PART C. PROJECT STRATEGY

C.1 Overall Goals and Objectives
The National Marrow Donor Program® (NMDP) proposes a project titled, **Payor-Partnered Approach to Community-Based Referral for Hematopoietic Cell Transplantation (HCT)**. The goal of this project is to identify specific clinical practice gaps among community hematology/oncology physicians (hem/oncs) regarding referral of patients diagnosed with Acute Myeloid Leukemia (AML) for consultation for HCT, also known as blood and marrow transplantation. As part of this proposal, we will partner with payors to develop educational interventions for community providers that address gaps at the system level. The end product of this project will be a valid process measure of referral by community hem/oncs for HCT along with tailored educational interventions. These deliverables will result in increased frequency and proportion of patients with AML referred for HCT in 1st complete remission (CR1), when outcomes for HCT are expected to be better than HCT at a later stage of disease. Specifically, our objectives are to:

**Objective 1)** Characterize reasons for lack of or delayed referral of patients diagnosed with AML for HCT consultation among community hem/oncs, establish preferences for education on HCT, and obtain feedback on ways to build referral relationships between community hem/oncs and HCT physicians practicing at transplant centers (hospitals with HCT programs).

**Objective 2)** Develop and evaluate educational interventions tailored to meet the unique needs of the referring hem/onc community, including non-educational strategies, as identified by the needs assessment.

**Objective 3)** With the expertise of the NMDP Advisory Group on Financial Barriers to Transplant (AGFBT), devise recommendations for health insurance companies on the implementation of educational, and potentially incentivized, programs focusing on optimal timing of referral for HCT consultation among hem/oncs in contracted provider networks.

C.2 Technical Approach

C.2.A Assessment of Need
HCT has been identified as an under-utilized therapy for patients with hematologic malignancies, including those with AML. Given that HCT is performed only at select transplant centers in the US, referral relationships and practices are critical to patient-centered care and transplant outcomes as well as management of health system costs. As the need for HCT grows, it will be critical to ensure that the health system has the capacity to serve all patients eligible for this life-saving therapy.

Outcomes Differential Based on Transplant Timing
AML is the single most common clinical indication for patients undergoing HCT each year. Classifications of AML disease risk factors based on cytogenetic and molecular abnormalities allow stratification into risk groups to select appropriate therapies. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for AML state that patients with poor-risk and intermediate-risk cytogenetics should be assessed for referral to HCT after achievement of CR1. The NCCN guidelines for AML mirror recommendations published by NMDP and the American Society for Blood and Marrow Transplantation (ASBMT) on optimal timing of referral for transplantation consultation. Despite these guidelines, almost half of
patients with AML who undergo HCT are transplanted during second complete remission (CR2) or later (unpublished data, CIBMTR 2008-2010). For those AML patients who have cytogenetic factors portending a poor outcome with chemotherapy alone, the delay in reaching a transplant program for consultation can prove fatal. Outcomes have improved dramatically in recent years for HCT recipients, making it a highly viable option for many patients, particularly those interested in a curative approach. (Table C1) (unpublished data on NMDP-facilitated HCT, CIBMTR 2012). Receipt of HCT (related or unrelated donors) early in AML disease stage (CR1) is associated with significantly higher survival (Figures C1 and C2). A 2009 meta-analysis demonstrated a statistically significant survival benefit of allogeneic (donor cells) HCT for intermediate- and poor-risk AML in CR1 over chemotherapy and autologous (patient’s own cells) transplantation.5

**Table C1: Improved survival after unrelated donor HCT* for AML**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Cases</th>
<th>1-Year Survival</th>
<th>2-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-2011</td>
<td>3,178</td>
<td>58%</td>
<td>45%</td>
</tr>
<tr>
<td>2005-2008</td>
<td>2,687</td>
<td>55%</td>
<td>43%</td>
</tr>
<tr>
<td>2000-2004</td>
<td>1,614</td>
<td>42%</td>
<td>34%</td>
</tr>
<tr>
<td>1987-1999</td>
<td>1,111</td>
<td>28%</td>
<td>21%</td>
</tr>
</tbody>
</table>

* Hematopoietic cell transplantation (HCT)

**Costs of Cancer Care**

The National Cancer Institute (NCI) projects that US health care spending on leukemia (all types) will increase from $5.4 billion in 2010 to $6.95 billion in 2020, making it the sixth highest in terms of spending across various cancer types.6,7 Half of the projected spending for leukemia patients is expected to occur in the last year of life, indicating that patients still experience expensive and frequent treatment during that time. In treating patients
with AML, appropriate referral for and timing of transplant will play an important role in decreasing unnecessary costs pre-transplant. In addition, patients with AML who undergo transplant later in their disease are at higher risk for complications, which research has shown drives higher costs of transplantation.\textsuperscript{8,9}

\textit{Clinician Knowledge and Practice Gaps}

The delay in timing of transplantation for appropriate HCT candidates likely reflects a number of knowledge gaps and/or negative perceptions of HCT on behalf of both the patient and the referring hem/onc. This project will build on baseline research conducted by NMDP.

\textit{Persistent clinical knowledge gaps}

To assess reasons behind delayed or non-referral, NMDP conducted national, in-depth quantitative market research in 2006 and 2010-2011. A web-based survey was conducted with U.S. hem/oncs, all of whom diagnose patients with leukemia, lymphoma, MDS, or multiple myeloma and refer for transplantation (Survey response N=134 and 150, respectively). Physicians who perform transplants were excluded.

Using a commercial database of clinicians, potential participants were pre-screened for the following criteria:

- Primary specialty is hematology, oncology, or both
- Treated adult patients (pediatric-only providers excluded)
- Board certified in their specialty
- More than 1 year of practice experience, post-fellowship
- Must not personally perform allogeneic and/or autologous stem cell transplantation

Qualified clinicians were recruited to complete a 45-minute web-based survey until 150 responses were received.

