FPD who received HSCT before the age of 20 years, those with less advanced disease at the

time of transplant appeared to have more favorable outcomes than those with MDS or more advanced HM.[40] However, several potential disadvantages of preemptive HSCT during childhood should also be considered, including (1) the inability of children to provide informed consent; (2) limited fertility preservation options before puberty, when only tissue cryopreservation is possible; (3) lengthy absence from school and impacts on social development throughout the transplantation process; and (4) the possibility that some children undergoing preemptive HSCT would never have developed an HM.

Familial risk

Although the lifetime risk of developing HM with *RUNX1*-FPD is 35%−50%,[12, 13, 17-20] there is evidence that the risk of HM for an individual may be higher in a family with a history of HM diagnoses. In a prospective natural history study, 28 of 45 (62%) *RUNX1*-FPD families had at least one case of HM, and 15 of 45 (33%) families had at least three cases of HM.[12] In our included case report, the decision to undergo preemptive HSCT was strongly influenced by family history, as four affected relatives developed HM. However, even among family members carrying the same germline *RUNX1* variant, the development of HM and the severity of thrombocytopenia, functional platelet defects, and bleeding may vary.[20, 23-25] For these reasons, a multidisciplinary care team with experience in counseling patients is essential in the decision-making process when an individual with *RUNX1*-FPD is contemplating a preemptive HSCT.

Changes in bone marrow morphology and blood counts

Megakaryocyte atypia with hypolobation, thrombocytopenia, and functionally defective platelets, which result in frequent bruising and persistent bleeding, are hallmarks of *RUNX1*-FPD.[8-13, 24, 41, 42] Approximately 50% of individuals with *RUNX1*-FPD present with hypocellular marrow as their “normal” baseline.[7] Monitoring for the worsening of any of these abnormalities or progressive dysplasias affecting additional lineages, which could

indicate progression to HM, is part of routine surveillance for *RUNX*1-FPD. Similar to other inherited bone marrow failure syndromes and germline HM predisposition syndromes, tracking shifts in blood counts in *RUNX1*-FPD is informative despite the absence of formal consensus guidelines for surveillance.[43] Importantly, bone marrow and blood count abnormalities may evolve asynchronously and can occur in the absence of overt MDS or AML (**Figure 2**).[8]

Bleeding and impact on quality of life

Easy bruising and persistent bleeding can impact quality of life. A large-scale longitudinal natural history study of *RUNX1*-FPD is ongoing, and quality of life data are not yet available. [7] Until such data emerge, findings from other congenital platelet disorders suggest that health-related quality of life is measurably impaired across age groups. Reduced quality of life scores are reported for children and adults compared with the general population, with deficits spanning physical, social, emotional, and school or work functioning. These impacts are closely tied to bleeding frequency and severity, underscoring that inherited platelet disorders affect multiple domains of daily life beyond the bleeding symptoms themselves.[44, 45] In addition, focus group discussions conducted by the *RUNX1* Research Program with patients with *RUNX1*-FPD have shown that bruising and bleeding are key contributors to diminished quality of life (unpublished data confirmed by KE, MB, and LB). Because women with *RUNX1*-FPD often suffer from severe menorrhagia that negatively impacts quality of life and may not always be controlled by oral contraceptives or other modalities.[46, 47] In our included case report, in addition to the prominent family history of HM, the potential for curing severe bleeding manifestations was a motivating factor in her decision to undergo preemptive HSCT.

Donor selection and availability

Given the hereditary nature of *RUNX1*-FPD and high incidence of HM within *RUNX1*-FPD families, use of a human leukocyte antigen (HLA)-matched related donor without underlying *RUNX1*-FPD for preemptive HSCT is often not possible. Matched unrelated donor (MUD) and haploidentical donor HSCT, which have steadily increased in frequency in the last decade and have been associated with encouraging survival outcomes among patients with MDS and AML,[48] may be the most feasible donor options for patients with *RUNX1*-FPD who elect preemptive HSCT. Among children in the general population, the use of haploidentical donors for first HSCT has sharply increased since 2015.[48] In our included case report, the patient with *RUNX1*-FPD received preemptive HSCT using MUD T cell–depleted stem cells.

