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Clinical impact of clonal hematopoiesis in hematopoietic cell transplantation: a review, meta-analysis, and call to action

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Author contributions

NG and AE contributed equally as co-first authors. NG conceptualized and designed the manuscript, helped screen articles for inclusion, led writing the manuscript, tables, and figures, and oversaw meta-analyses. AE designed the review search strategy, conducted the search, screened potentially eligible articles, and contributed to writing the manuscript, tables, and figures. ZJT conducted the meta-analysis

and contributed to figure generation and design. JAP contributed to writing the manuscript and provided a clinical perspective throughout. All authors reviewed and approved the final version of the manuscript.

Data sharing statement

Data used for this study consists of summary statistics from peer-reviewed publications. Citations for the data are included throughout the article. Questions can be directed to the corresponding author.

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ABSTRACT

Hematopoietic cell transplantation (HCT) is the only potentially curative treatment option for many patients with hematologic malignancies. While HCT outcomes have improved drastically over the years, patients and clinicians continue to face numerous survivorship challenges, such as relapse, graft-versus-host disease, and secondary malignancies. Recent literature suggests that clonal hematopoiesis (CH), the presence of a recurrent somatic mutation in hematopoietic cells, in HCT patients or donors may be associated with outcomes in autologous and allogeneic HCT. Herein, we perform a review of the literature and summarize reported associations between CH and clinical outcomes in HCT. For commonly reported outcomes, we used meta-analysis methods to provide estimates of effect sizes when combining results. A total of 32 articles with relevant and independent contributions were included, covering both autologous (n = 19) and allogeneic (n = 13) HCT. The articles report variable risk for developing outcomes according to CH characteristics, patient disease status, and method of HCT. Using meta-analysis of available results, HCT outcomes with statistically significant effects by CH status include therapy-related myeloid neoplasms (OR 3.65, 95%CI 2.18-6.10) and overall survival (HR 1.38, 95%CI 1.20-1.58) in autologous HCT and relapse (HR 0.80, 95%CI 0.68-0.94) in allogeneic HCT. However, heterogeneity, biases, and limitations in the literature provide challenges for informing the translation of CH to clinical decision-making. We conclude with a call to action and discussion of next steps to build upon the current literature and provide granularity to the true clinical impact of CH in the setting of HCT.

INTRODUCTION

For many patients with hematologic malignancies, hematopoietic cell transplantation (HCT) is the only potentially curative treatment option.[1-3] Despite improvements in survival rates of patients receiving HCT, disease progression, treatment toxicities (e.g., graft-versus-host disease), subsequent cancers, cardiovascular complications, and infections remain major challenges.[1, 4] Data suggest that clonal hematopoiesis (CH) may be an important biomarker for identifying patients at increased risk for poor outcomes from HCT.

CH is a pre-malignant hematological state characterized by somatic mutations in hematopoietic stem and progenitor cells without overt hematologic abnormalities.[5] The genes mutated in CH are largely the same as those pathogenic for myeloid malignancies.[6, 7] CH is strongly associated with aging, with a prevalence of 1% in healthy individuals younger than 40, 20% in those over 65, and almost ubiquitous (>90%) in individuals over 80 years of age;[6-8] however, the prevalence of CH varies greatly depending on the limit of detection of somatic mutations.[9, 10] Individuals with CH are at increased risk for incident hematologic malignancies, cardiovascular disease, chronic liver disease, severe COVID-19, and mortality.[7, 11-13]

Because CH is present in healthy individuals and patients with cancer,[14] HCT donors and patients may be carriers of these mutations. This article used a systematic approach and meta-analyses to synthesize the existing literature on the clinical impact of CH on HCT recipient outcomes stratified by disease and HCT types (i.e., autologous, or auto-, and allogeneic, or allo-HCT). We conclude with a discussion of knowledge gaps, next steps, and a call to action needed to make evidence-based recommendations regarding the management of CH in patients undergoing HCT.

Methods

Search Strategy and Article Selection

We systemically searched for articles indexed in PubMed, Scopus, Embase (Elsevier), and Web of Science (Clarivate). All database searches were last conducted on April 29, 2024. EndNote 20 (Clarivate Analytics, USA) was used to remove any duplicates and select eligible studies. After removal of duplicate articles, titles and abstracts were screened for inclusion. Articles eligible for inclusion were original articles or relevant letters or commentaries that reported measures of the effect of CH, identified in donors and/or recipients, on outcomes in patients undergoing allo- or auto-HCT. Exclusion criteria included reviews, case reports and series, abstracts, non-human studies, studies not written in English, and studies not reporting a measure of risk between groups by CH status. A comprehensive evaluation of the identified studies and abstracts was completed by one author and subsequently evaluated by another author for final inclusion. Inconsistencies that arose were handled through consensus. Additional details on the search strategy are provided in the **Supplementary Methods**.

Meta-analysis

To estimate the effect sizes of CH in HCT, we used meta-analyses for all outcomes reported in more than ten auto- and more than five allo-HCT studies. Hazards ratios (HR) and 95% confidence intervals (CI) for outcomes relative to CH status were abstracted from published articles. When HRs were not available, odds ratios (OR) and CIs were abstracted or calculated. Articles without HRs, ORs, or data sufficient for calculating ORs were excluded from meta-analyses. The measures of effect were combined using the general inverse variance weighting method, employing random effects models due to heterogeneity in the studies. The index of inconsistency (I^2) and τ^2 were used to assess the degree of heterogeneity among studies for each outcome. Sensitivity analysis was performed to explore differences in outcome across subgroups (e.g., cancer type or donor type). The assessment of publication bias was conducted by

the visual examination of funnel plots. Meta-analyses were performed using the meta package in R version 4.3.0.

Results

A comprehensive search strategy was employed and, as reassurance, all relevant articles known to us, in addition to others, were retrieved using this strategy. Thirty-two unique publications met inclusion criteria and investigated the effect of CH on outcomes in patients undergoing auto- or allo-HCT (**Figure 1**). One study that defined CH using X-inactivation based clonality by the human androgen receptor locus (HUMARA) assay was excluded due to heterogeneity of CH classification.[15] The included studies were published in between 2017-2024 and investigated the association between CH and HCT outcomes across disease cohorts [including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), lymphoma, multiple myeloma (MM), and heterogenous cohorts] (**Table S1**). Nineteen articles investigated outcomes in auto-HCT and thirteen articles involved allo-HCTs. Study sample sizes ranged from 12 to 1,727 participants.

The effects of CH on the outcomes of HCT patients are summarized in **Table 1, Table 2,** and **Table S1** and discussed in detail below. Additional outcomes reported in single studies or with null results are discussed in the **Supplementary Information**.

Auto-HCT in Lymphoid Malignancies

CH Metrics and Prevalence

In auto-HCT, most studies analyzed <100 genes for CH (**Figure 2A, Table S2**). The most common variant allele frequency (VAF) threshold reported was >2% (47.1%, 8/17) followed by >1% (**Figure 2B**). In auto-HCT, the recipient is also the donor; therefore, measurement of CH occurs exclusively in the patient, but can be measured either before or after HCT. Most studies with prevalence data assessed CH before auto-HCT (94.1%, 16/17), with a small number reporting CH before and after HCT (17.6%, 3/17),

and one study (5.9%) only assessing CH after auto-HCT (**Table S2**). The median prevalence of CH in auto-HCTs was 26.7% (range 7.6%-75.0%). Prevalence was higher in patients with lymphoma than MM (29.9% vs 21.6%); prevalence in AML (28.2%) was reported in one study (**Figure 2C**).[16]

Peripheral Blood Stem Cell (PBSC) Mobilization

One of the first steps for successful auto-HCT is mobilization and collection of $CD34^+$ PBSCs that can subsequently be transplanted. Poor PBSC mobilization can lead to HCT delay, longer time to engraftment, worse overall survival (OS), and increased risk for therapy-related myeloid neoplasms (tMNs).[17] Thus, upfront identification of patients at risk for poor mobilization may be important to optimize patient outcomes and inform management decisions.

Of seven studies that explored PBSC mobilization efficiency in auto-HCT, most (5 or 71%) found a significant association between CH and mobilization despite differences in classification of the endpoint (**Table 1; Table S1**). Measurements of PBSC mobilization efficiency in auto-HCT that have been statistically associated with CH status include poor mobilization,[18] days to collect an adequate number of PBSCs,[19] risk of failed mobilization and requirement for bone marrow harvest,[19] and mobilization efficiency (i.e., rate).[20] Some data suggest that low $CD34^+$ yield is associated with mutations in specific CH genes, including *PPM1D,*[21, 22] *TP53,*[21] and *DNMT3A,*[22] while other studies found no difference in $CD34^+$ yield by CH status.[23, 24] Taken together, these data suggest that CH may contribute to inefficient $CD34^+$ mobilization. Thus, CH prior to auto-HCT may be important to consider in risk stratification (along with other known risk factors) and for informing selection of patients who are more likely to benefit from plerixafor use.

Neutrophil and Platelet Engraftment

In cases of delayed engraftment or total engraftment failure after HCT, patients are at increased risk for severe infections, hemorrhage, relapse, and death.[25-27] Delayed engraftment also necessitates prolonged hospital stays, leading to increased costs and resource utilization. It has been hypothesized

that bone marrow engraftment may be delayed in patients with CH prior to HCT (i.e., in apheresis products).

Pre-HCT CH has consistently shown a negative effect on platelet engraftment, but the impact on neutrophil engraftment has had mixed results. In MM, the median time to platelet engraftment was 23 days later for patients with CH than those without ($p<0.0001$); there was no effect of CH on neutrophil engraftment.[28] The association of CH with platelet engraftment in MM was replicated in a gene-specific study (i.e., *DNMT3A*- and *PPM1D*-CH)[22] and in patients with lymphoma, who also had prolonged neutrophil recovery.[24] Post-HCT CH was also associated with prolonged neutrophil engraftment.[23] Taken together, these data suggest that CH may impact auto-HCT morbidity due to delayed hematopoietic engraftment, especially platelet engraftment.

Therapy-Related Myeloid Neoplasms

One of the most clinically challenging adverse events from cancer treatment, including HCTs, is tMNs. Defined as myeloid malignancies that occur after radiation or chemotherapy, tMNs are aggressive, treatment refractory malignancies with dismal survival rates.[29, 30] Although tMNs were historically believed to occur as a result of DNA damage from cytotoxic treatment, recent evidence shows that mutations that drive tMN pathogenesis, such as CH, are present prior to treatment, persist, and may expand.[31-33] In HCT, evidence largely suggests that CH mutations increase in number and VAF after HCT, but longer-term may become more stable (**Table S1**, **Supplementary Information**). This post-HCT expansion of CH is hypothesized to increase risk for progression to tMN.

Risk for tMNs is the most consistently studied outcome in the context of CH and auto-HCT. Of the 12 studies reporting effects of CH on tMN, 8 included sufficient data for meta-analysis. One of the excluded articles had no tMN cases in patients without CH, so an OR could not be calculated (there were three tMN cases in patients with CH).[21] The combined OR for the development of tMN for auto-HCT patients with CH compared to those without was 3.65 (95%CI 2.18-6.10) (**Figure 3A**). As assessed by

funnel plots, publication bias (**Figure S1**) and heterogeneity (I^2=23%) for the tMN outcome were low; however, differences in the impact of CH on tMN are apparent when considering cancer type. In lymphoma, risk for tMN was increased 4- to 7-fold in patients with CH at auto-HCT.[19, 34, 35] Using meta-analysis, the odds estimate for tMN in lymphoma patients with CH compared to those without CH is 4.96 (95%CI 2.14-11.52) (**Figure S2**). In line with biology of DNA damage driving tMNs, the effect of CH on tMN risk persisted when considering only DNA repair pathway mutations (DRP; i.e., *PPM1D*, *TP53*, *RAD21*, *BRCC3*);[34] in fact, the most frequent mutations in tMN cases were *PPM1D* and *TP53*, and having more than one CH mutation increased 10-year cumulative incidence of tMN (**Table S2**).[19, 35] The study that reported no difference in tMN incidence in patients with lymphoma by CH status only included seven cases of tMN, potentially limiting power to detect a statistical difference.[24] Contrary to findings in lymphoma, studies in MM did not find a significant association between CH before auto-HCT and risk for tMN (pooled OR 1.66, 95% CI 0.74-3.72) (**Figure S2**).[20, 36, 37] Risk for tMN was increased in MM HCT patients who received immunomodulatory (IMiD) drugs, but this risk was not potentiated by CH.[20]

Four studies included cohorts of mixed lymphoid diagnoses and found associations between CH and risk for tMNs after HCT despite various study designs.[21, 38-40] Most of the CH mutations had low VAFs (<2%) at auto-HCT and non-*DNMT3A* mutation VAFs significantly increased from auto-HCT to tMN (1% to 37%, p=0.002);[39] acquisition of additional CH mutations commonly occurred before tMN diagnosis.[38] Another study that found a 6-fold increased risk of tMN (p=0.003) for patients with non-*DNMT3A*- and non-*TET2*-CH at auto-HCT provides further evidence supporting the DNA damage hypothesis for tMNs, since the association with tMN risk was only observed after exclusion of non-DRP CH mutations.[40] Thus, presence of CH, especially in DRP genes, may be associated with increased risk for tMNs after auto-HCT but the absolute risk for tMNs, which are extremely rare events, remains low. Factors driving selective clonal expansion and evolution to promote progression to tMN have not been fully elucidated.

Survival

Disparate results on the impact of CH on survival after auto-HCT exist (**Table 1; Table S1**). Using meta-analysis of available data, auto-HCT patients with CH are at increased risk of death compared to those without CH (HR 1.38, 95%CI 1.20-1.58) (**Figure 3B**); however, due to skewing of the funnel plot, publication bias cannot be ruled out (**Figure S1**). Two studies report associations between CH and non-relapse mortality (NRM),[19, 41] especially driven by tMN and cardiovascular disease. While studies found that CH overall was an independent predictor of OS,[19, 24] some found that survival effects were specifically driven by DRP-CH,[24, 34] which may further speak to the impact of tMN or DNA damage repair effects on poor outcomes (**Table S2**).

The effect of CH on survival after auto-HCT was persistent when stratified by lymphoid cancer type (**Figure S3**), but the effect seems to be mediated by treatment in MM. Specifically, significant associations between CH and OS or progression-free survival (PFS) have been observed in MM patients treated with auto-HCT, but the negative impact dissipates when considering patients who received IMiD maintenance therapy.[20, 22, 36, 37] Furthermore, the effect of CH on NRM has not been observed in patients with MM.[28, 36] There was also no association with OS detected in patients with mantle cell lymphoma.[42]

Taken together, these data suggest that CH may be particularly important for auto-HCT patients with lymphoma, especially if the mutations occur in the DRP pathway; referral to cardiology and monitoring for tMN development may be especially critical. The negative effects of CH on survival in patients with MM may be abrogated by treatment with IMiD maintenance.