The 2010 and 2006 findings were compared to determine progress made, and to identify new and persistent barriers to referral and appropriate transplant care. Key findings included:

- Perceptions of transplant and transplant outcomes grew significantly more positive over four years. Of the 18 items on perceptions of transplant that were included in both surveys, 15 showed improvement since 2006 (10-point Likert scale of agreement):
  - In 2010, 74% agreed with the statement, “Patients over 60 years of age can benefit from transplantation”, compared with 47% in 2006.
  - A 24% percent increase in agreement was shown from 2006 to 2010 with the following, “There have been major advances in transplantation in the past five years” (59% v. 35%).
  - Agreement with the statement, “I have the information I need to understand when a patient should be referred for transplant consultation” increased over time (63% v. 42%).
  - In response to, “I have the information I need to understand which patients are eligible for transplant,” 54% of participants agreed in 2010 vs. 34% in 2006.

Specific attitudes about transplant continue to correlate with likelihood to refer early, refer older patients, and refer for allogeneic unrelated donor transplant (2010 v. 2006):
High frequency referrers (≥22% of patients) are more likely than low frequency referrers (<22% of patients) to agree that outcomes of related and unrelated donor transplants are similar (23% vs. 11%).

Low referrers are more likely to report that concern over post-transplant complications is important in their decision not to refer (45% vs. 20%).

High referrers were more likely to believe that HCT outcomes are better if the patient receives a transplant early in the disease process. In 2010, 37% disagreed or were neutral that “timing of when patients are referred affects transplant outcomes” (this question was not included in 2006).

Relationships between referring physicians and transplant centers are positive (77% agreed the relationship with transplant center was positive in both 2006 and 2010) but more can be done to help with transition before and after transplant. Before transplant, referring physicians indicate the need for guidelines on which patients should be referred (64% in 2010) and an effective referral process (69% in 2010). They also reported a need for proactive post-transplant care planning (72% in 2010). Credibility of NMDP as a provider of clinical education and other health professional services has increased over time; 77% viewed NMDP as a credible source for providing education on transplantation, compared with 69% in 2006. In comparison, NCCN was viewed as credible in this area by 81% of respondents in 2010 and 84% in 2006.

NMDP also conducted qualitative focus groups to provide context around the results of the quantitative study. Participants were recruited via telephone using the criteria outlined above. Five focus groups were conducted, with 3 participants each (N=15). The focus groups were conducted via telephone in July 2011, with guidelines shown and described via web for input. The recorded discussions were transcribed and analyzed. Key findings included:

- Seasoned hem/oncs reported relying on experience, established rules and training to make decisions on when to refer for transplant. Physicians felt that trained peers should know when to refer by committing the information to memory.
- However, some physicians also did not believe that firm data that shows earlier transplant provides superior outcomes compared to delayed transplant exists. This demonstrates that either their knowledge is not based on current research or they do not have confidence in the data or data source.
- Transplant centers should improve relationships with referring physicians by increasing the frequency and effectiveness of communications. Hem/oncs report that referral preferences are based on proactive and useful communications from transplant physicians.

Clinical practice gaps

The process for using an unrelated donor through the NMDP typically involves three steps:

1. Preliminary search for unrelated donor (preliminary search is a one-time search of Be The Match Registry® initiated by either the community hem/onc or transplant physician. The search identifies donors and cord blood units on the Registry that may potentially match the patient’s human leukocyte antigen (HLA) markers.
2. Formal search (formal search is activated by the transplant physician when the patient decides to proceed with HCT. This is a detailed search of the Registry when donors or cord blood units are selected for high-resolution HLA testing to determine degree of match).

3. Transplantation.

To understand barriers to HCT, including community physician referral practice, we analyzed rates of unrelated donor transplantation for different diseases that are treated with HCT. Potentially HCT-eligible population utilizing Surveillance, Epidemiology, and End Results (SEER) Program cancer data and estimated proportions of patients that were candidates for HCT based on disease, donor availability, age, and co-morbidity factors. The eligible population for each disease was then compared to current rates of unrelated donor transplantation. Results showed that in 2012, there were an estimated 2,557 patients aged 0-74 years in need of an allogeneic transplant for AML (Table C2). This indicates that many AML patients are referred for HCT consultation but do not proceed to HCT, likely for a variety of reasons. Anecdotally, we know that physicians may order a preliminary search without the patient’s knowledge, before determining eligibility. In addition, the analysis found that of those patients with AML who need an unrelated transplant, only 62% ultimately receive a transplant.

### Table C2: Rates of transplantation for AML by donor search stage in 2012

<table>
<thead>
<tr>
<th>Disease</th>
<th>Need for Unrelated Transplant (years)</th>
<th>Receive Preliminary Search (years)</th>
<th>Proceed to Transplant (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Need (0-64)</td>
<td>Need (0-74)</td>
<td>% of Need (0-64)</td>
</tr>
<tr>
<td>AML</td>
<td>2,134</td>
<td>2,557</td>
<td>117%</td>
</tr>
</tbody>
</table>

Late referral may be a factor for those patients whose condition deteriorates or who die prior to transplant. In 2008-2010, among patients with late referral who underwent transplantation (N=4,362), more than 47% were transplanted beyond CR1. More than 25% of patients received a transplant at 3rd complete remission (CR3) or greater (unpublished data, CIBMTR 2008-2010) a point at which HCT outcomes are decidedly inferior to HCT performed at an earlier disease stage.

**Educational interventions were effective**

By looking at rates of preliminary search over time, NMDP can measure the impact of disease-specific education efforts. The improvements in factors of interest show that education and non-education activities are successful, if targeted to known knowledge gaps. Monthly education programs and resources were developed based on research findings and delivered to hem/onc physicians. Programs focused on transplantation research in general as well as for specific diseases, selecting one disease per year. Preliminary search rates for AML rose
significantly in years when NMDP education focused on AML trends, outcomes, and importance of referral timing (Table C3). The same was true for non-Hodgkin’s lymphoma.