Potential risks and uncertainties of preemptive HSCT

Individuals with *RUNX1*-FPD could experience a variety of transplant-related complications, and quality of life may be negatively impacted. Thus, it is important for individuals with *RUNX1*-FPD considering preemptive HSCT, their caregivers, and their clinicians to carefully weigh these potential risks against the potential benefits (**Figure 3**).

Transplant-related mortality

The incidence of transplant-related mortality (TRM; ie, non-relapse mortality) has improved substantially in the last several decades, likely due to improvements in HLA typing, conditioning regimens, GVHD prophylaxis, and supportive care, including advances in infection prevention and treatment.[49-51] Conditioning regimen intensity remains central to TRM risk. Although reduced-intensity conditioning (RIC) can decrease acute toxicity, it may increase the likelihood of mixed chimerism and late relapse in malignant settings.[52]

Evaluation tools designed to define risk factors for TRM following HSCT enable clinicians, patients, and caregivers to make informed, personalized decisions before HSCT.[53, 54] Age is an important risk factor for TRM, as there have been reports of higher rates of TRM in patients of younger age compared with older chronologic or biologic age.[55-58] The primary causes of non-relapse mortality among adults who have undergone HSCT include infection, GVHD, secondary malignancy, multiorgan failure, and graft failure, and the comorbidities with the strongest association with TRM were cardiac disease, peptic ulcer disease, solid tumors, unrelated or mismatched donor, and high risk per HCT-CI.[49, 59] In children, individual risk factors for TRM following HSCT include use of mismatched donor, respiratory infection, central nervous system infection, infectious diarrhea, posterior reversible encephalopathy syndrome, epilepsy, structural central nervous system abnormality, and hepatobiliary disease.[54]

Understandably, as individuals contemplate whether to pursue a preemptive HSCT, quantitative data on the potential risk of TRM are essential for informed decision-making. However, it is difficult to predict the rates of TRM in the setting of a preemptive HSCT for *RUNX1*-FPD, as no studies have reported such outcomes in this population. The most relevant benchmark to date is a randomized phase 2 study in which children undergoing HSCT for non-malignant conditions who had matched sibling/family or matched unrelated donors had a higher rate of freedom from TRM to day +100 with treosulfan-based conditioning than with busulfan-based conditioning (100% vs 90%), as well as lower TRM (3.9% vs 12.0%) at 12 months.[60]

Recent studies reporting TRM with allogeneic HSCT among adults with non-malignant conditions are lacking, as most available studies include children or reflect earlier supportive care eras, and therefore, have limited applicability. Consequently, lower-risk MDS represents the closest adult comparator for contextualizing TRM. In a study by the Chronic Malignancy Working Party of the European Society for Blood and

Marrow Transplantation (EBMT) in 246 adults with lower risk MDS (79% intermediate-1 per classical IPSS), non-relapse mortality was 30%.[61] Until contemporary adult datasets are published, TRM estimates for preemptive HSCT in adults with *RUNX1*-FPD must be inferred cautiously and are likely higher than non-malignant pediatric benchmarks given the greater comorbidity burden, donor mismatch/age considerations, and GVHD risk. Prospective adult, non-malignant cohorts capturing TRM across donor types and conditioning intensities are needed.

Graft-versus-host disease

Graft-versus-host disease is a major cause of morbidity and mortality following HSCT among patients with malignant and non-malignant disease and is also an important consideration for individuals with *RUNX1*-FPD considering preemptive HSCT. The incidence and severity of acute and chronic GVHD following HSCT have decreased over the last few decades[49, 62] due, at least in part, to advances in GHVD prophylaxis and the availability of less toxic conditioning regimens. In adults and children undergoing HSCT for HM, improved outcomes with the use of haploidentical donors have been made possible by in vivo T cell depletion using post-transplant cyclophosphamide (PTCy) or rATG and ex vivo T cell depletion with techniques that include CD34 selection, CD3 depletion, and TCR αβ depletion.[63-70] In the large pediatric study of HSCT for non-malignant conditions with treosulfan-based conditioning or busulfan-based conditioning, 15.7%−30% overall developed GVHD, 2.0%−14.0% developed moderate/severe chronic GVHD, and 8.0%−13.7% developed acute GVHD.[60] In the lower risk MDS adult study by the EBMT, chronic GVHD occurred in 42% overall, with no significant differences between young and older adults.[61] GVHD rates in these studies may have been improved with the use of rATG, which has been successfully used to prevent severe GVHD in children with nonmalignant disorders who received haploidentical HSCT.[71]