Allo-HCT

CH Metrics and Prevalence

In allo-HCT, most studies analyzed <100 genes for CH; the most common VAF thresholds were >0.5% and >2% (23%, 3/13 studies each, **Figures 2A & 2B**). Most studies with prevalence data assessed CH before allo-HCT (69%, 9/13), with two studies reporting CH status before and after (15%), and two studies (15%) only assessing CH after allo-HCT. In allo-HCT, CH can be measured in the donors and/or

recipients. Most allo-HCT studies measured CH in recipients (9/13, 69%), of which three also included measurement of CH in all the paired donors; four studies (31%) focused primarily on CH measurement in donors (**Table S1**). The median CH prevalence reported for allo-HCT donors was 16.0% (range 4.0%-23.8%) and was similar in studies of matched-related donors (MRDs, 17.0%), most of whom were over 50 years (**Figure 2D**). A study with young matched unrelated donors (MUDs) identified CH at a VAF >2% in one donor, but in 44% at a VAF ≥0.1%.[43] The studies with mixed donor pools both assessed low-VAF CH (≥0.5%), but donors were younger in the study with the lower prevalence.[44, 45] Studies measuring CH in recipients were heterogenous, with differences in factors such as recipient diagnosis, treatment, and timing of sample relative to HCT, resulting in diverse measures of CH prevalence (**Figure 2D**). The median prevalence of CH in recipients (31%, range 4.5%-62%) was higher than donors. The study with a low prevalence in myeloid malignancy patients assessed CH post-HCT from young donors.[46] All studies (4/4) that measured CH in recipients prior to allo-HCT had a CH prevalence >15% (range 18%-62%) (**Table S2**).

Donor Cell Leukemia

Donor cell leukemia (DCL) is a rare but serious complication that may arise after allo-HCT, wherein the recipient is diagnosed with a *de novo* leukemia that develops from engrafted cells of donor origin. Data consistently show that donor CH successfully engrafts in recipients via HCT regardless of donor type (**Supplementary Information**); thus, it has been hypothesized that donor CH may increase risk for DCL. All three of the included articles that investigated DCL suggest an association with donor CH. Specifically, donor CH was associated with higher incidence of DCL[47] and progression to MDS[48] in MRD HCTs (**Table S1**). A study with MRDs and MUDs found that recipient DCL mutations were detected in 83% (5/6) of donors.[44] Thus, similar to tMN after auto-HCTs, DCL may be increased after allo-HCT from a CH-positive donor, but this event remains rare so identification of additional factors or second hits that drive progression is warranted.

Relapse

Relapse of the original malignancy is the most frequent cause of treatment failure and mortality after allo-HCT, occurring in up to 45% of patients.[49] Identifying factors that contribute to recipients' immune system evading after initial response to HCT is a critical first step to decreasing risk for relapse.

Although most published data do not show statistically significant associations between donor CH status and relapse (**Table 2**),[45, 50-53] pooled analysis suggests there may be an effect. Meta-analysis of the effect of CH on relapse across allo-HCT studies suggests decreased risk for relapse (HR 0.80, 95%CI 0.68-0.94) associated with CH (**Figure 4A**), with little evidence of publication bias (**Figure S4**). This result persists when removing one study that quantified CH in recipients rather than donors[54] (HR 0.76, 95%CI 0.60-0.96) and a trend persists when assessing studies that included only related donors (HR 0.83, 95%CI 0.61-1.14) (**Figure S5**). The beneficial effect of CH in MRDs was largely driven by *DNMT3A*-CH,[47] which was also seen in patients with various donor types who were treated with calcineurin-based graft-versus-host disease (GVHD) prophylaxis.[44] Pooled analysis estimated a 33% decreased risk of relapse (HR 0.67, 95%CI 0.48-0.94) for patients receiving allo-HCT from *DNMT3A*-CH donors. Conversely, donor *ASXL1*- and *TP53*-CH showed a trend for increased relapse in AML patients treated with allo-HCT.[55] Taken together, the literature suggests that donor CH may influence relapse in allo-HCT; however, the impact likely varies based on multiple factors, such as CH mutation, donor type, and treatments received.

Survival

Most data do not suggest an impact of CH on survival after allo-HCT, with only one study (1/7) reporting an association between CH overall with OS (**Table 2; Table S1**). The study showing an effect between CH and OS in allo-HCT differed from the others because CH was measured in recipients, rather than donors, prior to HCT.[54] Meta-analysis also suggests that CH does not impact OS in allo-HCT (HR 1.00, 95%CI 0.82-1.22), with moderate heterogeneity (I^2=46%) (**Figure 4B; Figure S4**); this result is

unchanged when removing the study that measured CH in recipients[54] (HR 0.93, 95%CI 0.80-1.08). As with other outcomes, gene- and subgroup-specific effects between CH and survival have been found (**Table S2**). For example, donor *DNMT3A*-CH was associated with improved OS (pooled HR 0.80, 95%CI 0.66-0.98)[44, 47] and PFS after allo-HCT, largely driven by patients who did not receive post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis.[44] An OS benefit was also noted in MDS and AML patients who received HCT in non-CR from donors with CH.[47] Suggestive trends for improved disease-free survival, NRM, and chronic GVHD (cGVHD) relapse free survival have also been reported, specifically in early-stage patients whose MSDs had CH, but these findings were limited by small sample sizes.[53] Finally, a study that showed beneficial effects of *TET2*- and *ASXL1*-CH on OS, but recipient pre-HCT samples were used to classify CH status so impact of donor CH on survival was unclear.[50]

Adverse Events: Graft-Versus-Host Disease

GVHD is a major cause of morbidity, NRM, and inferior quality of life in patients after allo-HCT.[56, 57] Presenting with multi-organ tissue inflammation or fibrosis, GVHD occurs as one of three syndromes: acute GVHD (aGVHD), cGVHD, or GVHD overlap syndrome. GVHD occurs when transplanted donor cells recognize the host (i.e., recipient's) cells as foreign and initiate an immune reaction against the host tissues. Thus, it is hypothesized that CH-mediated immune activation[58] in donor cells may contribute to increased risk for GVHD.

The literature on the impact of CH on risk for GVHD shows conflicting results (**Table 2; Table S1**). Meta-analysis does not indicate that donor CH increases risk for cGVHD (HR 0.85, 95%CI 0.54-1.35), but high heterogeneity in the data exists (I^2=85%) (**Figure 4C; Figure S4**). Sensitivity analyses without the stratified study[44] (HR 0.94, 95%CI 0.58-1.54) and confined to studies with related donors (HR 1.01, 95%CI 0.55-1.86) also do not detect an association between donor CH overall and risk for cGVHD, but high heterogeneity persists (I^2=77% and 83%, respectively) (**Figure S5**). However, donor CH was a predictor of risk for cGVHD in two studies, including one confined to MRDs in which the effect was largely driven by

donor *DNMT3A*-CH (**Table S2**).[47, 51] The gene-specific effect of donor *DNMT3A*-CH on risk for cGVHD was also found in a mixed cohort of patients who did not receive PTCy.[44] Studies in MSDs, young MUDs, and mixed donor types did not show an association between donor CH and cGVHD risk.[43, 45, 52, 53] When including all studies with sufficient data to quantify aGVHD risk, there is a trend toward increased risk for aGVHD with CH (OR 1.38, 95%CI 0.88-2.16); however, moderate heterogeneity is noted (I^2=43%) (**Figure 4D; Figure S4**). These results are consistent when including only studies that quantified CH using donor samples[45, 47, 52, 53] (OR 1.59, 95%CI 0.90-2.82), and studies with only related donors (HR 1.64, 95%CI 0.77-3.46), but there is high heterogeneity (**Figure S5**). Thus, the impact of donor CH on GVHD risk remains unclear, but data indicate that differences likely exist depending on factors such as donor type, prophylaxis received, and CH mutation.

DISCUSSION

In this review, we summarize the literature that investigates the impact of CH on outcomes of patients treated with HCT. Across studies, the median prevalence of CH in donors was 23% (range 4%-75%), corresponding to almost one quarter of HCT donors harboring CH mutations at the time of HCT. CH was more prevalent in auto-HCT than allo-HCT donors and was detected in both younger MUDs and older MRDs. Notably, in auto-HCT, CH is measured in patients who have been exposed to chemotherapy or radiation and, therefore, are more likely to have CH,[14] and characteristics of the mutations may be different compared to allo-HCTs where CH is measured in healthy donors. Data across auto- and allo-HCT show that CH mutations generally expand in recipients after HCT and may lead to the acquisition of new, more aggressive cancer-promoting mutations (**Supplementary Information**). Based on existing evidence, we posit that these CH dynamics likely explain the observed increased risk for secondary hematologic malignancies, including tMNs in lymphoma patients treated with auto-HCT and DCL in allo-HCT recipients. Aside from these consistencies, the current data is largely mixed regarding the impact of donor CH on other clinical outcomes with many nuances.

In auto-HCT, clinical outcomes associated with CH status include decreases in PBSC mobilization (5/7 studies report at least gene-specific effects), OS in patients with lymphoma (3/5 studies report at least gene-specific effects), OS in patients with MM if not treated with IMiDs, and increases in time to platelet engraftment (3/3 studies). While lymphoma patients with CH have an almost 5-fold increased risk for tMNs after auto-HCT, the impact of CH on risk for tMNs in patients with MM receiving auto-HCT is less certain. This may be explained, at least partly, by the fact that MM patients rarely receive cytotoxic chemotherapy or alkylating agents (except for melphalan as part of auto-HCT), which are strongly associated with tMN risk, whereas these treatments are standard for patients with lymphoma. In fact, experimental data suggests that CH tMN risk in MM may be treatment- and mutation-specific (e.g., higher in *TP53*-CH that survives myeloablative conditioning).[59] There is also no direct evidence to support an association between CH and risk of relapse for patients treated with auto-HCT; however, some studies report higher NRM in patients with CH, suggesting that mortality in patients with CH may not be due to relapse, but perhaps driven by tMNs or cardiovascular events, which are both increased with CH.[13, 32]

Although CH mutations engraft, expand, and persist, there are limited clinical outcomes consistently associated with donor CH status in allo-HCT. Time to leukocyte engraftment and DCL risk were associated with donor CH status in MRDs,[47] but not quantified in other allo-HCT studies. Although not statistically significant within most individual studies, pooled analysis suggests that donor CH may associate with an estimated 20% decreased risk of relapse after allo-HCT. Data suggests that donor *DNMT3A*-CH largely drives the observed associations with relapse, with the effect specifically seen in patients treated with calcineurin-based GVHD prophylaxis.[44, 47] These findings are particularly important with the increased use of PTCy,[60] given that the association between donor CH and increased cGVHD and improved relapse, PFS, and OS were only observed in patients not treated with PTCy.[44] These

nuanced results emphasize the importance of considering differences in patient characteristics, treatments, and CH mutations when translating findings to inform patient care.

The impact of donor CH with risk for aGVHD and cGVHD after allo-HCT also has mixed results across the literature, with moderate to high heterogeneity detected in meta-analyses. These differences may, in part, be due to differences in the study populations, which impact patient risk and, therefore, statistical power to detect associations. For example, the one study that reported a statistical difference in aGVHD risk by donor CH status included late-aGVHD and a relatively homogenous population.[52] Discordance in cGVHD findings across studies is challenging to explain, although the studies that do report an increased risk from donor CH found that the effect was driven by specific subgroups, including patients with *DNMT3A*-CH donors[47] who did not receive PTCy[44] or only when considering requirement for immunosuppression therapy.[51] Three studies that did not show a statistically significant association between donor CH and cGVHD had results in the opposite direction, where recipients with CH-negative donors trended toward higher incidence of cGVHD.[43, 52, 53] Other clinical outcomes explored in allo-HCT were reported in single studies and not associated with donor CH.

Overall, few clinical outcomes have been consistently associated with donor CH across HCT studies, with more disparate findings in allo-HCT than auto-HCT. Numerous factors could contribute to these differences. For example, study population affects baseline risk for outcomes, impacting the number of events and statistical power. Study characteristics important to consider include patient and donor demographics, diagnoses and treatment history, type of donors, conditioning regimens and intensity, graft source, GVHD prophylaxis (e.g., use of PTCy), duration of follow-up, etc. These criteria tend to be more diverse in allo-HCT studies and, thus, may help explain lack of associations and replication across studies. Another important difference between studies is the binary classification criteria of CH status. The genes, mutation types, and VAF thresholds used to define CH vary drastically across studies; however, most condense these criteria to classify individuals simply as CH positive or

negative. The gene-specific effects detected in some studies provide evidence that this approach is not optimal for identifying clinically important CH risk. Statistical power also plays a role in this context. Across the CH literature, including the studies here, *DNMT3A* is by far the most mutated gene. As such, power to detect gene-specific differences is higher when looking at *DNMT3A* than other CH mutations. For example, the largest allo-HCT studies detected *DNMT3A*-CH in 8% (40/500) and 9% (157/1727) of donors; the next most commonly mutated gene was *TET2*, which was mutated in 2% of donors in both studies.[44, 47] Therefore, statistical power is limited to detect gene-specific differences in even the largest studies, let alone most other studies that are smaller. This poses challenges since evidence across the CH literature points to stronger effects for less commonly mutated CH genes (e.g., *TP53, U2AF1,* and spliceosome mutations). Finally, substantial evidence suggests that low-VAF (i.e., <2%) CH in young and older donors engrafts via HCT and commonly expands; however, the various limits of CH detection across studies pose challenges for defining the clinically meaningful VAF cutoff for CH in HCT.