Table C3: Change in Preliminary Donor Search Rates in the U.S. by fiscal year

<table>
<thead>
<tr>
<th>Disease</th>
<th>FY08-FY09</th>
<th>FY09-FY10</th>
<th>FY10-FY11</th>
<th>FY11-FY12</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>AML</td>
<td>74</td>
<td>2.96%</td>
<td>339</td>
<td>13.19%</td>
</tr>
<tr>
<td>NHL</td>
<td>25</td>
<td>2.18%</td>
<td>-5</td>
<td>-0.43%</td>
</tr>
</tbody>
</table>

C.2.B Intervention Design and Methods
As reflected in our objectives, there will be three phases to our proposed project:

Phase 1: Conduct Needs Assessment
To better understand reasons for persistent clinical practice gaps (delayed or non-referral of AML patients for HCT consultation) among community hem/oncs, we propose to conduct market research, using a mixed method to apply quantitative survey and qualitative focus groups simultaneously, but focused specifically on AML and factors influencing referral decisions at each stage. In addition, focus groups will be conducted to obtain deeper understanding of the trends in clinical practice gaps identified in the national market research. Our team has expertise in conducting focus groups of HCT health professionals (Appendix A).

Market Research Procedures and Analysis
The market research will utilize a survey to assess relative contribution of understanding of research results to clinical decision-making, patient decisions, competing therapies, impact of non-clinical factors such as insurance benefits, availability of caregivers, and more. Through this research, we will seek insight on the tools and education resources needed by community hem/onc clinicians. We will conduct a web-based, cross-sectional survey to assess changes in perceptions of the HCT and referral/practice behaviors among hem/onc physicians. Additional questions specific to knowledge and clinical practice for patients with AML will be included.

Quantitative analytic methods
We will target a minimum of 150 respondents in order to perform descriptive analysis and significance tests for assessing variations in physician characteristics and their association with knowledge and practice gaps. To identify the target sample, we will use a professional society list serve (e.g., American Medical Association or American Society of Clinical Oncology) or pre-existing research panel. We will randomly sample approximately 500 hem-oncs (non-transplant) from the list serve or screen the entire panel for eligibility. Based on previous work, we anticipate 30% response rate. Hence, we will have at least 150 participants complete the survey. Analyses will be performed using SAS Enterprise Guide Version 4.3. Honoraria will be provided to participants.

Focus Group Research Procedures
For this phase of the needs assessment, we will conduct 8-10 telephone focus groups consisting of 3-5 participants each. Separate focus groups of 60-90 minutes duration will be conducted for
referring hem/oncs and for HCT physicians. Participants will be asked to review the NMDP/ASBMT Referral Guidelines for HCT prior to the focus group and respond to the guidelines during the discussion. A moderator with background knowledge of hem/onc referral practice and HCT will guide the discussion utilizing a semi-structured discussion guide. Proceedings will be recorded and transcribed for thematic content analysis. Focus group participants will be recruited through a vendor with demonstrated access to community hem/oncs and HCT clinicians and provided an honorarium. To ensure that we obtain a wide spectrum of perspectives, we will consider several factors that can affect clinical practice in the selection of focus group participants. For community oncologists, these will include type of clinician and geographic location. For HCT clinicians, we will consider center size (based on transplant volume), number of patients treated having AML, geographic location and surrounding referral area.

Qualitative analytic methods
Systematic analysis will be utilized concurrently with data collection to identify saturation of themes across the data. Two experienced reviewers will analyze the data in four steps. **Step 1:** The transcribed data will be organized by question in order to examine responses across all participants, looking for consistencies and differences. **Step 2:** Text will be segmenting into meaningful analytical units. We will use inductive codes developed through direct examination of the data. **Step 3:** Validity and reliability of results will be assessed through intra-coder statistical analysis. A simple measure of agreement will be used. To correct for the possibility that coders might agree by chance, we will calculate the kappa statistic (>0.90). A study team member will resolve any remaining inter-coder discrepancies in the text passages. **Step 4:** Coded textual data will be explored inductively using content analysis to generate categories and explanations. Themes will be reported with quoted text included as support and context. Computer assisted qualitative data analysis software, NVivo, will be used. Findings will be reconciled by the project team and used to tailor the educational interventions.

Phase 2: Develop, Tailor and Evaluate the Educational Interventions
Because national market research can be generalized to the broad oncology population and based on preliminary evaluation results, we will utilize these findings to inform the development and implementation of educational interventions specific to the needs of the referring hem/onc community. The interventions will be serial in design and will include resources such as web-based CME modules focusing on key HCT data and outcomes information. We will ensure a captive audience through payor partnerships (Phase 3). This will result in an anonymous panel of hem/onc physicians who treat patients with AML from the contracted provider network.

**Educational Strategies**
All education programs will adhere to Accreditation Council for Continuing Medical Education (ACCME) criteria:
- Needs assessment findings will be classified as knowledge-, strategy- or performance-causes of clinical practice gaps.
- Objectives of educational interventions will be tied directly to these causes.
Learner objectives will focus on competency (e.g., advances in research and guidelines on appropriate utilization of HCT), performance (e.g., initiation of preliminary donor search and referral for HCT consultation), and patient-centered care (e.g., rates of HCT in CR1).

Needs assessment findings (Phase 1) will inform the setting in which interventions are implemented.

Educational interventions will be developed in the context of desirable physician attributes utilizing the NCCN guidelines for AML and the NMDP referral guidelines. These attributes will be tied directly to the practice gap(s).

Based on the findings from Phase I, we may determine that other resources will be more beneficial, such as clinical case forums, guidelines, facilitation of local or regional consensus panels or conferences, to bridge existing clinical practice gaps. We will look to both the referring hem/onc and transplant community to optimize education strategies. Through our extensive experience in developing highly rated CME programs and innovative, credible educational resources, we can expertly tailor interventions to include those strategies most desired and beneficial.