Infection

Individuals with *RUNX1*-FPD who undergo preemptive HSCT are at risk of multiple types of infections, not only before and immediately after HSCT due to severe neutropenia associated with conditioning, but also for months up to several years after HSCT during reconstitution of the immune system.[72] The risk factors for infection following HSCT include intensity of conditioning, type of donor cells and HLA matching, GVHD, and underlying disease.[72] Late infections are a significant cause of mortality following HSCT and have been shown to be responsible for up to 30% of deaths occurring 2 years or later after HSCT in adults and children.[73]

Graft failure

Individuals with *RUNX1*-FPD who receive preemptive HSCT may experience graft failure, which is associated with increased morbidity and mortality. Both primary and secondary graft failure have been described, with reported rates ranging from 2% to 15% across studies.[66, 68, 70, 74-79] However, there have been relatively fewer studies examining graft failure in the era of PTCy prophylaxis. In a recent retrospective, single-center study in 958 adult patients with HM who received PTCy prophylaxis with first nonmyeloablative HSCT using predominantly mismatched donors, the rate of primary graft failure was 3.8%, the rate of secondary graft failure was 1.8%, and patients with graft failure had reduced overall survival.[79] There are a variety of risk factors for graft failure (eg, including stem cell donor type, HLA donor type, HLA matching, prior chemotherapy, T cell depletion, conditioning, and CD34+ cell count[76]) that should be considered by individuals with *RUNX1*-FPD who are considering preemptive HSCT.

Late complications

There are numerous potential late complications for patients who undergo preemptive HSCT, including secondary malignancies, GVHD, infection, infertility or gonadal failure,

osteopenia or osteoporosis, long-term organ toxicity (eg, pulmonary fibrosis or chronic kidney disease), endocrine complications, and neurologic complications.[80, 81] The potential for developing a post-transplant malignancy is especially noteworthy for an individual with *RUNX1*-FPD considering preemptive HSCT who has not developed HM. In the general population, secondary malignancies are responsible for up to 10% of late deaths following HSCT, and the incidence of a secondary solid tumor following HSCT is 2%−6% at 10 years and 4%−15% at 15 years.[82] Although the likelihood of developing a secondary malignancy following preemptive HSCT for *RUNX1*-FPD is unknown, the rate with preemptive HSCT should be lower than patients receiving HSCT post-malignancy treatment, given that the overall exposure to toxic therapies is much higher among individuals who have had cancer and bridged to HSCT. Regardless, regular screening will be important for individuals with *RUNX1*-FPD who undergo preemptive HSCT.

Infertility is common following HSCT and is largely driven by gonadal failure, with a recent meta-analysis demonstrating a prevalence of 61%−65% in women with benign and malignant hematologic disease, respectively, and 31%−41% in men with benign and malignant hematologic disease, respectively.[83] Although pregnancy is possible for women following HSCT, fertility is greatly reduced versus the overall population and is less likely among women who have received total body irradiation as part of their conditioning.[84] Cryopreservation of embryos, ovarian tissue, and testicular tissue improve the ability for pregnancy following HSCT even among children,[85, 86] but are not without challenges and may not be financially feasible for many people. Thus, individuals with *RUNX1*-FPD considering preemptive HSCT may prefer to delay transplantation until after having children. Counseling on family planning that includes fertility preservation options should be provided.