CONCLUSION AND CALL TO ACTION

The literature summarized suggests that CH may impact HCT outcomes; however, studies lack consistent conclusions and suffer from limited power. As well, CH mutation-specific findings (e.g., *DNMT3A*) may arise from higher prevalence of such mutations, rather than true absence of effect for less common mutations. To address these limitations, we suggest that next studies incorporate rigorous case-control designs and leverage larger combined data sets, which would require extensive collaboration and data sharing. The optimal gene panel and VAF threshold for NGS testing in HCT-CH research has yet to be defined, but standardized approaches across studies would improve reproducibility and make future clinical translation of findings more straightforward. Currently, we support use of any myeloid gene panel, as these contain the most clinically important CH genes and regions; a panel that also captures *PPM1D* (especially the fifth and sixth exons), which are common in CH but not necessarily myeloid malignancies, is preferred. Evidence suggests that low-VAF CH (e.g.,

≥0.5%) engrafts and persists in recipients, but the clinical impact of these mutations is unclear; this lower CH threshold (i.e., <1% or 2% VAF) may be particularly important for studies in allo-HCT (i.e., healthy donors) and MUDs (i.e., young donors). Weighing sensitivity, specificity, and cost-effectiveness, we recommend sequencing using molecular barcodes and coverage sufficient to detect VAFs ≥1%. Uniform methods to filter and classify CH mutations are equally as important; when in doubt, focusing on previously annotated variant lists[61, 62] is a reasonably conservative approach. Xenogenic mouse models may also provide a useful tool for studying the link between CH and adverse HCT outcomes (e.g., GVHD), especially for less common CH mutations.[58, 63, 64] There may also be important effects of CH on other clinical outcomes, which deserve further study. For example, cGVHD could be explored with respect to severity and phenotype of the syndrome or with attention to patient-reported outcomes. The impact of CH on HCT late effects including secondary malignancies and adverse cardiovascular outcomes, among others, also warrants additional study. Finally, we acknowledge that, while much attention has been paid to the impact of CH in older MRDs in allo-HCTs, clinical application of these findings is much more complex: Assuming CH were clinically available as part of routine donor evaluation, avoiding older MRDs with CH would reflect only one major aspect of clinical decision-making. Other major considerations would include patient-level disease risk, urgency in time to HCT, baseline probability to identify well matched MUDs, availability, and prioritization of alternative donors (e.g., related haploidentical and mismatched unrelated donors), and the possibility of CH being detected in any of these donors. While CH is not yet a validated and actionable biomarker in this regard, a future state following greater evidence development could include CH, akin to other donor selection strategies above the traditional uses of donor age and HLA matching (e.g., selection of killer cell immunoglobulin-type receptor-advantageous donors or *CCR5*Δ32 homozygous donors for HIV-infected recipients). In summary, evidence suggests that CH may be impactful for patients treated with auto-HCT but, in allo-

HCT especially, the heterogeneity of current literature poses insurmountable challenges to make concrete recommendations for or against donor CH testing in HCT.

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TABLES

	PBSC Mobilization	Platelet Engraftment	Neutrophil Engraftment	Cardiovascular Events	Incidence of tMN	Relapse	PFS	NRM	OS
Lymphoma									
Gibson et al. [19]	↓	-	-	-	↑	-	-	↑	↓[a]
Lackraj et al. [24]	ns	Delayed[a]	Delayed	-	ns	ns	ns	-	↓[a]
Husby et al. [34]	-	-	-	ns	↑[a]	-	-	-	ns[a]
Yan et al. [35]	-	-	-	-	↑[a]	-	-	ns[a]	ns
Eskelund et al. [42]	-	-	-	-	-	-	-	-	ns
Multiple Myeloma									
Mouhieddine et al. [20]	↓	-	-	ns	ns	-	↓[b]	-	↓[b]
Stelmach et al. [22]	ns[a]	ns[a]	-	-	-	-	-	-	ns[ab]
Li et al. [28]	-	Delayed	ns	-	ns	-	-	ns	ns
Wudhikarn et al. [36]	-	-	-	ns[b]	ns	ns	ns	ns	ns
Mouhieddine et al. [37]	-	-	-	↑	ns	-	ns	-	ns
Rhee et al. [65]	-	-	-	↑	-	-	-	-	-
Mixed Lymphoid									
Gifford et al. [18]	↓	-	-	-	-	-	-	-	-
Hazenberg et al. [21]	ns[a]	-	-	-	↑	-	-	-	ns
Ortmann et al. [23]	ns	-	Delayed[a]	-	-	-	-	-	-
Gramegna et al. [38]	-	-	-	-	↑	-	-	-	-
Soerensen et al. [39]	-	-	-	-	↑	-	-	-	-
Soerensen et al. [40]	-	-	-	-	↑[a]	-	-	-	-
Slavin et al. [41]	-	-	-	-	-	-	-	↑	-

[a]Mutation-specific effects; [b]Treatment-specific effects

Table 1. Summary of the literature investigating the effects of clonal hematopoiesis (CH) on clinical outcomes in autologous hematopoietic cell transplantation. Data are stratified by disease type. Down arrows (↓) mean outcome is decreased in presence of CH; up arrows (↑) mean outcome is increased in presence of CH; hyphen (-) means outcome is not reported. Data for specific effects are reported in **Supplementary Information**. NRM, non-relapse mortality; ns, no significant effect; OS, overall survival; PBSC, peripheral blood stem cell; PFS, progression-free survival; tMN, therapy-related myeloid neoplasm

	PBSC Mobilization	Neutrophil/ Platelet Engraftment	Leukocyte Engraftment	Incidence of DCL	aGVHD	cGVHD	Relapse	PFS	NRM	OS
Matched Unrelated Donors										
Wong et al.[43]	-	-	-	-	-	ns	-	-	-	-
Matched Related Donors										
Frick et al.[47]	ns	-	↑	↑	ns	↑[a]	↓[a]	↑[a]	ns	ns
Boettcher et al.[48]	-	-	-	↑	-	-	-	-	-	-
Matched Sibling Donors										
Oran et al.[52]	-	ns	-	-	↑	ns	ns	ns	-	-
Gillis et al.[53]	-	-	-	-	ns	ns[a]	ns	-	ns	ns
Mixed Donor Types										
Gibson et al.[44]	-	-	-	-	ns	ns[ab]	ns[ab]	↑[a]	ns	ns[ab]
Kim et al.[45]	-	ns	-	-	ns	ns	ns	-	ns	ns
Heumuller et al.[46]	-	-	-	-	-	-	-	-	-	-
Grimm et al.[50]	-	-	-	-	-	-	ns	-	-	ns[a]
Newell et al.[51]	-	ns	-	-	ns	↑	ns	-	-	ns
Imus et al.[54]	-	-	-	-	ns	-	ns	↓	↑	↓
Tanaka et al.[55]	-	ns[a]	-	-	-	-	ns[a]	-	-	-
Lueck et al.[66]	-	-	-	-	-	-	-	-	-	-

[a]Mutation-specific effects; [b]Treatment-specific effects

Table 2. Summary of the literature investigating the effects of clonal hematopoiesis (CH) on clinical outcomes in allogeneic hematopoietic cell transplantation. Data are stratified by donor type. Down arrows (↓) mean outcome is decreased in presence of CH; up arrows (↑) mean outcome is increased in presence of CH; hyphen (-) means outcome is not reported. Data for specific effects are reported in **Supplementary Information**. aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; DCL, donor cell leukemia; NRM, non-relapse mortality; ns, no significant effect; OS, overall survival; PBSC, peripheral blood stem cell; PFS, progression-free survival

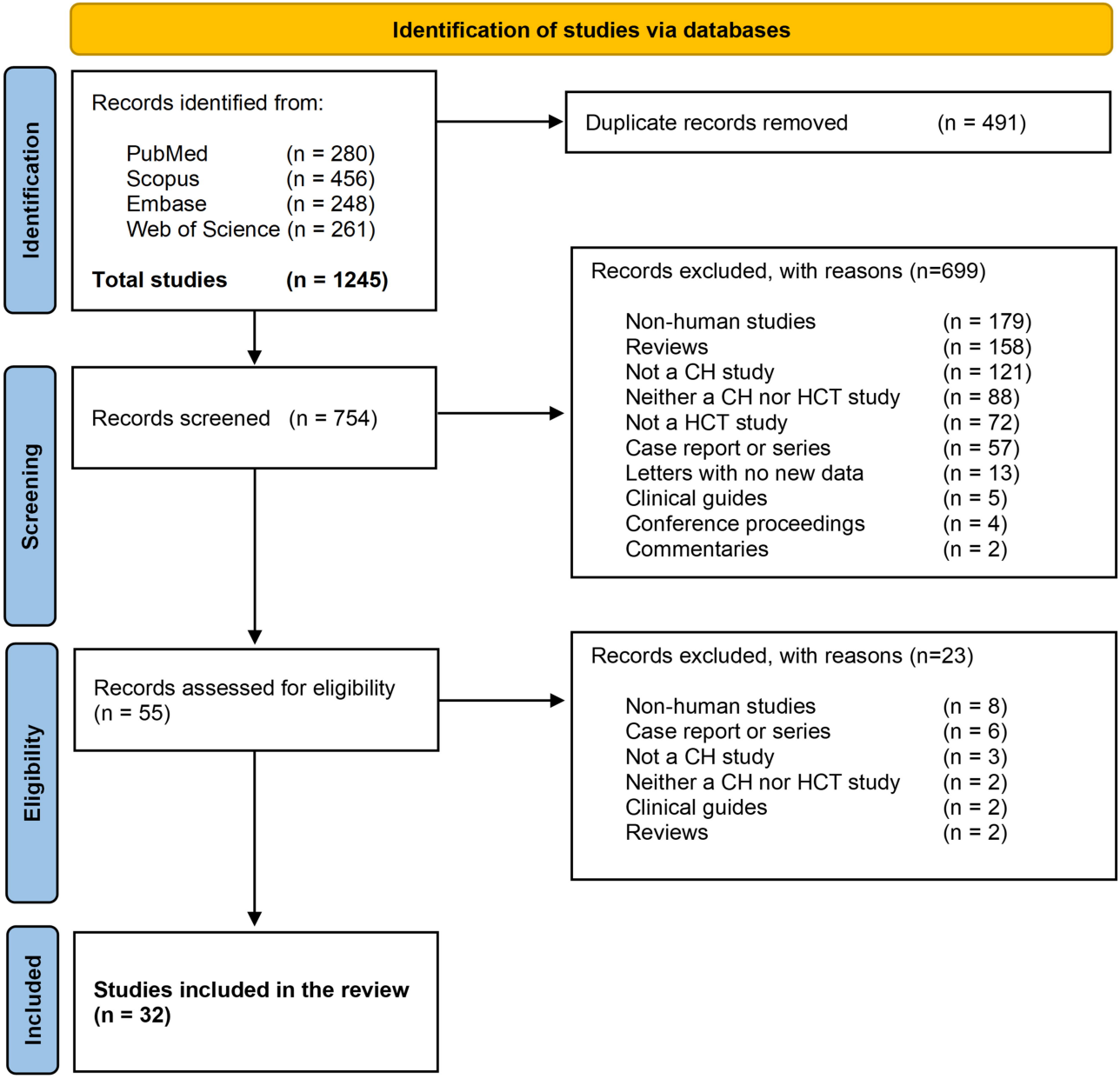
FIGURE LEGENDS

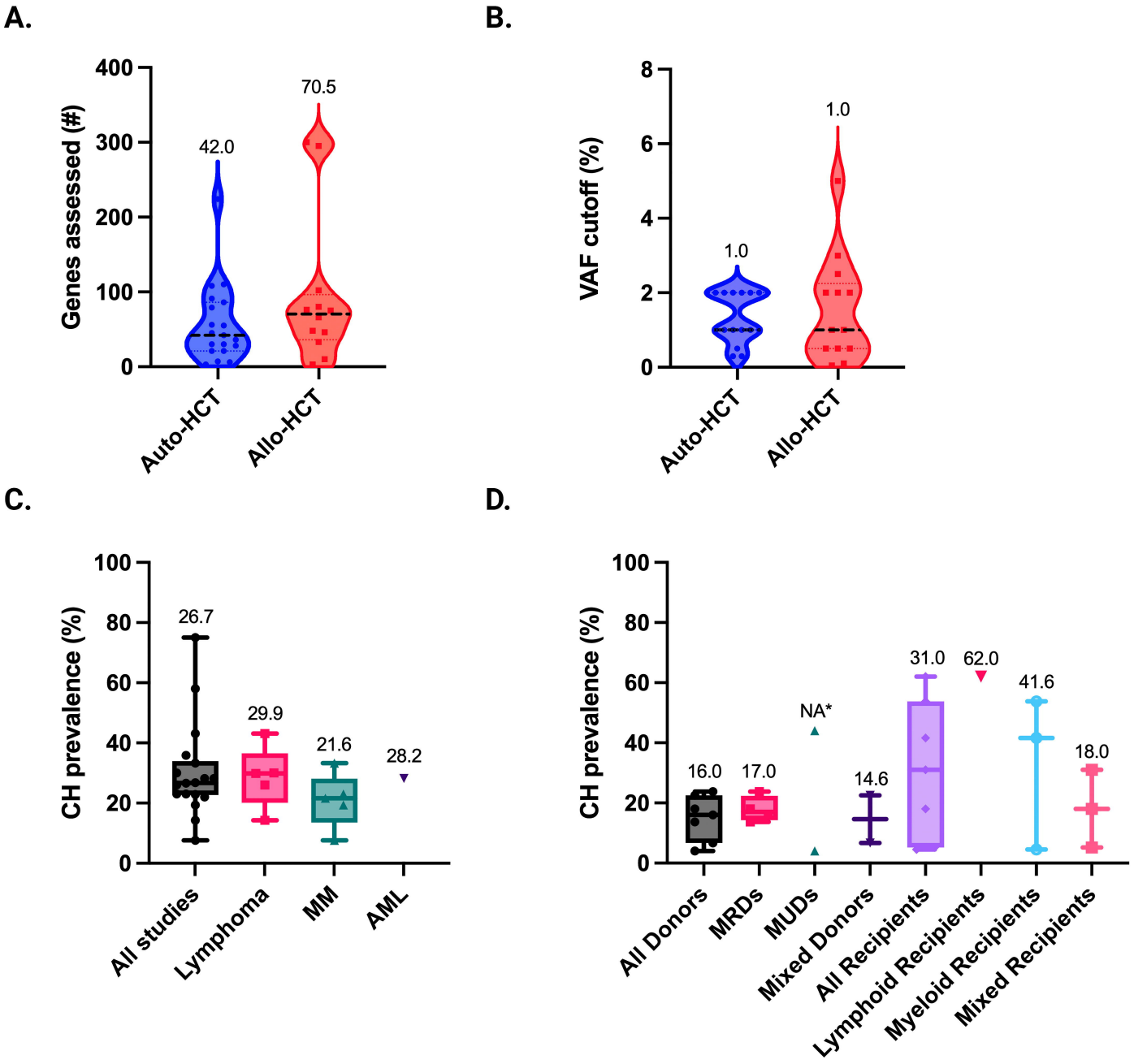
Figure 1. PRISMA flow diagram for the included studies that investigated hematopoietic cell transplantation (HCT) outcomes based on clonal hematopoiesis (CH) status.