**Non-Education Strategies**

We will also utilize patient-focused resources and health professional outreach programs to supplement the clinical education activities. NMDP has existing programs in place for outreach to health professionals regarding patient education resources. Through the programs, we provide free, patient-friendly educational resources on specific diseases, clinical trials and treatment decision-making, HCT as a treatment option, planning for transplantation, and survivorship care (**Appendix C**). We disseminate these resources to community hem/onc and transplant health professionals through attendance at national, professional meeting of societies and associations (e.g., Oncology Nursing Society, Association of Oncology Social Workers, and Association of Pediatric Hematology/Oncology Nurses), peer-reviewed publications, via our website BeTheMatchclinical.org, and direct mail. These strategies can enhance changes in practice as well as promote patient-centered care.\(^{14}\)

**Phase 3: Partnerships to Implement and Evaluate Educational Programs**

Through partnership with payors, we can better measure the effect of proposed NMDP education interventions on clinical knowledge and practice gaps.

**Existing Framework for Systems-Level Quality Improvement**

We have an existing framework for collaborating with payors through the NMDP Advisory Group on Financial Barriers to Transplant (AGFBT). The AGFBT is comprised of multi-disciplinary stakeholders within the transplant industry. The AGFBT includes representatives of major health insurance plans and third-party administrators (e.g., Blue Cross/Blue Shield, Anthem WellPoint, Aetna, Cigna and Multiplan) as well as leadership from transplant networks, such as LifeTrac and OptumHealth. Transplant program administrators and physicians are also actively involved in the AGFBT and ensure that clinical and patient-centered perspectives are addressed. This advisory group has produced several resources for use by the payor and health care purchaser community.\(^{15}\)
Several payor organizations in the AGFBT are interested in developing programs to support appropriate referral for specialty care. In addition, health plan purchasers are interested in assisting health plan members become or remain healthy. This is particularly true in the case of acute or chronic health care conditions that require specialized care, such as HCT. To help members choose where to receive specialty care, health insurance plans created information-only Centers of Excellence (COE) programs identifying specialty care centers for various medical subspecialties based on quality and outcomes data submitted by these hospitals. In recent years, many health plans have increased the financial incentives for patient utilization of these specialty centers by creating tiered medical benefit categories. As these referral strategies have been primarily on the side of informing and engaging the patient and consumer, health insurance plans are now considering new methods for reaching community physicians and modifying their referral behaviors, when needed. This framework ties directly with our project objectives and, if effective, our approach has the potential to positively impact clinical practice across multiple specialty care disciplines.

In Phase 3, we will collaborate with the AGFBT to investigate models for payor-based education, measurement and/or incentivization of community hem/onc referral practice and timing of transplant. We will sponsor a forum to initiate pilot projects that will address these issues. We will pilot at least one of the following systems approaches:

- Claims-based “flag” of patients with AML receiving chemotherapy to induce remission
- Requirement of participation in NMDP CME modules for hem/oncs in the payor network
- Financial incentives to refer early in the disease process, or
- Measurement of referrals for consultation for HCT among community hem/oncs and feedback as a performance indicator.

**C.2.C Evaluation Design**

The evaluation design will follow the Centers for Disease Control and Prevention (CDC) evidenced-based, six-step framework for program evaluation. A logic model will be created to map learner objectives for the educational interventions to practice gaps identified through the needs assessment. Validated and/or benchmark measures will be used in data collection instruments to ensure correlation between measure and construct. Data sources will be determined in Phase 3 of the project but will likely include primary data from survey instruments, private payor administrative claims data and outcomes registry data (Stem Cell Therapeutic Outcomes Database (SCTOD) operated by the CIBMTR, the research program of the NMDP). Through our Health Services Research program, the AGFBT and the SCTOD, we have access to and expertise on analysis of these datasets.

Changes in measures of competence, performance and patient outcomes (see learner objectives defined in Phase 2) will be analyzed in partnership with a payor(s). We will compare data on clinical practice and physician attributes (e.g., NCCN Guidelines for AML and NMDP/ASBMT Referral Guidelines for HCT) from an anonymous cohort of hem/onc physicians from the contracted provider network(s). The needs assessment will characterize the expected degree of change due to interventions. We will compare rates of change from 2006-2010 and
then 2010-2014. We expect the interventions to improve practice gaps to at least the same degree as previous interventions. Audience engagement will be measured using Google Analytics, evidence-based measures of engagement and qualitative feedback. For example, we could measure relationships between community physicians and local transplant centers, perceptions of the referral system, and/or rate of completion for serial educational interventions. We hypothesize that this systems approach to quality improvement will better address the multi-factorial barriers to transplant. For the two-year funding period, we will measure short-term outcomes. We plan to measure long-term outcomes, but as this requires at least one full year of follow-up, it is beyond the scope of the funding period. As part of utilization-focused evaluation strategy, we will report on findings and recommendations for broad implementation of educational interventions determined effective.

As described in the Detailed Work Plan and Schedule of Deliverables (Section C3), we will disseminate the findings from the need assessment and evaluation and project deliverables using myriad formats and venues. We will submit abstracts for presentation at three national, professional conferences (BMT Tandem Meetings, ASH annual conference and NCCN annual congress); promote the availability of resources via our website, BeTheMatchClinical.org, and other target marketing and communications campaigns; e-newsletters and periodic emails; and submission of manuscripts for publication in peer-reviewed journals.

C.2.D References Cited

**C.3 Detailed Work Plan and Schedule of Deliverables**

We will implement Phases 1-3 simultaneously as there are interdependencies across each (Table C4). Year 1 will focus on the design, conduct and analysis of the needs assessment (Phase 1). In addition, the AGFBT will begin deliberations on appropriate models for payor-based education and measures of clinical practice with an emphasis on systems thinking (Phase 3). At Year 1 end, we will produce a report on recommendations for the educational interventions that adheres to ACCME criteria (described in Section C.2.B). We will disseminate findings at national, professional meetings and through a peer-reviewed publication.