Impact on physical, psychological, emotional, social, and role function

Decreases in physical functioning may occur with preemptive HSCT due to the conditioning regimen or due to complications associated with HSCT transplantation. Factors that may affect physical functioning following conditioning and HSCT include fatigue, acute and/or chronic graft versus host disease, lower muscle mass, nutritional status, and corticosteroids.[87-90] Individuals with *RUNX1*-FPD who undergo preemptive HSCT could experience a variety of psychological and emotional impacts, such as anxiety, depression, stress, and disrupted sleep resulting from anticipation of or as a consequence of conditioning therapy, complications, recovery time, prolonged hospitalization, missed work or school, and separation from family and friends.[87, 91-93] Alternatively, preemptive HSCT could potentially lessen or remove the fear burden of later developing a HM, particularly for an individual in a *RUNX1*-FPD family with a history of HM. However, HSCT may also have psychological and emotional impacts that may persist for several years before full recovery occurs.[87, 94, 95] Vulnerability to the psychological and emotional impacts of HSCT may be augmented by disease-related, patient-related, and treatment-related factors.[92] Furthermore, tolerance of the perceived risk of harm from preemptive HSCT or from fear of missed benefit from not undergoing preemptive HSCT may vary greatly between individuals. Psychosocial and behavioral health support is a vital component of care at transplant centers for patients with HM that will be important for individuals with *RUNX1*-FPD who are contemplating preemptive HSCT.

Individuals with *RUNX1*-FPD who elect to receive preemptive HSCT may experience some degree of disruption in social function and role function (ie, work, school, or parenting). Among individuals who undergo HSCT following development of HM, a large proportion of those who survive without disease recurrence experienced significant improvement in social function and return to work within 3 to 5 years.[87, 94, 96, 97]

In comparison, patients with *RUNX1*-FPD who undergo preemptive HSCT could potentially experience a shorter time to return to normal social and work function. Transparency in communication of expectations to prevent discouragement and incorporation of rehabilitation planning with the support of multidisciplinary healthcare teams may facilitate an earlier “return to normal” psychological, emotional, social, and/or role function.

Ethical and financial considerations for preemptive HSCT

Ethical considerations are the central component of the preemptive HSCT shared decision-making framework and will serve as prompts during program development for informed consent discussions (**Figure 1**). Individuals with *RUNX1*-FPD will each weigh these factors differently when deciding whether their personal risk tolerances favor early intervention with preemptive HSCT versus continued surveillance.

During the individualized risk-benefit analysis (framework step 1), it is important to determine whether offering preemptive HSCT aligns with the treatment team’s mission and with the individual’s risk tolerance. During the shared decision-making between the individual with *RUNX1*-FPD and their healthcare providers (framework step 2), it is important to ensure that decisions respect the individual’s values, relationships, and social contexts. The framework enables the individual to include trusted family members, friends, or others in their social network who influence decisions. Safeguards should be implemented for those with limited decision-making capacity (ie, assent for children and other vulnerable populations) rather than excluding them from consideration. A supported decision-making model should be considered whenever possible to maintain the voice of the patient even if the patient is not fully capable of making the decision without guidance.

The third and final step in the shared decision-making framework is ethical and

practical implementation of the decision to proceed with preemptive HSCT. A sound ethical process supports the individual in making well-informed decisions in collaboration with their social network and healthcare team. Once the decision to proceed with preemptive HSCT has been made, the psychological impacts, including the stress of waiting for possible disease progression and the burdens of undergoing a HSCT, should not be underestimated. In addition, real-world and practical issues of the potential financial impact need to be accounted for in the timing of preemptive HSCT. Timing is particularly important for some young adults who may age out of their parents' health insurance. Insurance authorization for a preemptive HSCT may not be straightforward, and insurers may decline coverage. In such situations, active advocacy by the treating team with the insurance provider becomes a critical component of care. Multidisciplinary support from social workers, family physicians, ethicists, clergy, or trusted experts may be helpful. Although in most cases, an unrelated donor will be used, family members may be called upon as potential donors and may need counseling support to mitigate feelings of pressure or obligation.

Healthcare teams must ensure all providers in the preemptive HSCT process understand the unique considerations of a preemptive HSCT versus HSCT as part of HM treatment, which will help prevent moral distress among staff and protects the individual from receiving conflicting messages about the ethical appropriateness of their decision.

