

What the data now show about mismatched unrelated donor HCT

Steven Devine, MD • 10 min read • April 24, 2026

Quick takeaways

- **MMUD outcomes have significantly improved in the PTCy era**, with survival and GVHD outcomes now comparable to fully matched unrelated donor transplantation in many settings.
- **Prospective and real-world evidence support MMUD HCT across a range of mismatches**, including beyond a single HLA mismatch.
- **Ongoing ACCELERATE clinical trial continues to refine MMUD approaches and inform best practices.**
- **Early consideration of alternative donors can reduce transplant delays without compromising outcomes.**

How evolving evidence is reshaping outcomes, donor selection and access to allogeneic HCT

As transplant physicians, we've all been there. There's a patient with an acute leukemia who urgently needs an allogeneic hematopoietic cell transplant (HCT). You've searched the NMDP RegistrySM for a donor match. You've tested siblings. There's not an 8/8 matched unrelated donor (MUD), matched related donor or suitable haploidentical related donor. A cord blood unit isn't the best option for your patient either.

In years past, that left you with a suboptimal path forward for your patient. You saw the inferior outcomes when a patient received HCT using a mismatched unrelated donor (MMUD). It's a risk you weren't willing to take. Maybe that sense of trepidation is still with you today.

But, MMUD HCT isn't a compromise anymore.

MMUD HCT is a powerful tool giving us more options to treat our patients with hematologic malignancies and disorders—especially patients with diverse ancestry who often don't have a full donor match on international registries.¹

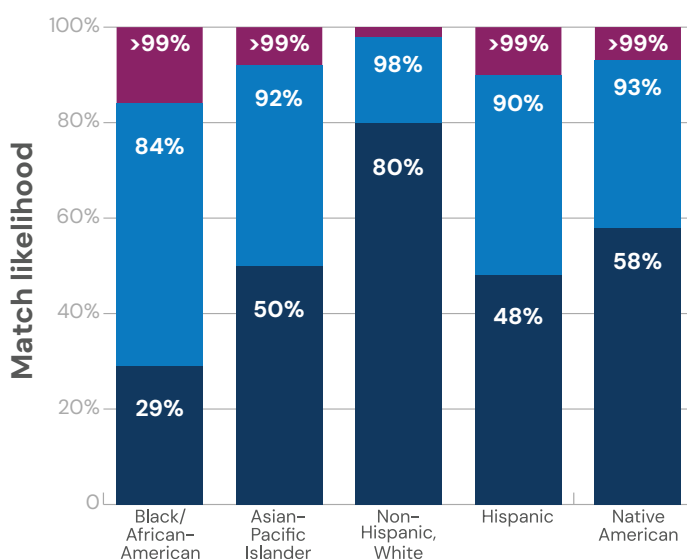


Figure adapted from Chowdhury et al, 2023

Advancements in GVHD prophylaxis strategies—such as the use of post-transplant cyclophosphamide (PTCy) protocols—have dramatically improved outcomes for our patients when used for MMUD transplant, effectively closing the outcomes gap with MUD transplant.²

That means with donor matching no longer as restrictive, you can prioritize other critical factors when selecting a cell source—such as donor age, availability and other non-HLA factors—to optimize outcomes and further individualize transplant care.

This article will discuss the latest advancements and data that support MMUD use as another option for your patients as we rapidly move closer to a future where having a full match no longer determines who receives HCT—and who doesn't.

PTCy's transformative impact on mismatched transplantation

Over the past decade-plus it's been astounding to see the profound impact PTCy has had on outcomes for patients who receive a mismatched transplant—and expanding access to treatment.

It started with haploidentical (haplo) related transplant and the pioneering researchers at Johns Hopkins who began using PTCy to make haplo transplant safer.³

Our CIBMTR® (Center for International Blood and Marrow Transplant Research®) colleagues from the Medical College of Wisconsin® (MCW) saw the success in haplo and wondered if the same approach could work for MMUD transplant.

With CIBMTR being an NMDPSM and MCW research collaboration, our MCW colleagues approached us with an idea—an NMDP-sponsored, CIBMTR-led clinical trial using bone marrow from partially matched unrelated donors and PTCy GVHD prophylaxis for adult patients.

If it worked, we knew it would be practice changing and open the door to transplant to so many more patients. That trial opened in 2015 and became known as 15-MMUD.

In the decade that's followed, NMDP and CIBMTR launched a series of [Donor for All trials](#) with results that will potentially enable near-universal donor access in the future.

From hypothesis to practice—changing Donor for All clinical trials

Key NMDP-sponsored, CIBMTR-led MMUD clinical trials using PTCy

2021: 15-MMUD clinical trial results exceed expectations

The 15-MMUD study (NCT02793544) showed PTCy supports excellent outcomes in adult patients receiving bone marrow.