Each year we will submit progress and findings updates for presentation at the NCCN Congress: Hematologic Malignancies and ASH conferences, both of which have broad attendance by hem/oncs. We will also engage stakeholders including payors, health care purchasers and HCT administrators at the AGFBT monthly and annual meetings and the ASBMT/CIBMTR BMT Tandem Meetings. Year 2 will focus on the design and implementation of educational interventions (Phase 2). This includes continued engagement of the AGFBT to inform the timing of measures of clinical practice as well as the design of the evaluation plan. The final deliverables at Year 2 end will include a resource for payors on education to improve adherence to practice guidelines and measures at the health system level.
<table>
<thead>
<tr>
<th>Phase</th>
<th>Deliverables</th>
<th>Timeline (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Execute contract with NCCN</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Initial discussion of education and incentive models by AGFBT; identify sub-group</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Develop protocol for needs assessment</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>AGFBT session at <em>Defining Quality and Value for Stem Cell Transplant</em> in Minneapolis, MN</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Submit protocol for IRB review</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Conduct quantitative market research</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Monthly meetings with AGFBT sub-group to vet proposed models</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Attend the NCCN Annual Congress: Hematologic Malignancies</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Analyze findings from market research; develop focus group discussion guides</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Recruit for and conduct focus groups</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Attend the American Society of Hematology annual meeting</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Analyze findings of needs assessment and provide recommendations</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Utilize market research findings to narrow options for payer-based model</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Develop educational interventions strategy and plan</td>
<td></td>
</tr>
<tr>
<td>Year 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Develop manuscript highlighting results of needs assessment</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Continue to discuss payer-based models</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Design education interventions, evaluation and instruments as necessary</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>AGFBT meeting, <em>Defining Quality and Value for Stem Cell Transplant</em>, location TBD</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Implement educational strategy and plan</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Attend the NCCN Annual Congress: Hematologic Malignancies</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Attend the American Society of Hematology annual meeting</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Develop guidance resource for payors on education and measures of clinical practice</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Develop manuscript on Phase 2 and Phase 3</td>
<td></td>
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</table>
PART D. ORGANIZATIONAL DETAIL

D.1 Leadership and Organizational Capacity
The applicant organization for this proposal is the National Marrow Donor Program (NMDP), a 501c3 organization incorporated in Colorado and based in Minneapolis, MN. For this project, the NMDP will be responsible for receiving and managing any contract received from NCCN/Pfizer, Inc. and will develop, negotiate and execute contracts with consultants and contractors. The PI (Dr. Murphy), Co-PI (Dr. Navarro) and several key personnel (Ms. Gedan, Ms. Haven, Ms. Farnia and Ms. Denzen) are NMDP employees.

NMDP has the facilities and equipment in place to immediately initiate and successfully perform the activities discussed in this proposal. NMDP is headquartered at 3001 Broadway Street NE in Minneapolis, MN, where it leases approximately 144,785 square feet of office space to support the activities of 935 employees based not only in Minnesota but nationwide as well. NMDP’s facilities have a multi-layered security system for building and computer access.

Finance and Contracts and Procurement Departments
NMDP’s Finance Department and Contracts and Procurement Department have well-developed financial and contract management systems that ensure accurate and timely management of government and other third-party awards. NMDP has successfully managed over 50 contracts, cooperative agreements and grants totaling over $795 million dollars. NMDP’s audited financial statements and schedule of expenditures of federal awards (OMB Circular A-133) substantiate the ability and importance that NMDP places on managing various financial resources. NMDP has never had a significant audit finding. Kiila Lee, Contracts Manager, will have primary responsibility for management and oversight of the NCCN contract. Ms. Lee has extensive experience in contract management. Ms. Lee reports to Nancy Poland, MA, Sr. Manager. She has been with the NMDP for nearly 18 years and has oversight of all contractual activities for NMDP’s research activities. Ms. Poland ultimately reports to Brian Lindberg, JD, Senior Vice President and General Counsel. Mr. Lindberg is responsible for ensuring NMDP’s compliance with the full scope of legal, regulatory, and ethical requirements and standards.

Kevin Weber, Government Cost Analyst, will have primary oversight of the financial aspects of the NCCN Contract. Mr. Weber has over 5 years experience in finance and accounting at the NMDP. Mr. Weber reports to Gina Graves, Assistant Controller and Senior Manager. In her current role, she manages the team responsible for organizational financial reporting, as well as reporting related to third party contracts. She is a Certified Public Accountant with inactive status. Ms. Graves reports to Brian Schmaltz, Director, Finance/Controller, who has 22 years of experience in overseeing financial activities and internal and external reporting.

NMDP Advisory Group on Financial Barriers to Transplant (AGFBT)
The AGFBT was formed in 2012 to address financial barriers to transplant, particularly those that are due to health insurance coverage or benefit issues. The AGFBT provides recommendations to the NMDP Payor Policy and Executive Leadership teams regarding
strategies to address financial barriers to BMT. The AGFBT includes representation from Health Plans, Transplant Networks, Transplant Center Administrators and BMT Physicians (Appendix D). The AGFBT focuses on initiatives that remove or reduce healthcare system barriers to HCT. Previous work has included a set of recommended health insurance benefits for HCT patients, a standard pre-authorization form that can be used by transplant centers to request individual approval for transplant, a white paper defining the various types of transplant-related infusions and a successful conference on transplant costs in June of 2013. The group is engaged, efficient and effective – their roles within their respective organizations ensure that the result of their work efforts are acknowledged and integrated within their corporate structures. Ms. Farnia is NMDP liaison to this Board of Directors advisory group.

D.2 Staff Capacity
The project team will consist of the Principal Investigator (PI), Dr. Murphy; Co-PI, Dr. Navarro; Project Manager, Ms. Gedan; key personnel; other significant contributors and consultants (Figure D1). Our research team is made up of experts with experience in clinical and patient education; systems thinking; hematology/oncology clinical practice; qualitative and market research; program evaluation; payor policy, analysis and relations; strategic marketing and communications. The research team will meet at least once a month via telephone conference calls, and more frequently as needed.