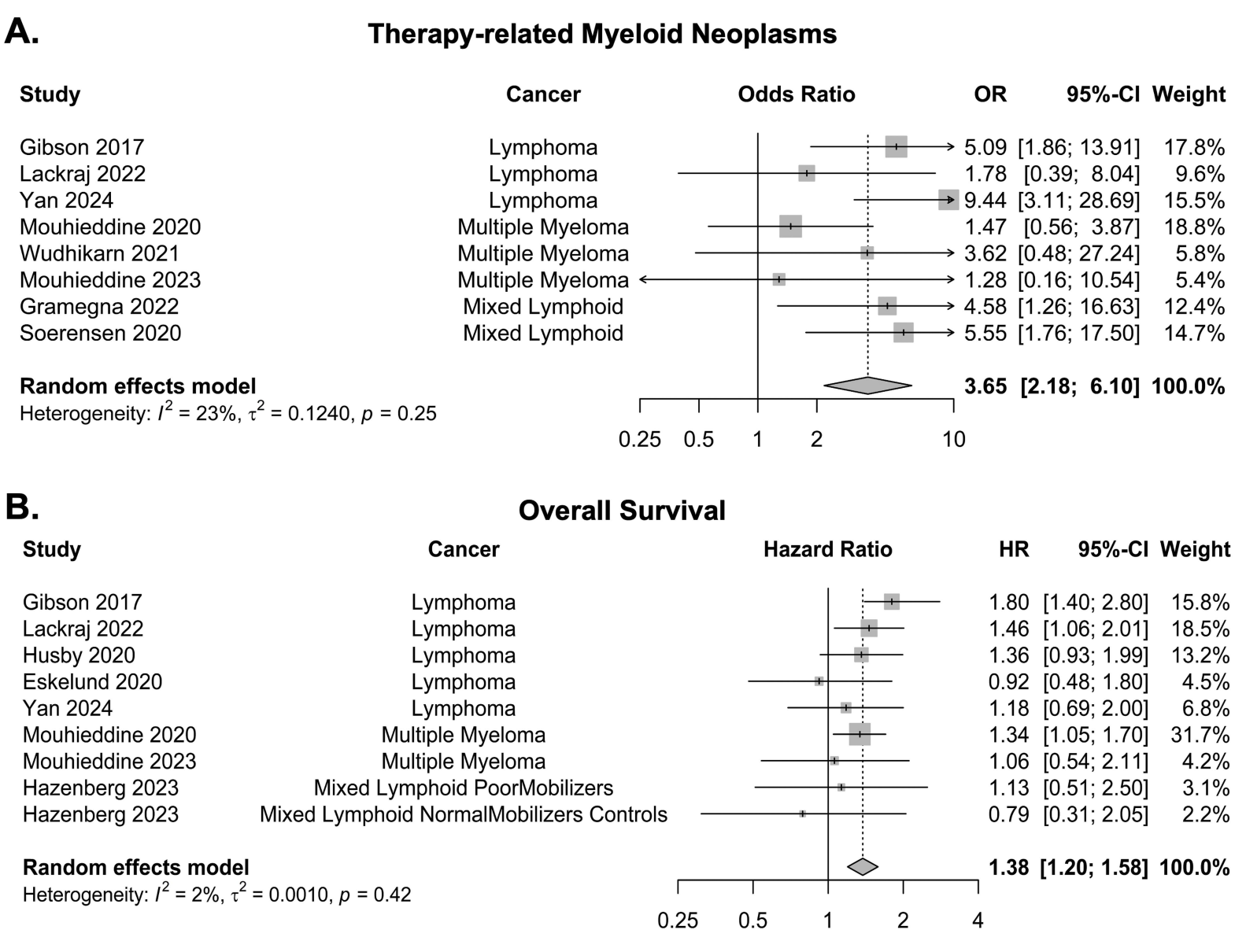
Figure 2. Clonal hematopoiesis (CH) metrics and results in published studies. **(A)** Number of genes assessed for CH mutations in autologous (auto-) and allogeneic (allo-) hematopoietic cell transplantation (HCT). **(B)** Variant allele frequency (VAF) cutoff used to define CH by HCT type. **(C)** Prevalence of CH reported in auto-HCT studies. Data is presented for all auto-HCT studies and studies that included lymphoma, multiple myeloma (MM), or acute myeloid leukemia (AML) patients only. **(D)** Prevalence of CH reported in allo-HCT studies. Data is presented for donors and recipients. Numbers presented are medians; bars are the minimum and maximum values.
MRDs: Matched-related donors; MUDs: Matched-unrelated donors. *Results for MUDs come from a single study that defined CH at a VAF of ≥2% and ≥0.1%.

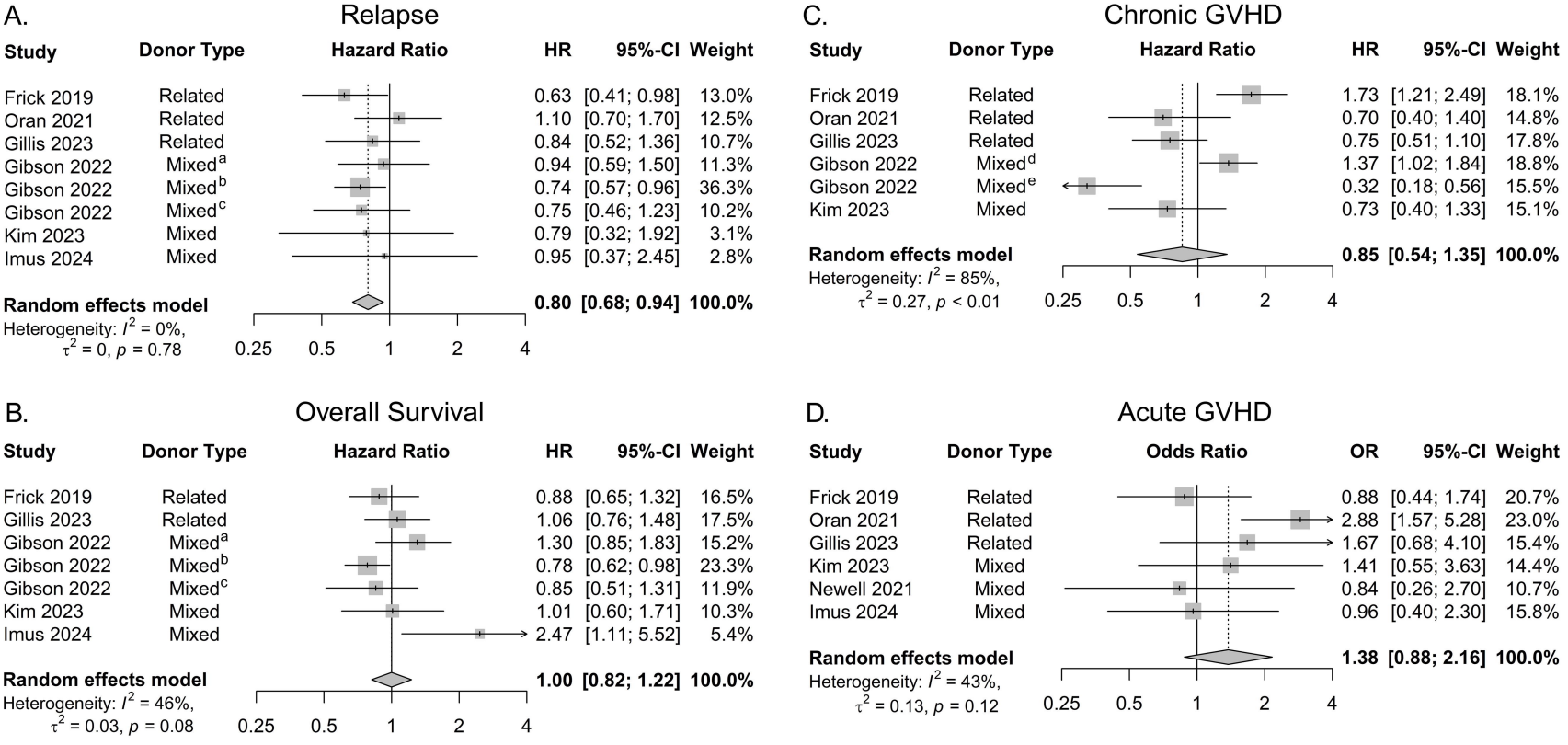
Figure 3. Meta-analyses of studies assessing clonal hematopoiesis as a risk factor for clinical outcomes in patients treated with autologous hematopoietic cell transplantation. **(A)** Forest plot for the outcome of therapy-related myeloid neoplasms. **(B)** Forest plot for the outcome of overall survival.
[a]Poor peripheral blood stem cell mobilizers; [b]Normal peripheral blood stem cell mobilizers

Figure 4. Meta-analyses of studies assessing clonal hematopoiesis (CH) as a risk factor for clinical outcomes in patients treated with allogeneic hematopoietic cell transplantation. **(A)** Forest plot for the outcome of relapse. **(B)** Forest plot for the outcome of overall survival. **(C)** Forest plot for the outcome of chronic graft-versus-host disease (GVHD). **(D)** Forest plot for the outcome of acute GVHD.
[a]Other CH (non-*DNMT3A*, non-*TET2*); [b]*DNMT3A*-CH only; [c]*TET2*-CH only; [d]*DNMT3A*-CH, no post-transplant cyclophosphamide; [e]*DNMT3A*-CH, received post-transplant cyclophosphamide


Identification of studies via databases
Identification
Records identified from:
PubMed (n = 280)
Scopus (n = 456)
Embase (n = 248)
Web of Science (n = 261)
Total studies (n = 1245)
Duplicate records removed (n = 491)
Screening
Records screened (n = 754)
Records excluded, with reasons (n=699)
Non-human studies (n = 179)
Reviews (n = 158)
Not a CH study (n = 121)
Neither a CH nor HCT study (n = 88)
Not a HCT study (n = 72)
Case report or series (n = 57)
Letters with no new data (n = 13)
Clinical guides (n = 5)
Conference proceedings (n = 4)
Commentaries (n = 2)
Eligibility
Records assessed for eligibility (n = 55)
Records excluded, with reasons (n=23)
Non-human studies (n = 8)
Case report or series (n = 6)
Not a CH study (n = 3)
Neither a CH nor HCT study (n = 2)
Clinical guides (n = 2)
Reviews (n = 2)
Included
Studies included in the review (n = 32)


A.
Genes assessed (#)
400
300
200
100
0
42.0
70.5
Auto-HCT
Allo-HCT
B.
VAF cutoff (%)
8
6
4
2
0
1.0
1.0
Auto-HCT
Allo-HCT
C.
CH prevalence (%)
100
80
60
40
20
0
26.7
29.9
21.6
28.2
All studies
Lymphoma
MM
AML
D.
CH prevalence (%)
100
80
60
40
20
0
16.0
17.0
NA*
14.6
31.0
62.0
41.6
18.0
All Donors
MRDs
MUDs
Mixed Donors
All Recipients
Lymphoid Recipients
Myeloid Recipients
Mixed Recipients


A.
Therapy-related Myeloid Neoplasms
Study
Cancer
Odds Ratio
OR
95%-CI
Weight
Gibson 2017
Lymphoma
5.09 [1.86; 13.91] 17.8%
Lackraj 2022
Lymphoma
1.78 [0.39; 8.04] 9.6%
Yan 2024
Lymphoma
9.44 [3.11; 28.69] 15.5%
Mouhieddine 2020
Multiple Myeloma
1.47 [0.56; 3.87] 18.8%
Wudhikarn 2021
Multiple Myeloma
3.62 [0.48; 27.24] 5.8%
Mouhieddine 2023
Multiple Myeloma
1.28 [0.16; 10.54] 5.4%
Gramegna 2022
Mixed Lymphoid
4.58 [1.26; 16.63] 12.4%
Soerensen 2020
Mixed Lymphoid
5.55 [1.76; 17.50] 14.7%
Random effects model
3.65 [2.18; 6.10] 100.0%
Heterogeneity: I^2 = 23%, τ^2 = 0.1240, p = 0.25
0.25
0.5
1
2
10
B.
Overall Survival
Study
Cancer
Hazard Ratio
HR
95%-CI
Weight
Gibson 2017
Lymphoma
1.80 [1.40; 2.80] 15.8%
Lackraj 2022
Lymphoma
1.46 [1.06; 2.01] 18.5%
Husby 2020
Lymphoma
1.36 [0.93; 1.99] 13.2%
Eskelund 2020
Lymphoma
0.92 [0.48; 1.80] 4.5%
Yan 2024
Lymphoma
1.18 [0.69; 2.00] 6.8%
Mouhieddine 2020
Multiple Myeloma
1.34 [1.05; 1.70] 31.7%
Mouhieddine 2023
Multiple Myeloma
1.06 [0.54; 2.11] 4.2%
Hazenberg 2023
Mixed Lymphoid PoorMobilizers
1.13 [0.51; 2.50] 3.1%
Hazenberg 2023
Mixed Lymphoid NormalMobilizers Controls
0.79 [0.31; 2.05] 2.2%
Random effects model
1.38 [1.20; 1.58] 100.0%
Heterogeneity: I^2 = 2%, τ^2 = 0.0010, p = 0.42
0.25
0.5
1
2
4