1-year OS:

- Myeloablative conditioning (MAC): **72%**
- Reduced intensity conditioning (RIC): **79%**⁴

Nearly 50% of those enrolled in the 15-MMUD clinical trial have **ethnically diverse ancestries**.

2025: ACCESS trial results continue to show PTCy benefit

ACCESS trial (NCT04904588) results from the first 145 adult patients show the benefit of PTCy extends to peripheral blood stem cell (PBSC) MMUD HCT.

1-year OS:

- MAC: **83.8%**
- RIC or nonmyeloablative (NMA): **78.6%**⁵

Results from a pediatric strata using bone marrow are expected in 2026.

Ongoing: OPTIMIZE trial explores a reduced PTCy dose

NMDP and CIBMTR opened the OPTIMIZE trial (NCT06001385) in late 2023.

The trial fully enrolled in 2025.

We aim to answer this question: Does a reduced dose of PTCy decrease infection risk while maintaining effective GVHD prevention in MMUD transplant for adults?⁶

Ongoing: ACCELERATE trial uses platform protocol to compare multiple novel GVHD prophylaxis strategies

The ACCELERATE clinical trial (NCT06859424)—which enrolled its first patient in August 2025—compares multiple novel GVHD prophylaxis strategies to standard of care within a single platform protocol.⁷

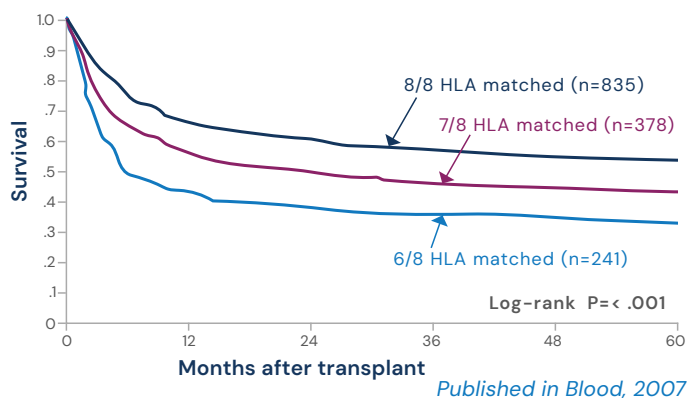
This leads to faster start up times at clinical trial sites and faster patient accrual. That means results get into your hands and put into practice sooner.

Early survival and GVHD outcomes reflected the limits of prior approaches

The results from recent clinical trials are truly game changing for patients who don't have a full donor match. The science has come a long way from where it was when I was a BMT fellow in the early 1990s. I saw the poor outcomes for patients in the rare cases when we used an MMUD. There's no sugarcoating it. Even by the early- to mid-2000s, patients who received mismatched transplants were still less likely to survive and more likely to develop severe graft-versus-host disease (GVHD) or experience graft failure.

Historical survival rates by degree of HLA match

Consider the numbers in a [study published in Blood in 2007](#), which reviewed outcomes for patients who received HCT between 1988 and 2003.



At that time, 1-year overall survival (OS) for MMUD HCT versus MUD HCT with calcineurin inhibitor (CNI)-based GVHD prophylaxis looked like this:

- 8/8: **52%**
- 7/8: **43%**
- 6/8: **33%**

Acute GVHD and chronic GVHD rates were also higher for patients who received MMUD HCT, especially those with multiple mismatches.⁸

I never imagined then that we could get to where we are today.

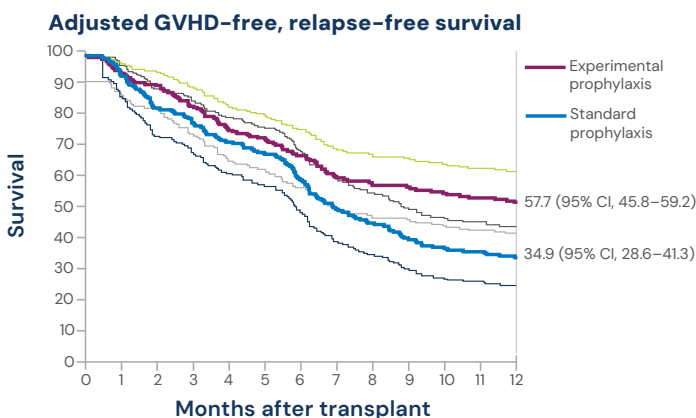
Contemporary evidence shows comparable outcomes with PTCy

With PTCy and [medicines like abatacept](#), which is FDA-approved for the prevention of acute GVHD, science is fundamentally changing what's possible in transplant medicine and creating a new standard of care for GVHD prophylaxis.