Conclusions

Preemptive HSCT is the only potentially curative therapeutic option for individuals with *RUNX1*-FPD with the potential to prevent the development of HM, which otherwise occurs in 35%−50% of individuals with the disease.[12, 13, 17-20] However, the potential benefits must be carefully weighed against the potential risks and uncertainties before

proceeding with a preemptive HSCT rather than continued surveillance (**Figure 3**). Preemptive HSCT may alleviate the burdensome daily symptoms of bleeding, the common atopic diseases, other immune dysfunction related symptoms, and the psychological and emotional impacts of *RUNX1*-FPD. The potential risks of preemptive HSCT include TRM, acute/chronic GVHD, infertility, and long-term complications, including organ dysfunction and secondary malignancies, all of which can significantly impact quality and length of life.

This conceptual framework outlines the key considerations for patient-centered decision-making on preemptive HSCT in RUNX1-FPD. Although the framework broadly informs discussions applicable across other HM predisposition syndromes, the considerations must be specifically tailored given the distinct differences syndrome in clinical manifestations, including solid tumor risk, organ system involvement, and chemotherapy and radiation sensitivity.[98-104] As with *RUNX1*-FPD, preemptive HSCT may prevent the development of HM and alleviate clinical symptoms resulting from bone marrow abnormalities in other HM predisposition syndromes but would not be expected to cure non-hematologic symptoms or prevent the development of solid tumors.

Given the rarity of *RUNX1*-FPD and the overall limited prospective outcome data, there is not yet a consensus regarding patient selection, optimal timing, or conditioning approach for preemptive HSCT. The shared decision-making framework presented here provides a foundation to assist individuals with *RUNX1*-FPD, their families, and their multidisciplinary healthcare teams in navigating the medical, emotional, psychological, and ethical factors that must inform these complex decisions.

Perhaps the most challenging part of this process is determining how early in the course of *RUNX1*-FPD a preemptive HSCT should be considered. Despite the advances in genetic screening and growing recognition that the frequency of CH increases over time,[28, 29] clinicians remain unable to accurately assign individualized HM risk based on

specific germline or somatic variants. Until risk prediction models incorporating both genetic and clinical variables are validated, clinical decisions will rely on longitudinal monitoring and multidisciplinary judgement in partnership with their patient and their families. Continuing improvements in comprehensive genetic diagnostics may allow greater flexibility continued surveillance approaches.

An ongoing large-scale, prospective natural history study of *RUNX1*-FPD is beginning to shed light on the sequence of cytogenetic and clonal changes that precede malignant transformation.[12] However**,** a longer observation period and larger participant numbers will be needed to define reliable biomarkers of progression and inform transplant timing. Integration of these data with insights from patient registries, such as those developed through the *RUNX1* Research Program and RUNX1 database (RUNX1db; https://runx1db.runx1-fpd.org), and international collaborations will be essential to establishing evidence-based guidelines for surveillance and candidate selection. Ultimately, these collective efforts will help refine when, and for whom, preemptive HSCT provides the greatest net benefit balancing cure against risk in a patient-centered manner.