A.
Relapse
Study
Donor Type
Hazard Ratio
HR
95%-CI
Weight
Frick 2019 Related 0.63 [0.41; 0.98] 13.0%
Oran 2021 Related 1.10 [0.70; 1.70] 12.5%
Gillis 2023 Related 0.84 [0.52; 1.36] 10.7%
Gibson 2022 Mixed[a] 0.94 [0.59; 1.50] 11.3%
Gibson 2022 Mixed[b] 0.74 [0.57; 0.96] 36.3%
Gibson 2022 Mixed[c] 0.75 [0.46; 1.23] 10.2%
Kim 2023 Mixed 0.79 [0.32; 1.92] 3.1%
Imus 2024 Mixed 0.95 [0.37; 2.45] 2.8%
Random effects model 0.80 [0.68; 0.94] 100.0%
Heterogeneity: I^2 = 0%,
τ^2 = 0, p = 0.78
0.25 0.5 1 2 4
B.
Overall Survival
Study
Donor Type
Hazard Ratio
HR
95%-CI
Weight
Frick 2019 Related 0.88 [0.65; 1.32] 16.5%
Gillis 2023 Related 1.06 [0.76; 1.48] 17.5%
Gibson 2022 Mixed[a] 1.30 [0.85; 1.83] 15.2%
Gibson 2022 Mixed[b] 0.78 [0.62; 0.98] 23.3%
Gibson 2022 Mixed[c] 0.85 [0.51; 1.31] 11.9%
Kim 2023 Mixed 1.01 [0.60; 1.71] 10.3%
Imus 2024 Mixed 2.47 [1.11; 5.52] 5.4%
Random effects model 1.00 [0.82; 1.22] 100.0%
Heterogeneity: I^2 = 46%,
τ^2 = 0.03, p = 0.08
0.25 0.5 1 2 4
C.
Chronic GVHD
Study
Donor Type
Hazard Ratio
HR
95%-CI
Weight
Frick 2019 Related 1.73 [1.21; 2.49] 18.1%
Oran 2021 Related 0.70 [0.40; 1.40] 14.8%
Gillis 2023 Related 0.75 [0.51; 1.10] 17.8%
Gibson 2022 Mixed[d] 1.37 [1.02; 1.84] 18.8%
Gibson 2022 Mixed[e] 0.32 [0.18; 0.56] 15.5%
Kim 2023 Mixed 0.73 [0.40; 1.33] 15.1%
Random effects model 0.85 [0.54; 1.35] 100.0%
Heterogeneity: I^2 = 85%,
τ^2 = 0.27, p < 0.01
0.25 0.5 1 2 4
D.
Acute GVHD
Study
Donor Type
Odds Ratio
OR
95%-CI
Weight
Frick 2019 Related 0.88 [0.44; 1.74] 20.7%
Oran 2021 Related 2.88 [1.57; 5.28] 23.0%
Gillis 2023 Related 1.67 [0.68; 4.10] 15.4%
Kim 2023 Mixed 1.41 [0.55; 3.63] 14.4%
Newell 2021 Mixed 0.84 [0.26; 2.70] 10.7%
Imus 2024 Mixed 0.96 [0.40; 2.30] 15.8%
Random effects model 1.38 [0.88; 2.16] 100.0%
Heterogeneity: I^2 = 43%,
τ^2 = 0.13, p = 0.12
0.25 0.5 1 2 4

SUPPLEMENTARY INFORMATION

Methods

Search Strategy

We systemically searched for articles indexed in PubMed, Scopus, Embase (Elsevier), and Web of Science (Clarivate). The general search terms used to search for the articles were ("clonal hematopoiesis" OR "clonal haematopoiesis" OR "clonal hematopoiesis of indeterminate potential" OR "age-related clonal hematopoiesis" OR "age-related clonal hematopoiesis" OR “CHIP” OR “ARCH”) AND (“stem cell transplantation” OR “hematopoietic stem cell transplantation” OR “haematopoietic stem cell transplantation” OR “bone marrow transplant*” OR “stem cell transplant*” OR “hematopoietic stem cell transplant*” OR “haematopoietic stem cell transplant*” OR “hematopoietic cell transplant*” OR “haematopoietic cell transplant*”). For Scopus, Embase, and Web of Science, a language filter was used to specify documents written in English, and a document type filter was used to specify articles or articles in press. For PubMed, language (English) and species (human) filters were applied.

Our search strategy within the four selected databases yielded 1,245 articles (280 from PubMed, 456 from Scopus, 248 from Embase, and 261 from the Web of Science. EndNote 20 (Clarivate Analytics LLC, USA) was used to remove any duplicates and select eligible studies from the database findings and other sources. After removal of 491 duplicate articles, we performed title and abstract screening for 754 articles.

Search Results

The process of selection of the final studies included is outlined using a PRISMA flow diagram (**Figure 1**). Out of the articles screened, 32 articles were included in this review. Among the 699 excluded articles, 179 (26%) were non-human studies, 158 (23%) were reviews, 121 (17%) were not CH papers, 88 (13%) were neither CH nor HCT papers, 72 (10%) were not HCT papers, 57 (8%) were case reports or series, 13 (2%) were letters with no new data, 5 (1%) were clinical guides, 4 (1%) were conference

proceedings, and 2 (0.3%) were commentaries. The 32 included studies are summarized in **Table S1**; the CH-related results are summarized in **Table S2**.

Results

Auto-HCT

Clonal Expansion and Evolution

In this article, we define clonal expansion as an increase in the VAF of pre-existing CH mutations; clonal evolution is acquisition of new CH mutations. Both scenarios represent progression of CH and, theoretically, increased CH-related risk.

Evidence largely suggests that CH mutations increase in number and VAF after auto-HCT, but longer-term may become stable. In mantle cell lymphoma patients, 98% (53/54) of post-treatment CH mutations were present before starting chemotherapy.[42] The median VAF of CH mutations increased after induction and after HCT (1.5% to 2.8%, p=0.001), but stabilized to an age-related rate during follow-up (growth rate 5.1% per year). A small cohort study found that, from the time of auto-HCT to tMN, VAFs of *DNMT3A* clones did not increase significantly (0.8% to 2.1%, p=0.63), whereas non-*DNMT3A* clones did (1% to 37%, p=0.002).[39] Most CH mutations (86%) were at VAFs < 2% before auto-HCT. A study in patients with post-HCT CH (n=18) showed that there was a mean 6.3-fold increase in VAF from auto-HCT to first follow-up.[23] Of the 28 CH mutations detected after auto-HCT, 9 (32%) had a VAF ≥ 2% and 7 (25%) had a VAF between 0.5% and 2% before auto-HCT. Evidence of clonal evolution was found with 12 CH mutations detected after but not before auto-HCT, which either arose from HCT or were below the level of detection (i.e., VAF < 0.5%).[23] As with other studies, longer-term, mutations became stable over time.

Relapse: Lymphoid Malignancies

No studies (0/3) reported an association between CH status and relapse after auto-HCT. In lymphoma, CH was not associated with time to relapse or PFS.[24] In MM, cumulative incidence of relapse

(CIR) did not significantly differ between patients with versus without CH (73.9% vs 64.9%, p=0.67).[36] Although the incidence of NRM was higher in patients with CH (4.3% vs 1.2% if no CH), this difference did not meet statistical significance (p=0.08).

Relapse and Survival: Myeloid Malignancies

One retrospective study in patients with AML who received auto-HCT investigated persistence of *DNMT3A, TET2*, and *ASXL1* (DTA) mutations.[16] Patients were considered to have CH if DTA mutations persisted despite complete remission (CR) and clearance of other pathogenic variants; if the DTA mutation was not detected at CR it was classified as a leukemia mutation. With these classifications, there was no association between CH status after auto-HCT and OS (HR 0.79, 95% CI 0.41-1.51, p=0.44) or PFS (HR 0.75, 95% CI 0.42-1.33, p=0.287). Relapse rate was also similar between patients with and without CH-like mutations (51.6% vs 41.7%, respectively, p=0.04).[16] Caution should be noted before weighing these findings as evidence of the impact of CH in HCT, since it is unclear whether persistence of DTA mutations at CR in AML patients is truly CH versus measurable residual disease.

Other Adverse Events: Lymphoid Malignancies

Several less frequently investigated outcomes were reported. In lymphoma, pre-HCT DRP mutations (not CH in general) were associated with more inpatient days during years 2 to 5 after auto-HCT (median 20 vs. 2 days; p=0.0025) and intensive care unit admissions.[34] Other adverse events investigated in lymphoma that did not meet statistical significance were risk for severe infections, cardiovascular events, and transfusions.[34] However, in patients with MM, pre-HCT CH was associated with risk for cardiovascular events (including heart failure, coronary artery disease, and stroke)[37, 65] and recurrent bacterial infections.[37] In another study of MM patients, although CH was not associated with overall risk for venous thromboembolism, there was evidence that incidence > 3 months after discontinuing lenalidomide was higher in patients with CH than those without CH.[36]

Allo-HCT

CH Engraftment: Heterogenous Groups

Data consistently show that donor CH successfully engrafts in recipients via HCT regardless of donor type. In a study of MRD HCTs, all donor CH mutations engrafted in the recipients except for one *SF3B1* mutation.[47] This was in line with another study in that detected all (7/7) matched sibling donor (MSD) CH mutations in recipients at day 56 or 90 post-HCT[53] and a third study that detected 84.3% (86/102) of donor CH mutations in recipients 12 months after allo-HCT.[44] When looking at *DNMT3A*-CH specifically, all *R882* mutations engrafted (10/10, 100% vs. 46/54, 85.2% for non-*R882*) and the VAF was significantly higher in recipients than non-*R882* mutations (**Table S2**).[44] Additional evidence of CH engraftment was presented in a study of young MUDs, where 19 CH mutations were identified in 44% (11/25) of donors, all of which engrafted in recipients.[43] A study that assessed long-term engraftment of CH mutations identified donor-engrafted CH in 50% (5/10) of donor CH cases.[48]

Clonal Expansion and Evolution: Myeloid Malignancies, Young Unrelated Donors

Two studies investigated rates of clonal expansion and evolution in HCTs with young MUDs but had differing methods and results. In one study (median donor age 26 years, range 20-58), most (74%) of the CH mutations persisted a year after allo-HCT, despite low VAFs (median 0.25%) in donors.[43] Of engrafted mutations, 3 (16%) expanded in recipients beyond VAF ≥2% at days 100 and 365. Moreover, within the first 100 days after allo-HCT, the mutational burden in recipients increased from 19 to 33 CH mutations (p=0.048). Some of these new mutations were present in MUDs at low levels (< 0.1%) and others were *de novo* mutations that arose after HCT. The second study included elderly individuals (n=22) at a median follow-up of 9.8 years after allo-HCT from young MUDs (<41 years old), and found a single *BCORL1* CH mutation in a recipient; however, the mutation was not detected in the donor or recipient pre-HCT at a VAF ≥0.05%.[46]

Clonal Expansion and Evolution: Heterogenous Groups

Other studies provide additional insight into the relationship between CH expansion and evolution with outcomes. In MRDs, engrafted CH mutations expanded after HCT and decreases in VAF paralleled decreases in donor chimerism and relapse.[47] Similarly in MSDs, donor CH mutations expanded most rapidly until day +56 then stabilized.[53] Furthermore, CH mutations expanded more rapidly than germline mutations, and non-donor-derived pathogenic mutations expanded most rapidly. In long-term allo-HCT survivors, CH mutations expanded more rapidly in recipients than MRDs (p=0.03).[48] Gene-specific differences in clonal expansion have also been reported (**Table S2**) and a study found that patients with the largest expansion of *DNMT3A*-CH died from HCT-related complications within a year.[51]

CH Persistence: Myeloid Malignancies

Multiple studies investigated the persistence of CH-related mutations throughout treatment, including HCT, for myeloid malignancies. In a study of AML patients who achieved CR after induction, post-CR CH persisted in 91% (39/43) of patients during and after post-CR treatment; however, 95% (20/21) of the patients who received allo-HCT had clearance of the post-CR CH.[55] In another study of AML patients who received allo-HCT, persistence of CH-related mutations from diagnosis to CR only occurred in 28% (21/75) of patients and did not affect 4-year cumulative instance of relapse or OS; post-HCT persistence of these mutations was not studied.[50]

Peripheral Blood Stem Cell Mobilization: Related Donors

One study reported results on differences in PBSC mobilization by CH status and found that in MRDs, CH status was not associated with the amount of harvested $CD34^+$ cells.[47]

Engraftment: Leukocytes, Neutrophils, Platelets, and Donor Cells

In MRD HCTs, the cumulative incidence of leukocyte engraftment at 15 days was higher in patients with CH+ donors.[47] Three studies found no difference in time to neutrophil or platelet

engraftment by donor CH status[45, 51, 52] and one study reported no difference in time to full donor chimerism by donor CH status.[51]

Other Adverse Events

Additional adverse outcomes reported in the allo-HCT studies include atrial fibrillation in-hospital, prolonged neutropenia, second primary malignancies, and telomere shortening. Although incidence of atrial fibrillation in-hospital was not statistically different between patients with and without pre-HCT DTA CH mutations, incidence was notably higher in patients with *DNMT3A*-CH (53% vs. 27% if no *DNMT3A*-CH).[66] Prolongation of neutropenia was associated with *TET2*-CH in AML HCT recipients.[55] Incidence of second malignancies (median follow-up: 13 years) was 6% and 14.8% in HCT recipients with CH+ and CH- donors, respectively; however, the two cases of second malignancy in recipients with CH+ donors were non-melanoma skin cancers.[43] Finally, one study investigated telomere shortening, a measure of aging, between donors and recipients of allo-HCT and found that the difference was equivalent to approximately 20 years of proliferative life history in the hematopoietic system of recipients; however, telomere shortening was not different between individuals with and without CH.[48]

Table S1. Summary of original studies investigating the association between clonal hematopoiesis (CH) and outcomes in hematopoietic cell transplantation (HCT).