For the first time, we have clear evidence that patients can safely receive mismatched unrelated donor grafts—including beyond a single mismatch—and achieve survival outcomes on par with those from fully matched donors.

BMT CTN 1703 establishes a new standard of care

The landmark Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1703 Phase III trial established the PTCy triple-drug regimen—cyclophosphamide, tacrolimus and mycophenolate mofetil (PTCy/Tac/MMF)—as the new standard of care for adults receiving matched related, matched unrelated and 7/8 MMUD reduced-intensity transplants.



When compared to those who received tacrolimus-methotrexate (Tac/MTX), the study showed that at one year, patients who received PTCy/Tac/MMF experienced:

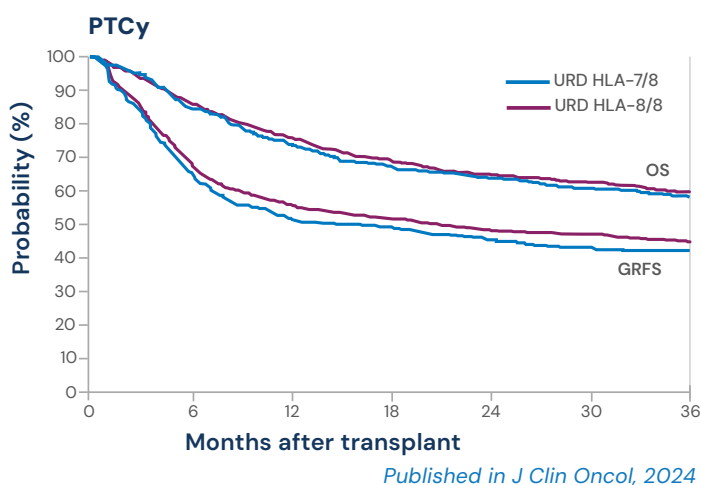
- Significantly better GVHD-free, relapse-free survival
- Less severe acute or chronic GVHD
- Higher rate of immunosuppression-free survival

Overall survival, disease-free survival, relapse, transplantation-related death and engraftment were comparable between the groups.

Published in the [New England Journal of Medicine in 2023](#), this randomized multi-center trial primarily included matched donors, however, it proved the safety and effectiveness of the PTCy platform, providing the necessary evidence to expand its use to mismatched donors.²

Large real-world analyses reinforce trial findings

In 2024, the Journal of Clinical Oncology published results from an [observational study of more than 10,000 adult patients in the U.S.](#) who received HCT for acute leukemia or myelodysplastic syndromes (MDS) from 2017–2021 with outcomes reported to CIBMTR.



The study showed:

- **Similar 3-year OS and GVHD-free, relapse-free survival (GRFS)** for patients who received 8/8 and 7/8 HCT using PTCy
- **Improved 3-year OS** after 8/8 PTCy HCT and similar OS for 7/8 PTCy HCT when compared to 8/8 HCT using CNI GVHD prophylaxis
- **Improved 3-year GRFS** for both 8/8 and 7/8 PTCy HCT compared to 8/8 CNI HCT
- **Lower risk of non-relapse mortality (NRM)** after 8/8 and 7/8 PTCy HCT compared to 8/8 CNI HCT⁹

Taken together, these findings reinforce what prospective trials have suggested: when PTCy is used, the degree of HLA mismatch alone is no longer the dominant driver of outcomes. Importantly, expanding acceptable donor criteria substantially increases donor availability across all ancestry groups—without compromising survival.

It's important to note that an [EBMT observational study of more than 17,000 adult patients in Europe](#) that was published in the same issue of the Journal of Clinical Oncology reached a slightly different conclusion. The study suggested that certain HLA mismatches may still carry risk even in the PTCy setting.¹⁰

[An accompanying editorial](#) points to differences in patient populations, transplant approaches and study design as likely contributors to these nuances, underscoring that our understanding continues to evolve.¹¹

ACCESS moves the field forward

While observational studies like these provide important validation—and highlight areas of ongoing discussion—prospective clinical trials remain essential for defining and refining standards of care.

The ACCESS trial, which built on the earlier success of PTCy trials, was designed to prospectively evaluate MMUD transplantation using PTCy across a broader range of mismatches and with PBSC as the cell source—addressing key unanswered questions from earlier studies.