Project Management
Viengnee Thao, MS (Project Manager) is a Health Services Research Analyst at NMDP. She has demonstrated experience leading research initiatives and conducting quantitative analyses in addition to manuscript development. Ms. Thao will dedicate at least 20% effort to this project for two years as described in the project work plan. Any effort above 25% will be provided in kind by NMDP. Through bi-weekly meetings with the PI, Co-PI and Phase leads and monthly project team meetings, she will consistently monitor timelines and milestones; coordinate the activities of each Phase; and monitor the budget. She will work with Contracts and Finance department staff to ensure deliverables and activities are completed as planned. In her current work, Ms. Thao is responsible for leading projects as well as facilitating collaborative work across departments and industries. She reports directly to Ms. Denzen.

Key Personnel
Darlene Haven (Medical Marketing) directs marketing and communications strategy for the clinical, patient, and research functions of NMDP/Be The Match. She has expertise in implementing education programs and clinical resources for physicians and other health care professionals. Ms. Haven’s responsibilities include direction on the design, conduct and analysis of the needs assessment and educational interventions.

Stephanie Farnia, MPH, PhD candidate (Phase 3 lead) has expertise on and leads initiatives focused on removing financial barriers through improving insurance coverage, coding practices and provider reimbursement for HCT. Her responsibilities include direction of Phase 3 activities. She will supervise Ms. Gedan in her role as Project Manager.
Ellen Denzen, MS (Researcher) has experience in the conduct and analysis of qualitative and quantitative health services research and program evaluation. Ms. Denzen’s responsibilities include oversight of the needs assessment, evaluation and manuscript preparation.

Heather Moore, MPH (Evaluator) has more than 8 years experience in health program design and evaluation including expertise on translating research and evaluation findings into practice. Ms. Moore’s responsibilities include qualitative and evaluation design and conduct.

Lih-Wen Mau, PhD, MPH (PhD Statistician) is an experienced investigator in health services research and community health with focus on economic analysis of care. Dr. Mau’s responsibilities for this project will include input on design and analysis plan for the needs assessment and evaluation. She will provide statistical oversight for the project.

Figure D1: Project team organizational chart
March 7, 2014

Dr. Elizabeth Murphy  
National Marrow Donor Program  
3001 Broadway Street NE, Suite 100  
Minneapolis, MN 55413-1753  

RE: National Comprehensive Cancer Network/Pfizer, Inc. Application  

Dear Dr. Murphy,

It is my pleasure to support your National Comprehensive Cancer Network application entitled, “Payor-Partnered Approach to Community-Based Referral for Hematopoietic Cell Transplantation (HCT).”

This project will have a significant impact on improving adherence among community hematologists/oncologists to guidelines on referral for HCT consultation at transplant centers and optimal timing of hematopoietic cell transplantation (HCT) for patients diagnosed with acute myelogenous leukemia. There exists a need to build relationships between referring physicians in the community and transplant physicians. Addressing this critical need means patients are more likely to have access to and improved outcomes of HCT. This proposal will help us understand better the informational and education preferences of community hematologists/oncologists and will lay the groundwork for broad implementation of effective education and non-education strategies.

By leveraging the strengths of National Marrow Donor Program and its payor partners through the NMDP Advisory Group on Financial Barriers to Transplant, you will have access to a captive audience of community physicians as well as data on clinical practice. You may also take advantage of the qualitative and health services research expertise and resources available through the NMDP Patient and Health Professional Services/CIBMTR joint Health Services Research Program to identify specific barriers and facilitators to the implementation of study findings in the hematology/oncology community.

The full resources of the NMDP will be made available to you in order to complete this project.

Sincerely,

Jeffrey W. Chell, MD  
Chief Executive Officer  
National Marrow Donor Program
March 3, 2014

Elizabeth Murphy, EdD, RN  
Vice President, Patient & Health Professional Services  
National Marrow Donor Program / Be The Match  
3001 Broadway Street NE, Suite 100  
Minneapolis, MN 55413-1753

Dear Dr. Murphy:

We are pleased to submit this letter in support of your NCCN/Pfizer proposal, “Developing a Payor-Partnered Approach to Community-Based Referral for Hematopoietic Cell Transplantation,” in response to the Community Oncologist Education and Support Systems - Renal Cell Carcinoma and Hematologic Malignancies request for proposals.

The Advisory Group on Financial Barriers to Transplant (AGFBT) includes a panel of representatives of payor organizations, cancer center administrations and transplant clinical research scientists. The group has been charged with identifying and resolving health insurance or health care reimbursement issues that could be problematic to patients who may be eligible for transplantation procedures and services as appropriate for their individual situations. After discussion with our membership, the group feels that investigating payor-based referral programs and incentives could increase the likelihood of patients receiving hematopoietic cell transplantation within the clinically optimal timeframe. If successful, the models that are proposed within this grant application could be utilized across other areas of specialty care.

As Chairs of the AGFBT, as you well know, we have previously collaborated with the NMDP team on resource development, authorship and dissemination activities, and planning and facilitation of focused meetings on topics of key relevance to the payor and provider communities. We have reviewed the application and are excited about the potential for the creation of these novel strategies that could enhance the outcome of patients with hematologic malignancies, and we are confident in the ability of the NMDP team to achieve the objectives that are outlined in your proposal.

We fully support this current effort and, personally, we are willing to fully support the NMDP in achieving the goals that you propose to pursue within this grant.

Sincerely,

Patricia Martin, RN, BSN  
Director, Specialty Network Management  
Anthem BCBS/WellPoint, Inc.

Richard T. Maziarz, MD  
Medical Director, Adult Blood and Marrow Stem Cell Transplant Program  
Knight Cancer Institute  
Professor of Medicine  
Oregon Health and Science University
March 3, 2014

Dear Dr. Murphy,

I am pleased to submit this letter in support of your NCCN/Pfizer proposal, “Developing a Payor-Partnered Approach to Community-Based Referral for HCT”, in response to the Community Oncologist Education and Support Systems - Renal Cell Carcinoma and Hematologic Malignancies request for proposals.

The University of Kansas Medical Center has relied on and benefited from the expertise and support of the National Marrow Donor Program (NMDP) to improve referrals from community-based cancer centers. As Medical Director of the Blood and Marrow Transplant Program, I am acutely aware of the issues resulting from barriers to referral and access to hematopoietic cell transplantation. NMDP shared their insights and expertise on effective education and outreach efforts, and offered assistance and educational resources that we could use.