Study	Study design	Donor type	Cancer type(s)	Sample size	Follow-up (median)	Outcome[a]	Effect
AUTOLOGOUS HCT							
Heini et al.[16]	RC	Self	AML	110	51.3 m	OS	No difference by CH status
							Early mortality (100 d) higher in CH (12.9 vs 1.3% if no CH, p=0.022)
						PFS	No difference by CH status (16.7 vs 26.9 mo if no CH, p=0.29)
						Relapse	No difference by CH status
Gifford et al.[18]	CS	Self	Lymphoid	96	NA	PBSC mobilization	CH more common in poor CD34+ mobilizers than normal mobilizers (28% vs 3.4%, p=0.018)
Gibson et al.[19]	PC	Self	Lymphoma	413 (401 PC)	10 y	NRM	Higher in CH (26.2%) than non-CH (11.1%), p<0.01
						OS	Lower in patients with vs without CH (30.4% and 60.9%, respectively)
						PBSC mobilization	Patients with CH more likely to fail peripheral mobilization and required more days to collect sufficient stem cells
						tMN	14.1% (CH) vs 4.3% (no CH), p=0.002
							25.3% (multiple mutations) vs 9.9% (single mutation), p<0.001
Mouhieddine et al.[20]	RC	Self	MM	629	9.7 y	Cardiovascular events	No difference by CH status
						Clonal expansion/tMN	8/10 tMN cases had mutation present prior to HCT (4 with VAF < 1%)
						OS	Lower in patients with CH (5.3 vs 7.5 y if no CH; HR 1.34, p=0.02)
						OS (by treatment)	No IMiD maintenance group: CH worse OS (3.6 vs 6.6 y if no CH, p=0.013)
							Yes IMiD maintenance group: No difference by CH status
						PBSC mobilization	CH decreased efficiency compared to no CH (5.8 vs 8.3 cells/kg/day, p=0.03)
						PFS	Lower in patients with CH (2.2 vs 2.6 y if no CH; HR 1.45, p<0.001)

						PFS (by treatment)	No IMiD maintenance group: CH worse PFS (1.1 vs 1.8 y if no CH, p<0.001) Yes IMiD maintenance group: No difference by CH status
						tMN	CH prior to HCT not associated with increased risk (p=0.6)
Hazenberg et al.[21]	NCC	Self	Lymphoid	179 (for CH analysis)	43.6 m	OS	No difference by CH status in cases or controls
						PBSC mobilization	No difference in CH prevalence in poor mobilizers (31% vs 22% of controls, p=0.24)
						tMN	All patients who developed tMN (3/3) had CH at mobilization
Stelmach et al.[22]	PC	Self	MM	457	NA	OS	Gene-specific effects in patients not treated with maintenance (*Table S2*)
						PBSC mobilization	Gene-specific effects (*Table S2*)
						Platelet engraftment	Gene-specific effects (*Table S2*)
Ortmann et al.[23]	PC	Self	Lymphoid	81	2 y	Clonal evolution	12 new CH mutations detected post-HCT
						Clonal expansion	Increase in mean VAF from ~2% to ~9% at first follow-up, p=0.0002
						Neutrophil engraftment	Longer for patients with post-HCT CH (8.1 vs 6.7 d if no CH, p=0.008)
						PBSC mobilization	No difference by post-HCT CH status
Lackraj et al.[24]	RC	Self	Lymphoma	420	4.5 y	Baseline blood counts at HCT	No difference by CH status
						Neutropenia	Longer in CH (11.0 vs 10.7 d in no CH, p=0.01)
						OS (5-y)	Worse in CH (51.8 vs 59.3% in no CH, p=0.018)
						PBSC mobilization	No difference by CH status
						Platelet recovery	Longer in CH (15.3 vs 13.7 d in no CH, p=0.016)
						PFS	No difference by CH status
						Relapse	No difference by CH status
						tMN	No difference by CH status (3.3 vs 3.0% in no CH, p=0.45)
Li et al.[28]	RC	Self	MM	41	100 d	Neutrophil engraftment	No difference by CH status (20 vs 17 days in no CH, p=0.12)
						NRM	No difference by CH status (data NR)
						Platelet engraftment	Delayed in patients with CH (42 vs 19 days if no CH, p<0.0001)
						Severe infections	No difference by CH status (data NR)

						Survival	No difference by CH status (data NR)
						tMN	No difference by CH status (data NR)
Husby et al.[34]	PC	Self	Lymphoma	440	9.1 y	Cardiovascular events	No difference by CH status overall
						EFS	No difference by CH status overall
						ICU admission	No difference by CH status overall
						In-patient days	No difference by CH status overall
						OS	<1 y: AdjHR 1.12, 95% CI 0.73-1.73, p=0.6 ≥1 y: AdjHR 1.36, 95% CI 0.93-1.99, p=0.11
						Severe infections	No difference by CH status overall
						tMN	Increased risk if CH, AdjHR 6.5, 95% CI 2.34-18.03, p=0.0003
						Transfusions	No difference by CH status overall
Yan et al.[35]	RC	Self	Hodgkin lymphoma	321	6.5 y	NRM	No difference by CH status; gene-specific effects
						OS, relapse-related mortality	No difference by CH status
						tMN	Increased risk (AdjHR 4.5, CI 1.54-13.19)
Wudhikarn et al.[36]	CC	Self	MM	101	11 y	NRM & relapse	No difference by CH status
						OS	No difference by CH status (100.2 vs 135.6 mo if no CH, p=0.24)
						PFS	No difference by CH status
						tMN & SPM	No difference by CH status
						VTE	No difference by CH status (30% vs 24% if no CH, p=0.4) Time to VTE: CH more likely to have VTE > 3 mo after stopping IMiD (p=0.04)
Mouhieddine et al.[37]	RC	Self	MM	986 (529 received HCT)	5.5 y (HCT patients)	Bacterial infections	Increased in CH (p=0.01)
						Cardiovascular disease	Increased in CH (p=0.003)
						Cerebrovascular accidents, Coagulopathies	No difference by CH status
						OS	No difference by CH status (in HCT cohort: HR 1.06, CI 0.54-2.11, p=0.86)
						PFS	No difference by CH status (in HCT cohort: HR 0.92, CI 0.59-1.46, p=0.74)
						SPM (hematologic or solid)	No difference by CH status
Gramegna et al.[38]	CC	Self	Lymphoid	45	6 y	Clonal evolution (at tMN diagnosis)	Increase in the number of CH mutations from 16 to 46 from HCT to tMN

						Clonal expansion (at tMN diagnosis)	Increase in VAF from 13.2% at HCT to 33.2% at tMN, p<0.05; attributable to new mutations
						tMN	Pre-HCT CH more common in tMN cases than controls (58% vs 23%, p=0.029); VAF similar in cases and controls
Soerensen et al.[39]	PC	Self	Lymphoid who developed tMN	12	4 y	tMN	75% of patients had CH at HCT that persisted at tMN; 8/14 (57%) of CH mutations were <2% VAF at HCT
Soerensen et al.[40]	CC	Self	Lymphoid	72	3.5 y	Clonal expansion	1/5 pre-HCT CH mutations expanded at tMN (4/5 were no longer present at tMN)
						tMN	When excluding *DNMT3A* and *TET2*, increased in CH (OR 5.9, 95% CI 1.8-19.1, p=0.03)
Slavin et al.[41]	CC	Self	Lymphoid	39	2 y	NRM	NRM cases more likely to have pre-HCT CH (70% vs 24% of controls, p=0.002)
Eskelund et al.[42]	PC	Self	Mantle cell lymphoma	149	8 y	Clonal expansion	VAF increased after induction (median relative increase 44%) and after HCT (median relative increase 42%) but remained constant during follow-up (median relative increase 5%)
						OS	No difference by CH status (HR 0.92, CI 0.48-1.8, p=0.82)
Rhee et al.[65]	RC	Self	MM	1,036	5 y	Cardiovascular disease	Incidence higher in CH (21.1% vs 8.4%; HR 2.72, CI 1.69-4.39); also significant for individual outcomes (i.e., heart failure, coronary artery disease, and stroke)
ALLOGENEIC HCT							
Wong et al.[43]	RC	Matched unrelated	AML	25 donor-recipient pairs, young donors	1 y	Clonal evolution	Mutation burden increased at 100 d (from 19 pre-HCT to 33, p=0.048)
						Chronic GVHD	No difference by CH status (1-yr post-HCT, p=0.17); *Note:* limited sample size
						Engraftment	100% of donor CH (19/19) engrafted in recipients; 74% persisted through 1 y
Gibson et al.[44]	PC	Mixed donor types	Mixed	1,727 donors	5 y	Acute GVHD, NRM Chronic GVHD, Relapse, OS	No difference by CH status Effects only in *DNMT3A*-CH (*Table S2*)

						DCL	Difference by CH status not reported; 83% of recipient DCL mutations were detected in donors
						PFS	Improved PFS if donor CH VAF ≥1% (HR 0.79, 95%CI 0.66-0.95, p=0.011)
Kim et al.[45]	PC	Mixed donor types	Mixed	744 (372 donor-recipient pairs)	13 y	Acute GVHD (100-d)	No difference by donor CH status (80% vs 77% if no CH, p=0.49)
						Chronic GVHD (3-y)	No statistical difference by donor CH status (48% vs 64% if no CH, p=0.22)
						Neutrophil/platelet engraftment	No difference by donor CH status
						NRM (10-y)	No difference by donor CH status
						OS (10-y)	No difference by donor CH status (48% vs 41% in no CH, p=0.97)
						Relapse (10-y)	No difference by donor CH status
						SPM	No difference by donor CH status
Heumuller et al.[46]	CS	Mixed donor types	Myeloid	22 recipients who had young donors	9.8 y	Post-HCT CH	4.5% (1/22) patients had CH after HCT; not detectable in donor or recipient at HCT
Frick et al.[47]	RC	Related donors	Mixed	500 donors	3.3 y	Acute GVHD	Incidence not different by donor CH status
						Chronic GVHD	5-y incidence: higher if CH+ donor (53% vs 36% if CH- donor, p=0.008)
						Clonal expansion	21/22 donor CH mutations expanded linearly or disproportionately (i.e., doubling) over time in recipients
						DCL	More common if CH+ donor (2/82 vs 0/426 if CH- donor, p=0.026)
						Leukocyte engraftment	Faster if CH+ donor (15-day incidence 64% vs 51% if CH- donor, p=0.023)
						OS	No difference by donor CH status (AdjHR 0.88, 95% CI 0.65-1.32, p=0.43)
						NRM	No difference by CH status
						PBSC mobilization	No difference by CH status
						Relapse	5-y CIR/P: lower if CH+ donor (p=0.027)
Boettcher et al.[48]	CS	Related donors	Mixed	84	16 y	Clonal expansion	VAF increased in recipients relative to donors (p=0.03)

				(42 donor-recipient pairs)		DCL/MDS	1/5 donor-engrafted CH cases progressed to MDS in donor and recipient; no inherited predisposition
						Telomere length	T/S greater in recipients than donors (~20-y premature aging, p <0.0001) T/S not different by CH status in donors (0.6 vs 0.75 if no CH) or recipients (0.45 vs 0.55 if no CH)
Grimm et al.[50]	PC	Mixed donor types	AML	113 recipients	4.4 y	Clonal persistence	35.4% of CH mutations in 28.0% of patients persisted from diagnosis to CR; not associated with OS or relapse
						OS	71.7% (CH) vs 55.1% (No CH), p=0.06
						Relapse	CIR: No difference by CH status (35.3% vs 38.7% if no CH, p=0.41)
Newell et al.[51]	CC	Mixed donor types	Mixed	290 recipients (confirmed in donors)	25.8 m (CH cases); 37.2 m (controls)	Acute GVHD	No difference by donor CH status (53% vs 57.8% in no CH, p=0.74)
						Chronic GVHD	Higher incidence of chronic GVHD requiring immunosuppressive therapy if CH+ donor (73% vs 56% if CH- donor, p=0.045)
						Donor chimerism	No difference in time to full donor chimerism by CH status
						GVHD-free relapse-free survival	No difference by donor CH status
						Neutrophil/platelet engraftment	No difference by donor CH status
						OS	No difference by donor CH status
						Relapse	No difference by donor CH status
Oran et al.[52]	PC	Matched sibling	AML/MDS	363 donors	5.3 y	Acute GVHD	6-m cumulative incidence higher in CH (e.g., grade II-IV 53% vs 28% in no CH, HR 2.4, p < 0.001)
						Chronic GVHD	No difference by CH status (5-y incidence 23% vs 35% if no CH, p=0.2)
						Neutrophil/platelet engraftment	No difference by donor CH status
						PFS	No difference by donor CH status
						Relapse	No difference by donor CH status
						Treatment-related mortality	No difference by donor CH status
Gillis et al.[53]	RC	Matched sibling	Myeloid	299 donors; 13 recipients	48.4 m	Acute GVHD	Higher incidence if CH+ donor (37.5% vs 25.1%), but cumulative incidence ns (HR 1.35, p=0.47)

						Chronic GVHD	No difference by CH status (HR 0.75, 95% CI 0.51-1.1, p=0.14)
						CRFS, DFS, NRM	No difference by donor CH status; suggestive decreased risk for early-stage patients (p<0.05), but small numbers
						GRFS	No difference by donor CH status
						OS	No difference by donor CH status
Imus et al.[54]	RC	Mixed donor types	Lymphoid	97 recipients	32 m	aGVHD	No difference by CH status
						Cytokine release syndrome	No difference by CH status
						NRM	Higher if recipient had pre-HCT CH (35% vs 11%, HR 3.4)
						OS	Worse if recipient had pre-HCT CH (3-y OS 47% vs 78% if no CH, HR 3.1)
						PFS	Worse if recipient had pre-HCT CH (3-y PFS 39% vs 60% if no CH)
						Relapse	No difference by CH status
Tanaka et al.[55]	PC	Donor types NR	AML	43 recipients (longitudinal)	467 d	Clonal persistence	91% of post-CR CH mutations persisted until HCT; 95% of post-CR CH mutations were eradicated by HCT
						Relapse	CIR: No difference by CH status (p=0.17)
Lueck et al.[66]	CC	Mixed donor types	Myeloid only for CH analysis	52 recipients for CH analysis	NA	AFiH	No statistical difference by CH status (46 vs 21% in no CH, p=0.08)

[a]Clonal expansion is defined here as an increase in the VAF of pre-existing CH mutations; clonal evolution is acquisition of new CH mutations.

AdjHR, adjusted hazard ratio; **AFiH**, atrial fibrillation in-hospital; **Allo**, allogeneic; **AML**, acute myeloid leukemia; **CC**, case-control; **CH**, clonal hematopoiesis; **95% CI**, 95% confidence interval; **CIR**, cumulative incidence of relapse; **CIR/P**, cumulative incidence of relapse or progression; **CR**, complete response; **CRFS**, cGVHD relapse-free survival; **CS**, cross-sectional; **d**, days; **DCL**, donor cell leukemia; **DFS**, disease-free survival; **EFS**, event-free survival; **GRFS**, GVHD-free relapse-free survival; **GVHD**, graft-versus-host disease; **HCT**, hematopoietic cell transplantation; **HR**, hazards ratio; **ICU**, intensive care unit; **IMiD**, immunomodulatory imide drugs; **m**, months; **MDS**, myelodysplastic syndromes; **MM**, multiple myeloma; **NA**, not applicable/available; **NCC**, nested case-control; **NRM**, non-relapse mortality; **OS**, overall survival; **OR**, odds ratio; **PBSC**, peripheral blood stem cells; **PC**, prospective cohort; **PFS**, progression-free survival; **RC**, retrospective cohort; **SPM**, second primary malignancy; **tMN**, therapy-related myeloid neoplasm; **T/S**, telomere to single copy ratio, a measure of telomere length; **VAF**, variant allele frequency; **VTE**, venous thromboembolism; **y**, years

Table S2. Summary of clonal hematopoiesis (CH) results in original studies investigating the association between CH and outcomes in hematopoietic cell transplantation (HCT).