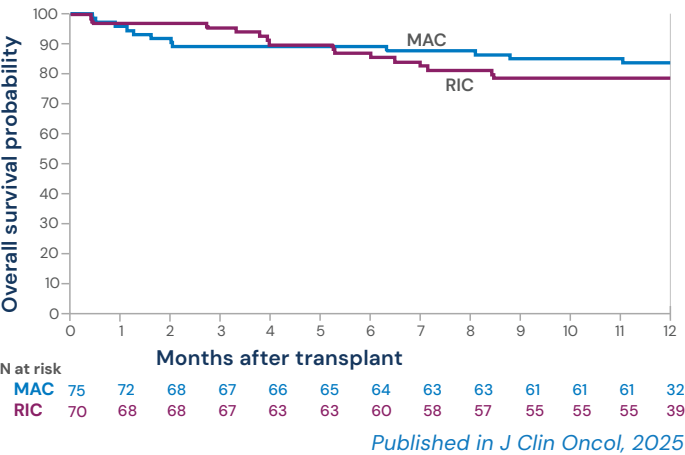
ACCESS was a Phase II, multicenter trial where adult patients received:

- PTCy, tacrolimus and mycophenolate mofetil as GVHD prophylaxis
- MAC or RIC/NMA conditioning
- PBSCs from 4–7/8 matched donors who were ≤35 years old

We originally planned to enroll 140 adult patients—with 70 in each cohort. However, the RIC cohort accrued so quickly that we expanded it to include an additional 120 patients.

This was not only a positive for patients, it also allowed us to have data from more recipients of <7/8 grafts.

The Journal of Clinical Oncology published results from [the first 145 patients enrolled on ACCESS](#).



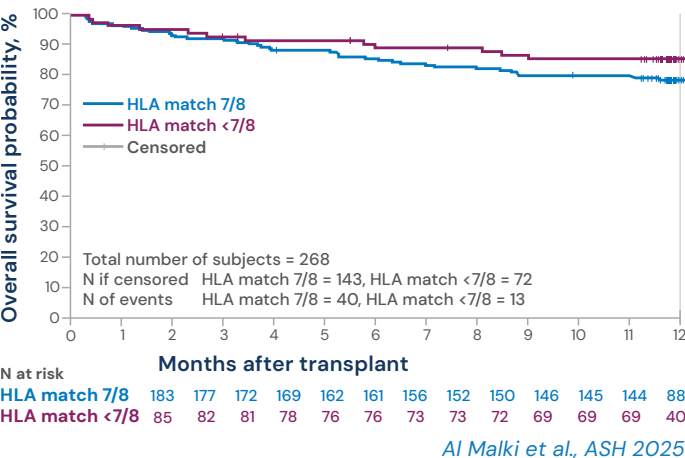
The research showed:

- **No significant difference in OS** between patients with 7/8 HLA-matched versus <7/8-matched unrelated donors
- OS at 1-year post-HCT **consistent with historical benchmarks** for 8/8-matched donors
- **Low rates of acute and chronic GVHD**
- **59% of participants** self-identified as members of racial and ethnic groups traditionally underrepresented in clinical trials⁵

Expanded ACCESS analysis supports broader applicability

Subsequent analyses [presented at the 2025 ASH Annual Meeting](#) extended these findings to an even broader cohort of 268 patients:

- **1-year OS of 86% for recipients of <7/8 grafts**, compared to 79% in 7/8 recipients
- **Relapse, non-relapse mortality and GVHD rates similarly favorable and consistent** between the two groups
- Racially and ethnically diverse cohort, with **61% of those receiving <7/8 grafts identifying as other than non-Hispanic white**¹²



The outcomes results are impressive, but just as impressive who is benefitting from MMUD HCT.

More than 50% of patients in the ACCESS trial are ethnically diverse. These are patients who, in the past, likely wouldn't have had access to a fully matched donor.

Patient-reported outcomes add important context to survival data

We also wanted to understand how patients felt about their quality of life (QOL) after HCT, which is just as important as the clinical outcomes. We asked patients to complete patient reported outcomes (PRO) surveys pre-HCT and again at 100 days, 180 days and 1 year after transplant to better understand their QOL and financial well-being.

At the 2025 ASH Annual Meeting, we presented a [poster abstract](#) comparing QOL and financial well-being for patients enrolled on ACCESS with no or mild chronic GVHD to those with moderate or severe chronic GVHD. We found that QOL at 1 year after HCT was similar to the general population.

However, for the small number of patients in the PRO study who had moderate or severe chronic GVHD, symptoms like fatigue and worse physical function were higher. That underscores the need for us as health care professionals to offer targeted support for those with chronic GVHD and continue efforts to reduce GVHD following HCT.¹³

We also shared [additional ACCESS PRO findings](#) at the 2026 Tandem Meetings examining whether patient-reported outcomes differed by donor match level. Patients who received 7/8 and <7/8 MMUD transplant showed similar recovery trajectories across measures including QOL, physical function, fatigue and financial well-being. At 1 year after transplant, patient-reported QOL and physical function had returned to baseline, with no meaningful differences observed between groups.¹⁴

OPTIMIZE, ACCELERATE and the future of MMUD research

There's been astounding progress in MMUD HCT over the last decade but we know that as a transplant community we must work to continually refine and improve MMUD protocols for patients.