Since that time we have revised our referral outreach visits, adopted use of their educational guidelines and innovative online/mobile educational resources, held a regional symposium on the advances in Blood and Marrow Transplantation, and launched a pilot quarterly newsletter to referring physicians, all in collaboration with NMDP.

We have been fortunate to be able to work with individuals at NMDP who share our vision and are equally committed to improving the lives of those we serve. I enthusiastically support their application for this grant.

Sincerely,

Joseph McGuirk, D.O.
Professor of Medicine
Interim Director Hematology/Oncology
Medical Director
Blood and Marrow Transplant
The University of Kansas Medical Center Kansas City, KS
March 5, 2014

Re: Support for the proposal: **Developing a Payor-Partnered Approach to Community-Based Referral for Hematopoietic Cell Transplantation (HCT)**

To: Elizabeth Murphy, Ed. D, RN
National Marrow Donor Program
Director, Office of Patient Advocacy.
3001 Broadway Street N.E., Suite 100
Minneapolis, MN 55413-1753
Phone: (612) 627-5860
E-mail: emurphy@nmdp.org

Dear Dr. Murphy,

I am very pleased to give my highest recommendation and letter of support for your proposal: **Developing a Payor-Partnered Approach to Community-Based Referral for HCT**, in response to the National Comprehensive Cancer Network (NCCN)/Pfizer request for proposals.

I am the Director of the Blood and Marrow Transplantation (BMT) Program at Roswell Park Cancer Institute (RPCI), Buffalo NY, a NCCN-designated cancer center. I am a Professor of Oncology at RPCI. I have been a BMT physician and Hematologist/Oncologist since finishing my fellowship training in 1989. I have been the BMT director at RPCI since 1997. I am a member of the Alliance for Clinical Trials in Oncology (ACTION), formerly the Cancer and Leukemia Group B (CALGB) cooperative clinical trials group, the Center for International Research on Blood and Marrow Transplantation (CIBMTR) as well as a member of the editorial boards of two BMT journals. I have participated in NMDP programs as a member of patient support committees for improving patient access to HCT. I am a member of the Alliance (CALGB) Transplant Committee and Associate Chair of the Multiple Myeloma Committee. I am a member of the board of directors of the Foundation for the Accreditation of Cellular Therapy (FACT), the accrediting body of transplant programs and a member of the Advisory Board of the CIBMTR. I recently completed a 3 year term as a member of the board of directors of the American Society of Blood and Marrow Transplantation (ASBMT). I have been a clinical investigator in hematology/oncology, in particular BMT, for more than 20 years having previously worked at another outstanding comprehensive cancer center, the Dana Farber Cancer Institute/Brigham and Women’s Hospital, Boston, Massachusetts. I am a member of the ASBMT, the American Association for Cancer Research, the American Society of Hematology and the American Society of Clinical Oncology.
I have worked closely with the NMDP on efforts to assess the barriers to appropriate referral for hematopoietic cell transplantation. I have previously collaborated with your staff on research to assess attitudes and perceptions of hematologists/oncologists who refer patients for HCT. This collaboration has resulted in a publication demonstrating a significant percentage of patients with hematologic disorders are not referred for consideration of an unrelated donor HCT as a potentially curative treatment. The NMDP has shown tremendous dedication in assessing the barriers to referral and also in using the results of the research and analyses to overcome these barriers.

Your proposal is innovative. It will incorporate health care payor support in promoting adherence to clinical guidelines among community oncologists. Further the NMDP will continue to develop cutting-edge education so as to reduce barriers to appropriate referral and access to HCT. With improved education and access, this should result in improved HCT outcomes.

I give my highest recommendation and support for your study. I wish you all the best for your grant submission and look forward to collaborating with you on this project. I am confident that as a recipient of this grant award, the NMDP will make a demonstrable difference in the clinical practices of community hematologists/oncologists regarding the care of patients with hematologic malignancies.

Sincerely,

Philip L. McCarthy, M.D.
Professor of Oncology
Director, Blood & Marrow Transplant Program
Department of Medicine
Roswell Park Cancer Institute
Appendix C

Selected Be The Match Clinical Education Resources

These resources are available online at BeTheMatchClinical.org

1. **Improving Referral Consultation Timing:** 2013 NMDP/ASBMT *Recommended Timing for Transplant Consultation*. These guidelines are published jointly by NMDP and ASBMT and highlight disease categories that include patients at risk for disease progressions and who should be referred for hematopoietic cell transplant (HCT) consultation. For some patients, early transplant may be indicated; for others, transplant may be needed later or not at all. Because appropriate planning and early donor identification are critical for optimal outcomes, early consultation is appropriate, even for patients who may never need HCT.

   **Use:** These guidelines are available in a mobile app, online, and in print. We also provide these at no charge to transplant centers for use in education to local referring clinicians in-person meetings or mailing. In addition, these guidelines are available in a slide set to use in these educational events.

2. **Improving Understanding of Key Findings for application of HCT in AML:** For several diseases, NMDP has developed “clinical fact sheets” that summarize key findings of research that should be considering when selecting treatments for a patient. These serve as a quick reference to highlight patient selection, guidelines, trends in treatment, and improvements in survival.

   **Use:** These clinical fact sheets are available online and print. We have completed mailings to all U.S. hem/onc physicians and also provide these (free of charge) to transplant centers to distribute to local referring physicians.

3. **Improving Understanding of New Research and Outcomes data for HCT in AML through CME:** A four-part CME program on AML and MDS in older patients has been viewed by more than 4,100 clinicians. Based on a live symposium preceding ASH (American Society of Hematology) annual meeting. To increase participation, we conducted an effective online and print promotional campaign.

   **Use:** This and other CME programs can be used for clinicians’ self-education and also provided to care teams within the transplant center and to referring communities.