Study	Samples used	Sample collection timepoint	Age, median (range)	Genes (n)	Sequencing depth	VAF included/ median	CH prevalence	Gene-specific effects: Outcome[a]	Gene-specific effects: Results
AUTOLOGOUS HCT									
Heini et al.[16]	BM, PB, or cell apheresis product (2.8%)	Post-HCT (2.8% pre-HCT)	54 (40-61)	3, persistence of DTA mutations after HCT	NR	≥2% NR	28.2%	OS PFS	DTA: No difference (54.4 vs 80.9 if no DTA, p=0.44) DTA: No difference (16.7 vs 26.9 if no DTA, p=0.29)
Gifford et al.[18]	Cell apheresis products	Pre-HCT	63 (19-72)	6	1209 (median)	≥2% 3.3%	13.5%	NR	NR
Gibson et al.[19]	Cell apheresis products	Pre-HCT + pre/post-HCT (n=12)	NR	86	NR	≥2%	29.9%	OS (10-y)	*PPM1D* 20.8% vs 39.9% if no *PPM1D* (p=0.02)
Mouhieddine et al.[20]	Cell apheresis products	Pre-HCT	58 (24-83)	224	978x	≥1% 2.7%	21.6%	OS PFS	*DNMT3A R882*: 1 y if no IMiD maintenance (p=0.008 vs no CH) *DNMT3A R882*: 0.9 y if no IMiD maintenance (p=0.007 vs no CH)
Hazenberg et al.[21]	PB	Pre-HCT	59 (51-64)	28	5619x (mean)	≥1% 2.6%	26.8%	PBSC mobilization CD34+ yield	*PPM1D* mutations more common in poor mobilizers (20 vs 1 control, p=0.005) *TP53* mutations only in poor mobilizers (p=0.06) Lower in *PPM1D*- or *TP53*-CH (4.26 vs 8.2 x10^6/kg if no CH, p=0.007)
Stelmach et al.[22]	Cell apheresis products	Pre-HCT	59 (28-72)	56	NR	≥1% NR	33.3%	CD34+ yield OS Platelet engraftment	*DNMT3A* and/or *PPM1D*: lower yield (4.65 vs 7.5 x10^6/kg if no CH, p=0.009) *DNMT3A* and/or *PPM1D*: in patients not treated with maintenance, decreased OS compared to no CH (p=0.048) *DNMT3A* and/or *PPM1D*: Delayed platelet engraftment compared to no CH (p=0.02)

								Platelet transfusions	*DNMT3A* and/or *PPM1D*: 1.41x more platelet transfusions 20 days after HCT than non-CH patients (p=0.02)
Ortmann et al.[23]	Cell apheresis products or PB	Pre- and post-HCT	60 (IQR 51-68)	55	14,572 (median)	>0.5% 10.7%	22% (post-HCT)	Neutrophil engraftment	DRP: longest time to neutrophil engraftment (10.5 vs 7.38 if non-DRP CH and 6.66 d if no CH, p=0.001)
Lackraj et al.[24]	Cell apheresis products	Pre-HCT	53 (18-70)	36	NR	Not set 2.9%	43.1%	Platelet recovery OS	*PPM1D*: longer time, HR 1.92 (FDR p=0.0005) DTA: HR 1.56 (p=0.017) *PPM1D* in DLBCL: HR 2.41 (FDR p=0.02)
Li et al.[28]	BM MNC minus CD38/CD138+	Pre-HCT	57 (43-62) (IQR 61-62)	7	>1500x	≥2% NR 3.2%	NR (CH identified in 6 and matched to patients without CH)	NR	NR
Husby et al.[34]	Cell apheresis products	Pre-HCT	57 (47-63)	21	~4000x (median)	≥2% 4.9%	26%	Cardiovascular events ICU admission In-patient days OS (median) Severe infection tMN Transfusions	DRP: ns DRP: AdjHR 1.85 (p=0.035) DRP: 20 vs 2 d if no DRP (p=0.003) DRP: 2.2 vs 9.0 y if no DRP (p=0.0005) ≥1 y OS AdjHR 2.37 (p=0.0007) DRP: AdjHR 1.48 (ns) DRP: AdjHR 5.63 (p=0.003) DRP: RR 1.46 (ns)
Yan et al.[35]	PB	Pre-HCT	34 (18-71)	91	>1000x	≥1%	14.3%	NRM tMN	*TP53* and/or *PPM1D* associated with 4.17-fold hazard compared to no CH *TP53*: All patients with *TP53*-CH developed tMN *TP53* and/or *PPM1D* associated with 7.29-fold risk compared to no CH

									DNMT3A: No patients with *DNMT3A*-only CH developed tMN Cumulative incidence increased with number of CH mutations and VAF
Wudhikarn et al.[36]	BM MNC minus CD38/CD138+	Pre-HCT	61 (54-67)	42	NR	NR 6.0%	23%	NR	NR
Mouhieddine et al.[37]	PB	Newly diagnosed (pre-HCT)	63 (27-93)	110	113x (mean)	≥2% 7%	10% (7.6% in HCT patients)	OS, PFS Clonal evolution (n=52 w/ serial samples)	DTA: No difference by CH status No difference by CH clone size CH prevalence increased following initiation of therapy (5.8% to 25%); most common emergent mutation was *DNMT3A*
Gramegna et al.[38]	Cryopreserved HSCs	Pre-HCT and tMN (for cases)	63 (34-71)	45	≥ 500x	≥1% 13.2%	23% (controls) and 58% (tMN cases)	tMN	*TP53* mutations most common at tMN; *RUNX1, NRAS, KRAS* mutations only detected at tMN (not prior to HCT)
Soerensen et al.[39]	Cell apheresis products and BM MNCs (at tMN)	Pre-HCT and tMN	63 (37-69)	30	≥ 3000x	≥0.3% 1.1%	75% (pre-HCT)	Clonal expansion	*DNMT3A* low-level expansion from HCT to tMN (0.8-2.1%, ns)
Soerensen et al.[40]	Cell apheresis products	Pre-HCT		30, excluded *DNMT3A* and *TET2* from primary analysis	~8800x (median)	≥0.3% NR	NR	tMN	*Non-DNMT3A* high-level expansion from HCT to tMN (1-37%, p=0.002)
Slavin et al.[41]	Mobilized PB HSCs	Pre-HCT	65 (39-75)	79	560x (mean)	>2% NR	35.9%	NR	NR
Eskelund et al.[42]	BM or PB	MRD-negative post-HCT + paired pre-HCT (n=59)	58 (IQR 61-62)	21	> 5000x (mean)	≥1% 3.2%	30%	Clonal expansion	DRP genes (*PPM1D, RAD21, BRCC3*): greater increase in VAF than non-DRP (1.7 vs 0.48, p=0.008) after induction

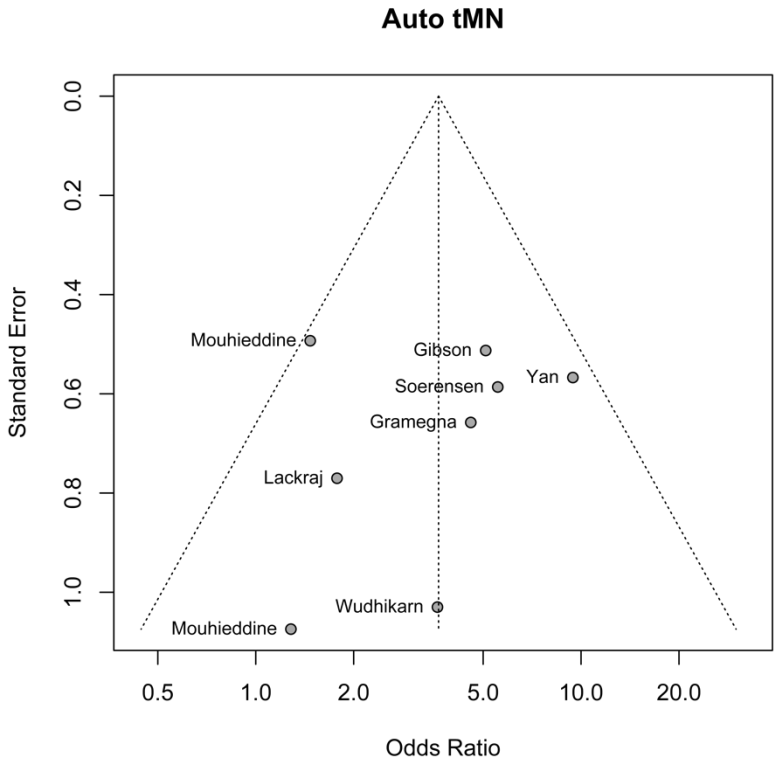
Rhee et al.[65]	PB	Pre-HCT	60 (35-77)	108	560x (mean)	≥2% NR	19.4%	Cardiovascular disease	Incidence increased with increasing number of CH mutations No difference in risk by VAF *ASXL1*: Strongest risk for cardiovascular disease; also risk for heart failure and stroke
ALLOGENEIC HCT									
Wong et al.[43]	BM or PB	Pre- and post-HCT; donors only pre-HCT	26 (20-58) for donors	80	9200x (mean)	≥0.1% 0.25%	at > 2% VAF: 4% at ≥ 0.1% VAF: 44% (donors)	NR	NR
Gibson et al.[44]	PB or BM	Pre-HCT	51 (40-80)	46	≥ 1000x	≥0.5% NR	22.5% (donors)	Death/OS PFS Relapse Chronic GVHD Clonal expansion	No PTCy, *DNMT3A*: HR 0.65 (p=0.01) *DNMT3A*: HR 0.72 (p=0.003) No PTCy, *DNMT3A*: HR 0.59 (p=0.014) No PTCy, *DNMT3A*: HR 1.37 (p=0.04) *DNMT3A R882:* 10/10 engrafted and had higher VAF at 12-months than non-*R882* (VAF 5% vs 2% if non-*R882*, p=0.004)
Kim et al.[45]	PB	Pre-HCT	48 (17-71)	33	8540x (mean)	>0.5% 1.86%	18% (recipients) 6.7% (donors)	NR	NR
Heumuller et al.[46]	PB	Post-HCT (≥ 5 y)	78 (69-82)	NR	≥ 200x	≥0.05% NR	4.5% (recipients)	NR	NR
Frick et al.[47]	PB or BM	Pre-HCT	~64 (55-79)	66	2033x (mean)	≥2% 5.9%	16% (donors)	Chronic GVHD CIR/P OS	*DNMT3A*: AdjHR 1.99 (p=0.002) *DNMT3A*: Lower risk (p=0.029) *DNMT3A*: No difference (p=0.57)
Boettcher et al.[48]	PB	Post-HCT (median 16 y)	59 (29-95)	102	582x (mean)	≥1% 3%	31% (recipients) 23.8% (donors)	NR	NR
Grimm et al.[50]	PB (n=113) and	Pre-HCT (BM was	64 (32-76)	10 (PB samples);	≥ 500x	≥3% 11.1%	41.6% (recipients)	Relapse	*DNMT3A, TET2,* or *ASXL1:* No effect

	BM (n=75, results not discussed here)	pre-any treatment)		54 (BM samples)				OS	*DNMT3A*: No effect (p=0.71) *TET2*: 88.1% vs 57% if no *TET2* (p=0.02) *ASXL1:* 4-y OS 100% vs 58.6% if no *ASXL1* (p=0.02)
Newell et al.[51]	BM	Pre- and post-HCT	56 (37-68) for cases	76	2286x (mean)	≥0.5% 5.1%	5.2% (defined as mutation post- but not in pre-HCT sample, confirmed in donor samples)	Clonal Expansion	*DNMT3A*: 2-fold on average (11.4 m follow-up); most rapid increases died within 1 y *ASXL1*: 2-fold on average (3.5 m follow-up) Others, including *TET2*: stable VAF
Oran et al.[52]	PB	Pre-HCT	~62 (55-78)	300	289x (median)	≥2% 6.1%	18% (donors)	Acute GVHD	DTA: No difference in risk between mutations in these genes
Gillis et al.[53]	PB	Pre-HCT	63 (55-80)	75	3873 (median)	≥2% 3.1%	13.7% (donors)	Chronic GVHD	*DNMT3A*: Lower incidence if donor + (34% vs 57%, p=0.04)
Imus et al.[54]	PB or BM	Pre-HCT in recipients	67 (60-78)	48	NR	≥1% NR	62% (recipients)	NRM, OS	Worse with increased VAF and number of mutations
Tanaka et al.[55]	BM	Pre-HCT (post-CR)	53 (17-85)	295	NR	>2.5% 14%	NR	Neutropenia Relapse	*TET2* prolonged neutropenia *ASXL1* (p=0.07) or *TP53* (p=0.05) mutations increase risk: >1 CH mutation increases risk (p=0.04)
Lueck et al.[66]	NR	Pre-HCT	~62 (51-67)	3: DTA	> 100x	≥5%	53.8% (recipients)	AFiH	*DNMT3A*: Incidence in mutated (53%) higher than non-mutated (27%)

[a]Clonal expansion is defined here as an increase in the VAF of pre-existing CH mutations; clonal evolution is acquisition of new CH mutations.

AdjHR, adjusted Hazard Ratio; **AFiH**, atrial fibrillation in-hospital; **BM**, bone marrow; CH**,** clonal hematopoiesis; **CIR/P**, cumulative incidence of relapse/progression; **CR**, complete remission; **d**, days; **DLBCL**, diffuse large B-cell lymphoma; **DRP**, DNA repair pathway genes; **DTA**, *DNMT3A*, *TET2*, or *ASXL1* mutations; **FDR**, false discovery rate; **GVHD**, graft-versus-host disease; **HCT**, hematopoietic cell transplantation; HR, hazards ratio; **HSC**, hematopoietic stem cell; **HUMARA**, human androgen receptor assay; **ICU**, intensive care unit; **IMiD**, immunomodulatory imide drugs; **IQR**, interquartile range; **m**, months; **MNC**, mononuclear cell; **MRD**, measurable residual disease; **NA**, not applicable; **NR**, not reported; **ns**, not statistically significant; **OS**, overall survival; **PB**, peripheral blood; **PBSC**, peripheral blood stem cell; **PFS**, progression-free survival; **PTCy**, post-transplant cyclophosphamide; **RR**, risk ratio; **tMN**, therapy-related myeloid neoplasm; **VAF**, variant allele frequency; **y**, years

Figure S1. Funnel plots of autologous (auto) hematopoietic cell transplantation studies assessing clonal hematopoiesis-associated risk for therapy-related myeloid neoplasms (tMN) and overall survival (OS) with sufficient data to be included in the meta-analysis.