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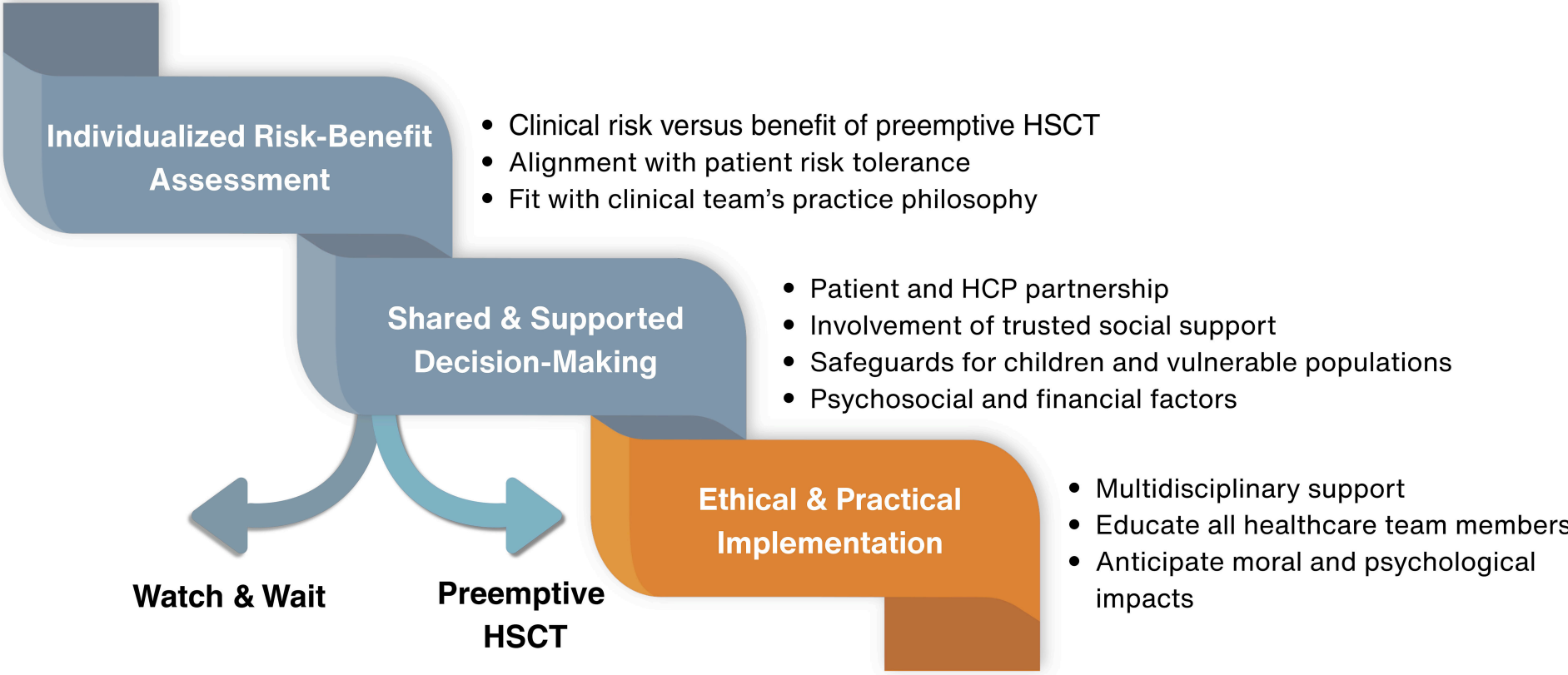
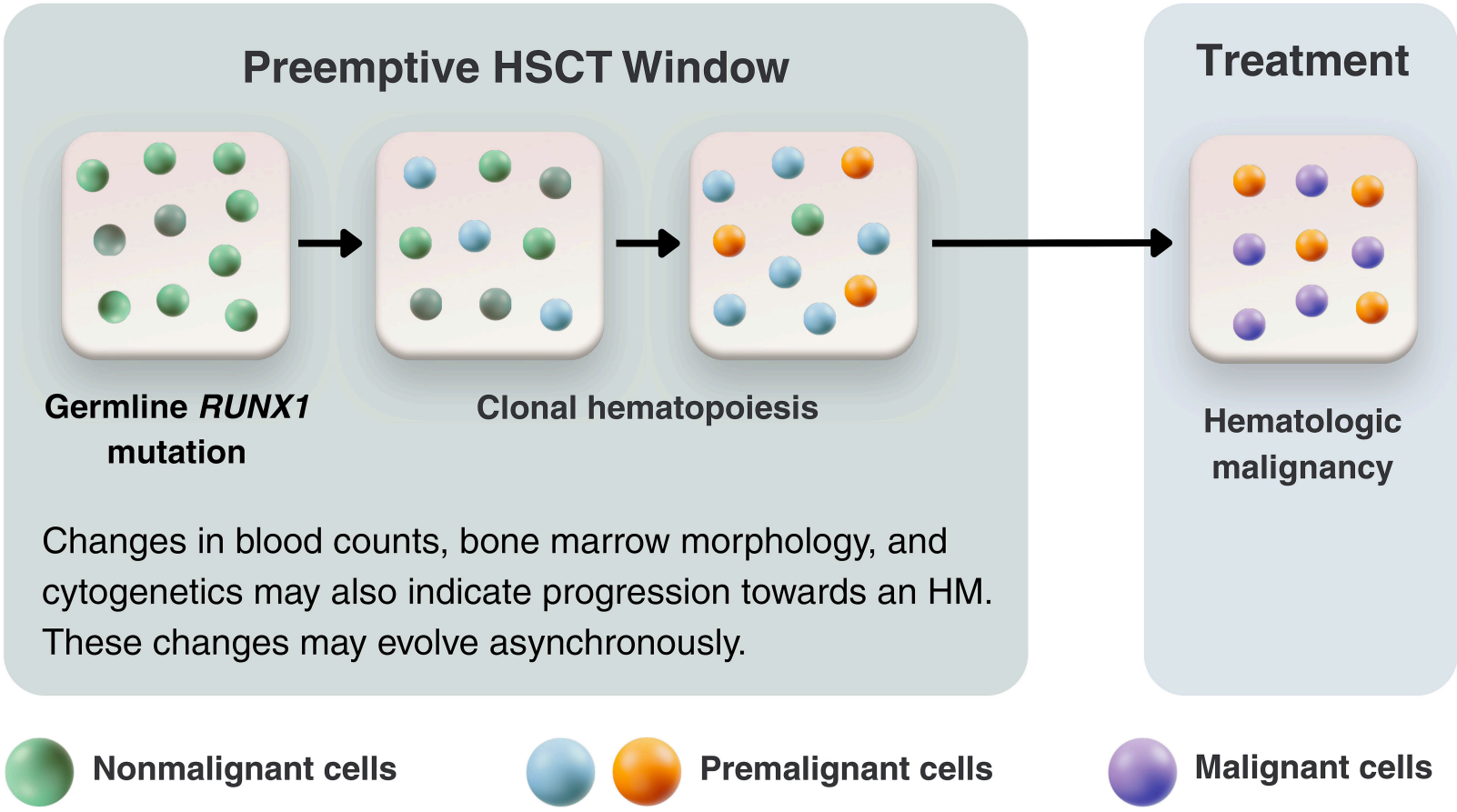
Figure Legends