[The OPTIMIZE clinical trial](#)—which completed enrollment in 2025—was the first step. OPTIMIZE aims to understand if a reduced dose of PTCy (25 mg/kg vs. standard 50 mg/kg) can safely prevent GVHD while reducing infection risk for patients. We anticipate having results in 2026. If OPTIMIZE shows that a lower dose maintains GVHD protection while improving infection-free survival, that will be another step forward for patients.⁶

The current ACCELERATE clinical trial for MMUD HCT using PTCy represents where MMUD research is headed. Unlike traditional clinical trials, ACCELERATE is an adaptive platform trial that continually evaluates new innovations against a shared control group. If a new approach performs better, it can quickly replace the control arm and become the new standard—helping patients benefit from discoveries years sooner.

That means:

- **Faster progress** with promising approaches added or retired without launching new trials
- **Broader participation** with easier activation for clinical trial sites that speeds enrollment and reduces barriers
- **Universal impact** because discoveries in partially matched donor transplants can improve outcomes for fully matched transplants, too

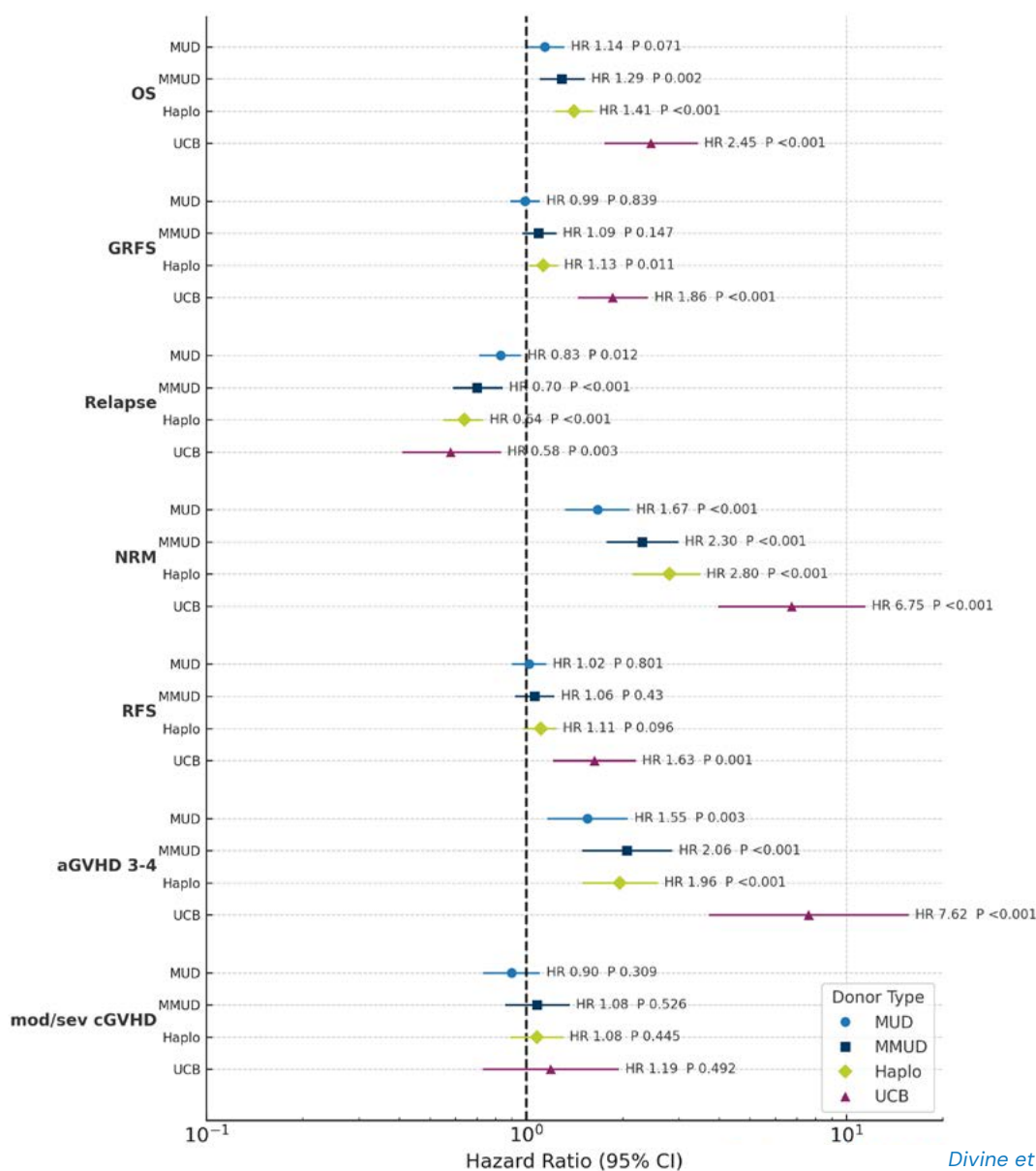
All clinical trial participants will be randomly assigned to the control or investigational study arm. The primary endpoint is GRFS at 1 year, with secondary endpoints of OS, disease-free survival, acute and chronic GVHD, relapse, infection and patient-reported QOL through 1 year. The [first patient enrolled in August 2025](#). If found safe, the first two ACCELERATE interventions will be studied in a randomized phase with 318 patients enrolled at up to 60 investigational centers across the U.S.⁷