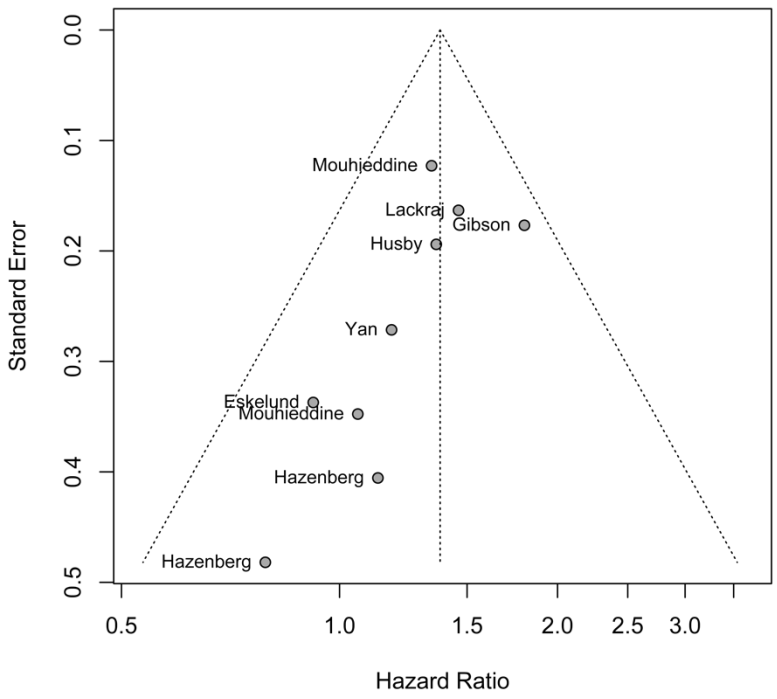


Figure S2. Stratified meta-analysis of the association between clonal hematopoiesis and risk for therapy-related myeloid malignancies (tMN) in patients with lymphoma (top) and multiple myeloma (bottom) receiving autologous (auto) hematopoietic cell transplantation.

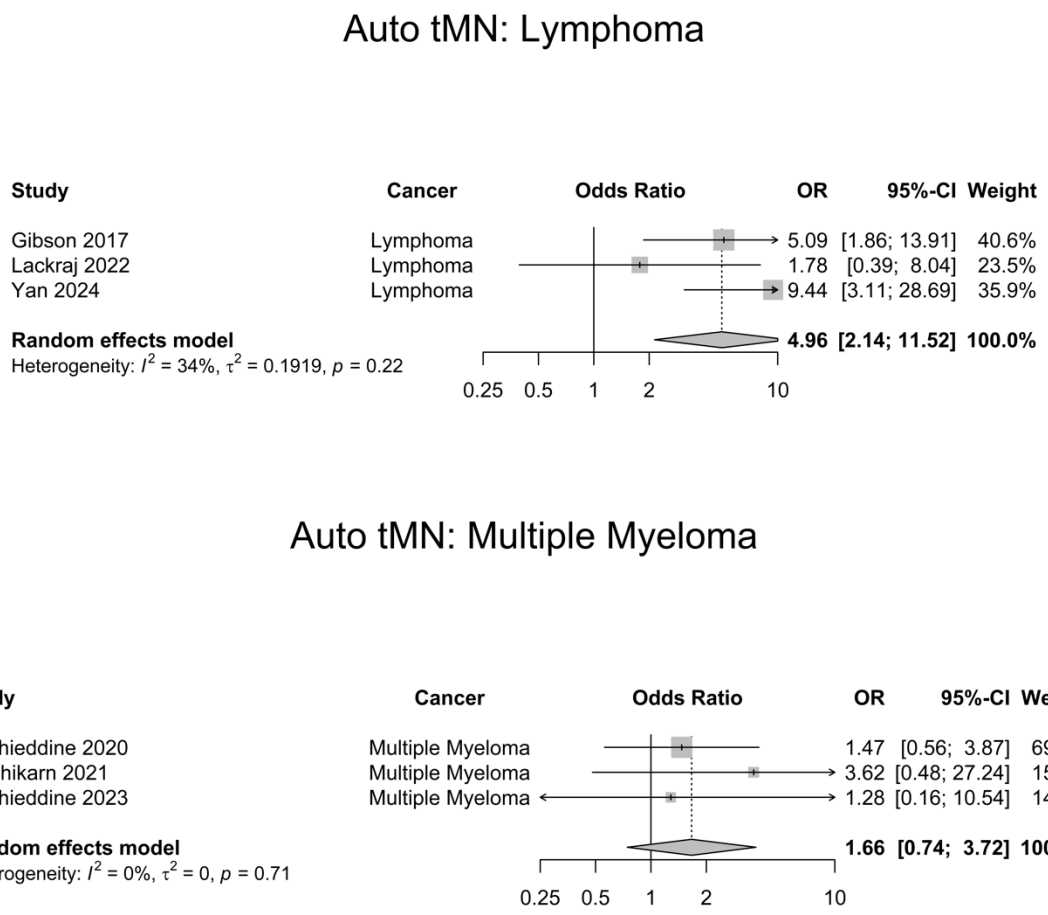


Figure S3. Stratified meta-analysis of the association between clonal hematopoiesis and overall survival in patients with lymphoma (top) and multiple myeloma (bottom) receiving autologous (auto) hematopoietic cell transplantation.

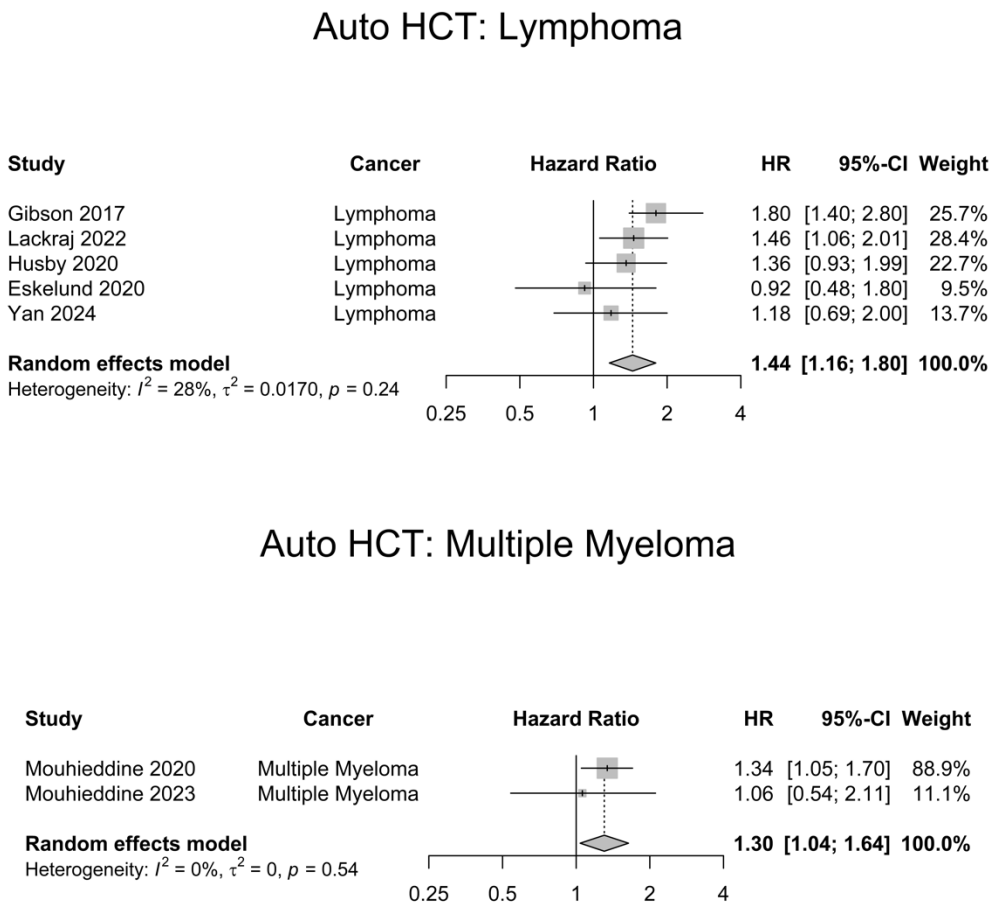


Figure S4. Funnel plots of allogeneic (allo) hematopoietic cell transplantation studies assessing clonal hematopoiesis-associated risk for relapse, overall survival (OS), chronic graft-versus-host disease (cGVHD), and acute graft-versus-host disease (aGVHD) with sufficient data to be included in the meta-analysis.

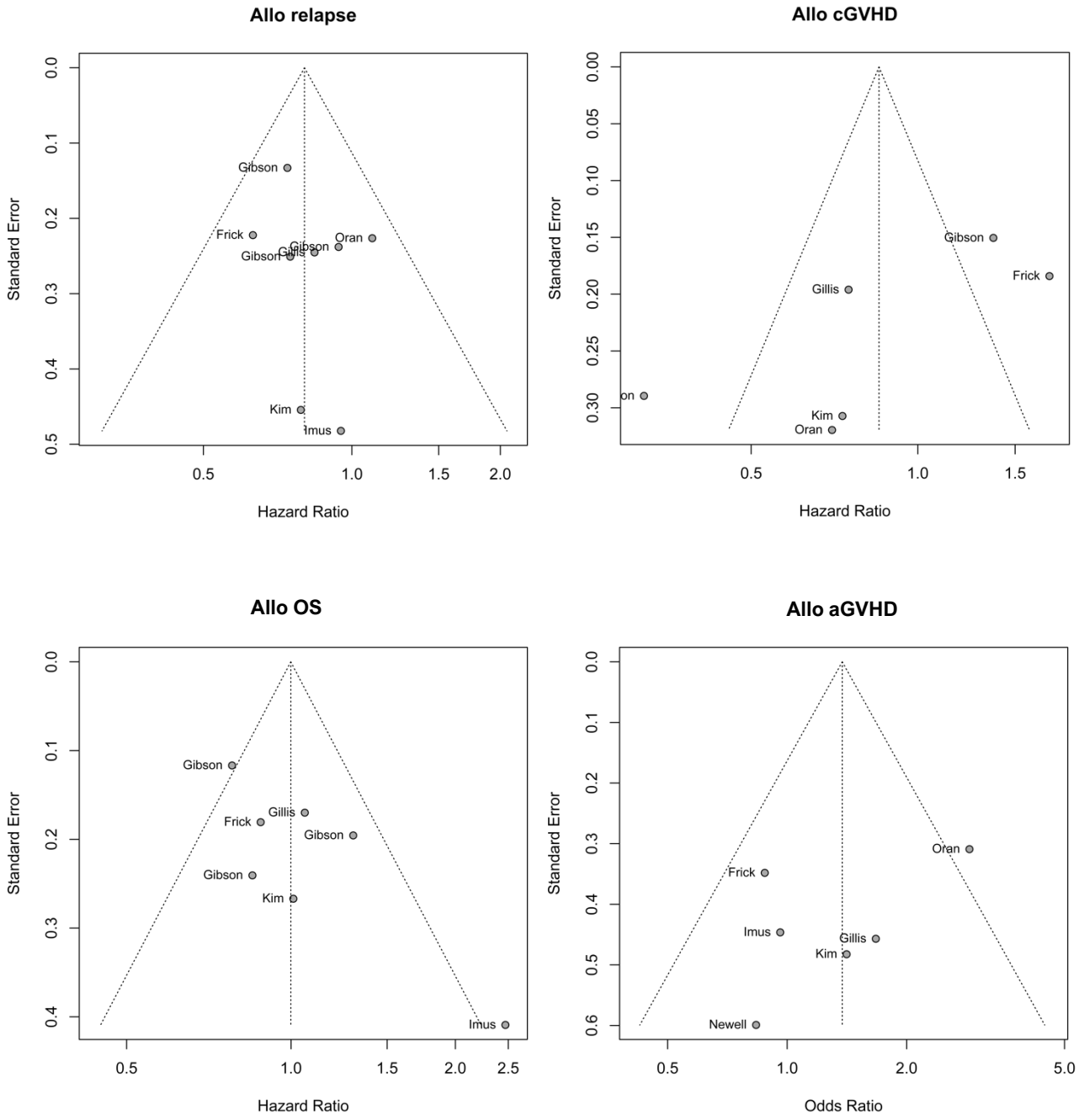
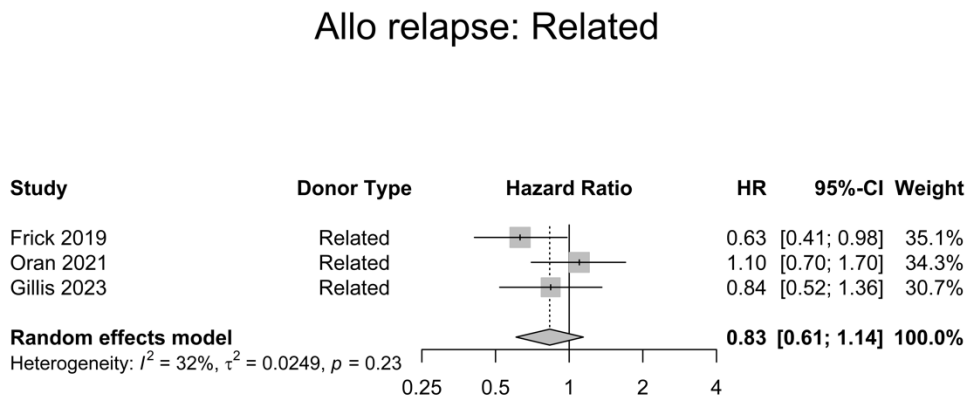
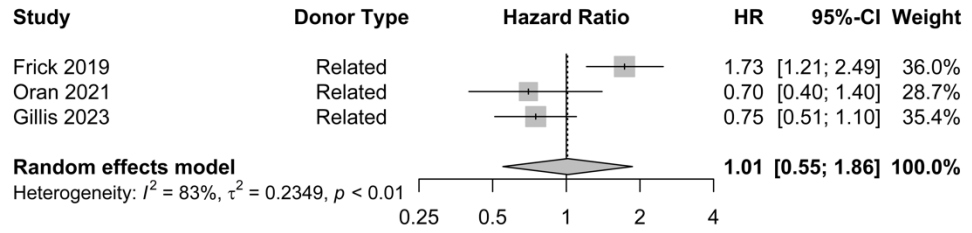
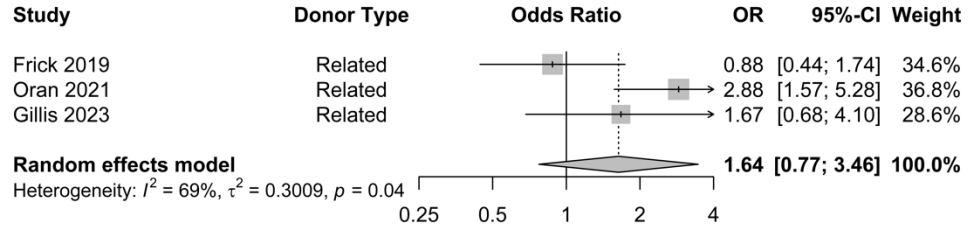


Figure S5. Stratified meta-analysis of the association between clonal hematopoiesis and outcomes (relapse, chronic graft-versus-host disease or cGVHD, and acute GVHD or aGVHD) in studies that included only related allogeneic (allo) hematopoietic cell transplantation donors.







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