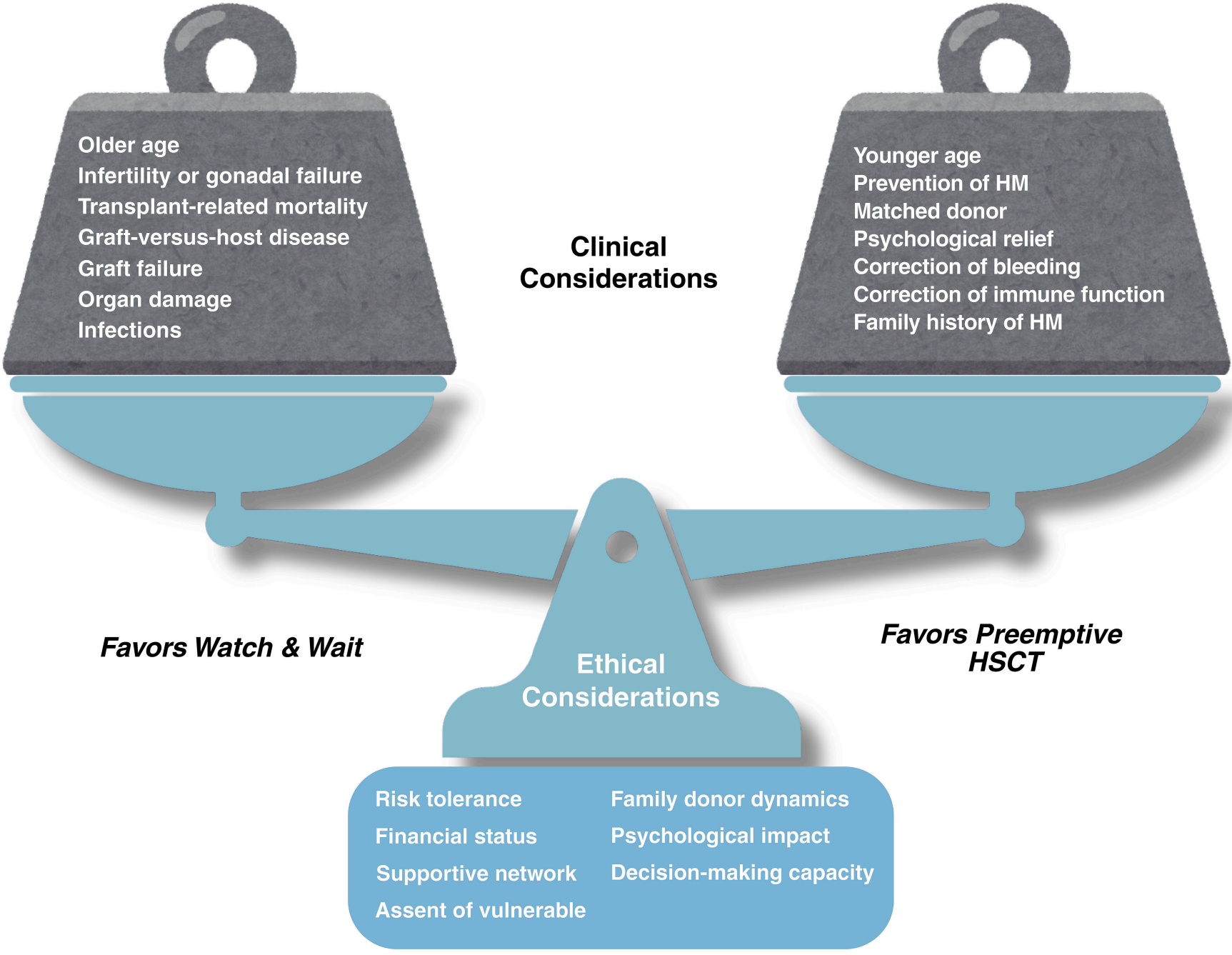
Figure 1. **Preemptive HSCT shared decision-making framework.** HCP, healthcare provide; HSCT, allogeneic hematopoietic stem cell transplant.