How MMUD outcomes compare to MSD, MUD, haplo and cord blood HCT

As you review the data on MMUD transplant, you may wonder how it compares to outcomes for other donor types. In 2025 and 2026, I presented oral abstracts at the EBMT Annual Meeting that shared the results of CIBMTR retrospective registry analyses that compared patient outcomes by donor type. We found that, even in the PTCy era, outcomes do vary by donor type.

Summary of multivariable analysis – MSD reference

We used the CIBMTR outcomes database to assess how donor type and HLA matching influence patient outcomes. Donor types included matched sibling/related donor (MSD), matched unrelated donor (MUD), 7/8 MMUD, haplo and umbilical cord blood (UCB).



Divine et al, EBMT 2026

The analysis presented in 2025 evaluated 1-year outcomes for 10,021 adult patients with AML, ALL or MDS transplanted between 2017 and 2022. In 2026, we expanded the analysis through 2023, which allowed us to evaluate 2-year outcomes for 13,336 adult patients. With the exception of cord, which used CNI-based prophylaxis, all donor types used PTCy-based prophylaxis.

At 1 year, the analysis showed:

- **Better OS** and **less GVHD** and **NRM** for MSD recipients
- **Similar OS** and **GRFS** for MUD and MMUD recipients
- **Better GRFS** and **lower NRM** for MMUD compared to haplo
- **Worse outcomes** for UCB recipients, except for relapse¹⁵

At 2 years, the analysis showed:

- **OS was highest in MSD and MUD recipients** and lowest in UCB recipients
- **No significant difference in moderate-to-severe chronic GVHD** among the donor groups, but a **higher risk of moderate-to-severe acute GVHD** in all groups compared to MSD
- **Worse GRFS** in haplo and UCB when compared to MSD, but **no significant difference** with MUD or MMUD
- **Lower relapse** in MUD, MMUD, haplo and UCB compared to MSD, however, these groups had **higher NRM** compared to MSD¹⁶

The results suggest donor selection strategies should prioritize MSD and MUD, when available. However, MMUD and haplo do have favorable outcomes when using PTCy and search strategies should evolve to minimize delays getting a patient to transplant.

Implications for donor selection in clinical practice

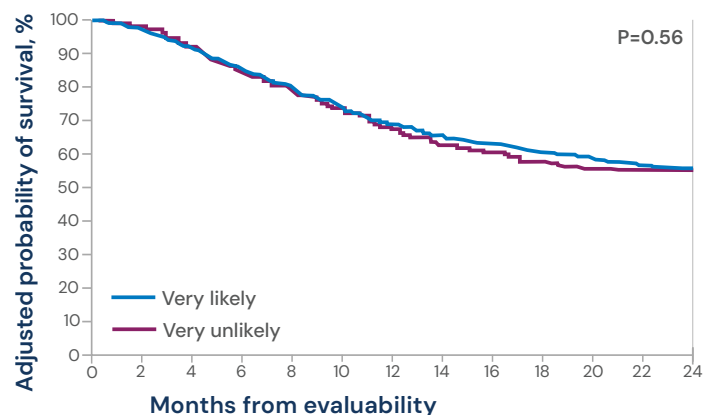
With these data, the practical question becomes how these differences influence your donor search strategy. Outcomes with alternative donor transplants have improved, so the calculus has shifted. **The best donor is an available donor**, whether that's an MSD, MUD, MMUD, haplo donor or cord blood unit (CBU). You no longer need to wait for fear of missing the "perfect" match. Considering these options early in the search process can help move your patient to transplant sooner.

Why delaying transplant to wait for a perfect match carries risk

I understand if you feel hesitant about moving to an alternative donor search early. We've all wondered if waiting just a little bit longer might yield that 8/8 match. However, the [Blood and Marrow Transplant Clinical Trials Network \(BMT CTN\) 1702 study](#) supports using a concurrent search approach.

Similar transplant success regardless of match likelihood

BMT CTN 1702 showed that a donor-search prognosis strategy enables physicians to move patients to HCT faster, resulting in similar transplant success regardless of the likelihood of finding a matched unrelated donor.



Published in J Clin Oncol, 2025

The study, which was published in the Journal of Clinical Oncology in September 2025, found:

- **No difference in OS** two years post-evaluability between patients with high and low probabilities of finding an MUD
- **No differences in other transplant clinical outcomes**, such as relapse, treatment-related mortality, disease-free survival and GVHD
- **Similar the median time to transplant** across all groups¹⁷

The risk isn't in using an alternative donor—it's in delaying transplant while disease progresses.

Updated donor selection guidance in the PTCy era

In response to advancements in GVHD prophylaxis with PTCy, CIBMTR brought together a panel of multidisciplinary experts to review clinical research and provide enhanced considerations for selecting donors for allogeneic HCT. Published in Transplantation and Cellular Therapy in 2025, the [updated the donor selection guidelines](#) incorporate the latest research on:

- Prioritizing **available donor types**
- **HLA matching considerations**
- Non-HLA factors to consider, such as **donor age**¹⁸

Donor selection resources for your transplant center

Selecting the best donor or CBU involves applying standardized donor selection guidance while considering the clinical factors unique to each patient.

To support your transplant center team, NMDP developed quick resources to inform donor selection decisions:

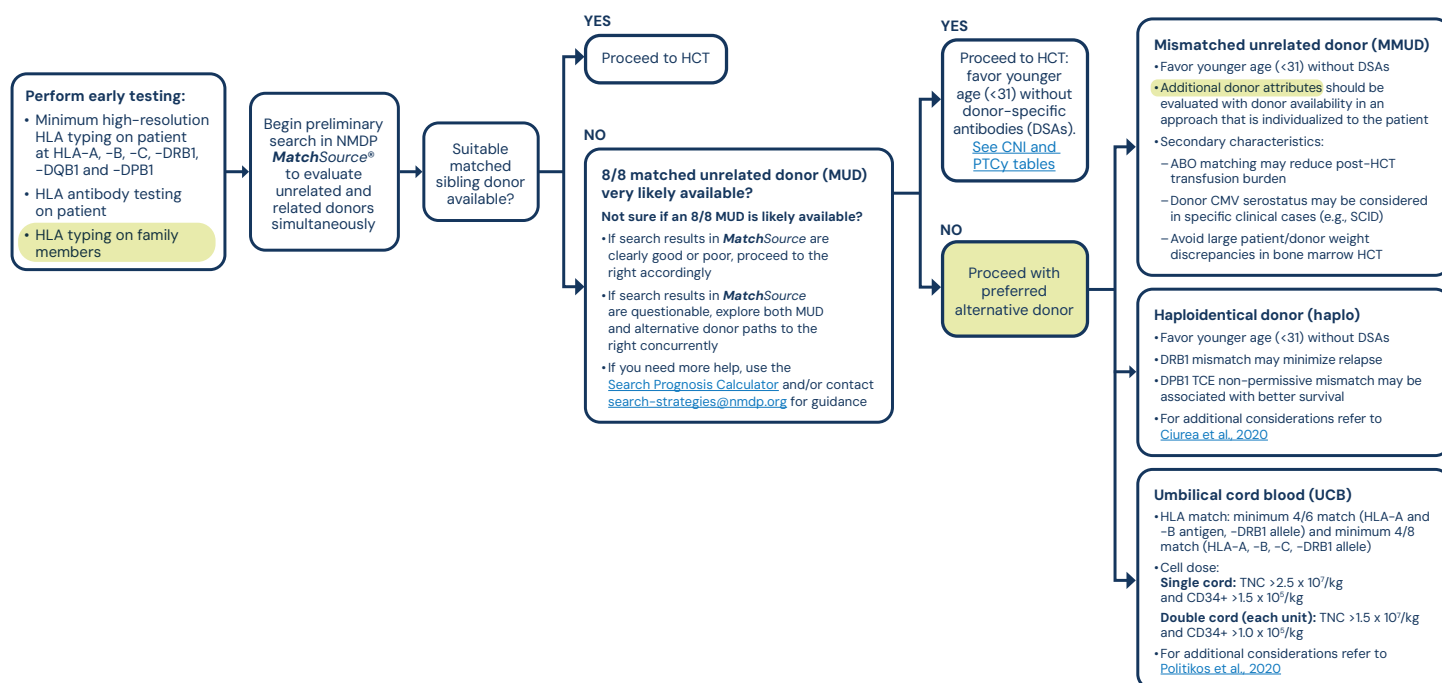
- [Quick reference donor selection guidelines PDF](#) for your transplant center to download
- [Donor and cord blood unit selection guidelines](#) webpage for you to bookmark

Both include key considerations for PTCy-based and CNI-based prophylaxis settings. The webpage also offers key considerations for CBUs.