Figure 2. **Determining the optimal timing for preemptive HSCT.** Schematic representation of disease progression in *RUNX1*-FPD, highlighting the window for preemptive allogeneic hematopoietic stem cell transplantation (HSCT). Individuals with a pathogenic germline *RUNX1* mutation (g*RUNX1*) may over time acquire somatic mutations that drive clonal hematopoiesis,[13, 17, 20, 23, 26-34] ultimately leading to hematologic malignancy. Changes in blood counts, bone marrow morphology, and cytogenetics can signal disease progression, but these features may evolve asynchronously. The window for preemptive HSCT lies before progression to overt hematologic malignancy, after which conventional treatment is required. HM, hematologic malignancy; HSCT, allogeneic hematopoietic stem cell transplant.

Figure 3. **Clinical and ethical considerations for preemptive HSCT in *RUNX1*-FPD.** HM, hematologic malignancy; HSCT, allogeneic hematopoietic stem cell transplant.


Individualized Risk-Benefit Assessment
Clinical risk versus benefit of preemptive HSCT
Alignment with patient risk tolerance
Fit with clinical team's practice philosophy
Shared & Supported Decision-Making
Patient and HCP partnership
Involvement of trusted social support
Safeguards for children and vulnerable populations
Psychosocial and financial factors
Ethical & Practical Implementation
Multidisciplinary support
Educate all healthcare team members
Anticipate moral and psychological impacts
Watch & Wait
Preemptive HSCT


Preemptive HSCT Window
Treatment
Germline *RUNX1* mutation
Clonal hematopoiesis
Hematologic malignancy
Changes in blood counts, bone marrow morphology, and cytogenetics may also indicate progression towards an HM. These changes may evolve asynchronously.
Nonmalignant cells
Premalignant cells
Malignant cells


Older age
Infertility or gonadal failure
Transplant-related mortality
Graft-versus-host disease
Graft failure
Organ damage
Infections
Clinical Considerations
Younger age
Prevention of HM
Matched donor
Psychological relief
Correction of bleeding
Correction of immune function
Family history of HM
Favors Watch & Wait
Favors Preemptive HSCT
Ethical Considerations
Risk tolerance
Financial status
Supportive network
Assent of vulnerable
Family donor dynamics
Psychological impact
Decision-making capacity