To guide your donor searches at key decision-making moments:

- View and download the [allogeneic HCT donor search strategy flowchart](#)

Allogeneic HCT donor search strategy



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Flowchart key:

= program-specific decision

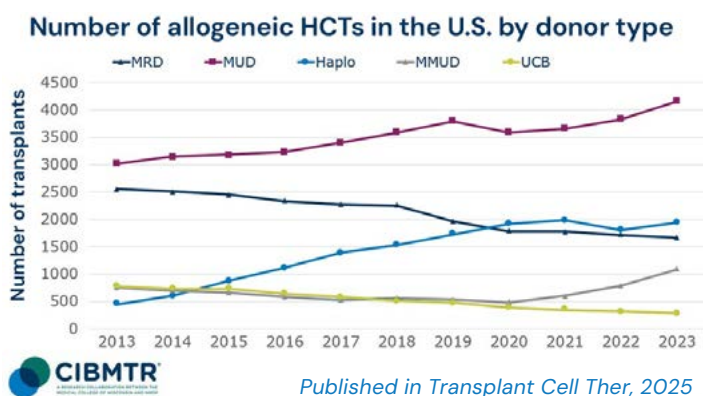
Applying donor selection guidance with clinical decision support

As evidence continues to evolve—including studies examining outcomes with matched and alternative donors—you have more data than ever to guide your donor selection decisions. Applying this evidence into practice can help expand access to curative transplants for patients who might otherwise face prolonged donor searches or be told they lack a suitable donor. This is particularly impactful for your patients with diverse ancestry, who historically have a lower likelihood of having a fully matched, available donor.

For cases where additional expertise may be useful, the NMDP Clinical HLA Services team can help you assess donor options for your patients, including MUDs and alternative cell source options. If you'd like assistance, contact search-strategies@nmdp.org for guidance.

MMUD use is increasing in clinical practice

We're beginning to see practice patterns change. CIBMTR data show a steady increase in the use of MMUDs since 2020.¹⁹



Among NMDP-facilitated transplants, the proportion using MMUDs more than doubled in just four years—from 6% in 2020 to 14% in 2024.²⁰

These incremental changes represent a meaningful shift in how we approach HCT, particularly for patients who might not have been able to proceed to HCT because they lacked a suitable donor.

What was once a high-risk proposition is now a highly viable option.

What this means for your practice

MMUD HCT in the PTCy era is a highly effective and safe option, with outcomes increasingly comparable to MUD HCT. For your practice, this means you can:

- **Critically evaluate your donor options** and choose the best donor for your patient based on current evidence and their transplant timeline
- **Seek out ongoing clinical trials** for your patients to help shape the future of alternative donor transplant
- **Consider the updated donor selection guidelines** when selecting a donor

MMUD transplantation expands access without compromising outcomes

This is an exciting time in transplant medicine. We now have more options than ever before to treat patients with hematologic malignancies.

If you're just starting to incorporate MMUD HCT into your practice, you don't have to do it alone. Leverage the resources available from NMDP. Talk to your NMDP clinical operations partner. Reach out to the NMDP Clinical HLA Services team. We're all here to help.

Our shared goal is to provide every patient with the best possible chance at a cure. By embracing recent advances in MMUD research and donor selection strategies, we'll be one step closer to ensuring every patient can receive the life-saving transplant they need, without compromising outcomes.

About the author



Steven Devine, MD, is the chief medical officer of NMDP and the senior scientific director of CIBMTR. He's currently leading clinical research efforts within CIBMTR to improve outcomes in recipients of MMUD transplants.

His major research interest is in the application of HCT for patients with acute myeloid leukemia (AML). He's served as chair of two multicenter NIH-supported clinical transplantation trials in AML. A current board-certified medical oncologist, Dr. Devine practiced for 25 years in the field. Before joining NMDP in March 2018, Dr. Devine was the director of the Bone Marrow Transplant/Cell Therapy program at The Ohio State University (OSU).

Dr. Devine is dedicated to improving patient outcomes and helping advance the next generation of leaders in HCT and cell therapy.

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