4. **Providing Quick Access to Online Disease Focus Areas of Research and Resources:** Based on research to identify needs for online resources, we developed a new website for clinicians who treat patients who may be eligible for transplantation. The clinicians requested disease-focus areas to help them quickly access resources for themselves and for patient care. Each disease area, including AML, provides access to the latest research studies, slides for use in presentation, referring timing guidelines, and related clinical resources (such as CME programs and clinical fact sheets). We have also included downloadable patient-friendly fact sheets that the clinicians can use for patient education.

   **Use:** Clinicians who care for patients before, during and after transplantation, and who educate others. Transplant centers can also provide links to this online site and...
distribute flyers with the web resources to local referring community. All slides on the site are downloadable and available to use in educational presentations as well.

5. **Providing Template Newsletters for Transplant Centers to use with local Referring Clinicians:** The NMDP market research indicated that referring clinicians wanted brief, relevant communications on advances in transplantation and patient eligibility. In response, NMDP piloted a quarterly newsletter in partnership with University of Kansas. The newsletter is co-branded with an NMDP Network transplant center, with shared contribution to articles.

   **Use:** Transplant centers have access to ready-to-distribute content to increase frequency of communications with local referring clinicians.

**Selected Be The Match Patient Education Resources**
These resources are available online at BeTheMatchClinical.org

1. **Transplant and Acute Myelogenous Leukemia:** This informational fact sheet will introduce patients with a diagnosis of acute myelogenous leukemia (AML) to transplant as a treatment option. It details questions for patients to ask their doctors, outcomes of transplant for AML patients and what to consider when making a treatment decision, along with resources patients can review for additional information.

2. **Referral guidelines for HCT:** These guidelines highlight disease categories and who should be referred for a consultation for transplant. They were developed by the National Marrow Donor Program/Be The Match and the American Society for Blood and Marrow Transplantation and are based on current clinical practice guidelines.

3. **Patient and Family Resources Webpage:** Leukemia, lymphoma, a other life-threatening blood disease patients and their families can navigate to this webpage for an introduction to their disease and treatment options, along with an introduction to the donor search process and the next steps if transplant is an option.

4. **Transplant Center Directory:** Patients considering a transplant can use the Transplant Center Directory to compare transplant centers based on the following characteristics: type of transplant center performs, diseases treated, transplant outcomes, and general cost associated with transplant.
Recommended Timing for Transplant Consultation

Published jointly by the National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation
Recommended Timing for Transplant Consultation

Intent of guidelines

These guidelines highlight disease categories that include patients at risk for disease progression and who should be referred for a consultation for autologous or allogeneic hematopoietic cell transplant (HCT).

For some patients, early transplant may be indicated; for others, transplant may be needed later or not at all. Because appropriate planning and early donor identification are critical for optimal outcomes, early consultation is appropriate, even for patients who may never need HCT.

If allogeneic transplant is an option, high-resolution HLA typing of the patient and potential family donors should be completed early after diagnosis, and if no matches are found, a preliminary unrelated donor search of the Be The Match Registry® should be done.

These 2013 guidelines were developed jointly by the National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation and are based on current clinical practice, medical literature, and evidence-based reviews.¹

¹ Evidence-based Reviews, developed by the American Society for Blood and Marrow Transplantation, 2003–2012. Published in Biology of Blood and Marrow Transplantation and available online at the “Guidelines, Policy Statements and Reviews” page at ASBMT.org
**Acute Myelogenous Leukemia (AML)**

*High resolution HLA typing is recommended at diagnosis for all patients*

Early after initial diagnosis, all AML patients including:
- CR1—except favorable risk AML [defined as: t(16;16); inv 16; t(8;21); t(15;17); normal cytogenetics with NPM1 or biallelic CEBPA mutation and without FLT3-ITD]
- Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))
- Treatment-related leukemia
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

**Acute Lymphoblastic Leukemia (ALL)**

*High resolution HLA typing is recommended at diagnosis for all patients*

Early after initial diagnosis, all ALL patients including:
- CR1
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

**Myelodysplastic Syndromes (MDS)**

Any intermediate or high IPSS score

Any MDS with poor prognostic features, including:
- Treatment-related MDS
- Refractory cytopenias
- Adverse cytogenetics
- Transfusion dependence

**Chronic Myelogenous Leukemia (CML)**

- Inadequate hematologic or cytogenetic response after trial of tyrosine kinase inhibitor (TKI)
- Disease progression
- Intolerance to TKI
- Accelerated phase
- Blast crisis (myeloid or lymphoid)

**Chronic Lymphocytic Leukemia (CLL)**

- High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p); ZAP70, CD38 positivity; unmutated Ig VH mutational status)
- Short initial remission
- Poor initial response
- Fludarabine-resistant
- Richter's transformation
### Acute Myelogenous Leukemia (AML)

*High resolution HLA typing is recommended at diagnosis for all patients*

Early after initial diagnosis, all AML patients including:
- CR1—except favorable risk AML [defined as: t(16;16); inv 16; t(8;21); t(15;17); normal cytogenetics with NPM1 or biallelic CEBPA mutation and without FLT3-ITD]
- Primary induction failure or relapse
- Monosomy 5 or 7
- Age <2 years at diagnosis
- Treatment-related leukemia
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

### Acute Lymphoblastic Leukemia (ALL)

**Infant at diagnosis**
- High Risk CR1 including:
  - Philadelphia chromosome positive
  - WBC >100,000 at diagnosis
  - 11q23 rearrangement
  - Mature B-cell phenotype (Burkitt’s lymphoma)
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

### Lymphomas

#### Non-Hodgkin Lymphoma

- **Follicular**
  - Poor response to initial treatment
  - Initial remission duration <12 months
  - First relapse
  - Transformation to diffuse large B-cell lymphoma

- **Diffuse Large B-Cell or High-Grade Lymphoma**
  - At first or subsequent relapse
  - CR1 for patients with high or high-intermediate IPI risk
  - No CR with initial treatment
  - Second or subsequent remission

- **Mantle Cell**
  - After initiation of therapy

- **Other High Risk Lymphomas**
  - After initiation of therapy

#### Hodgkin Lymphoma

- Primary induction failure or relapse
- Second or subsequent remission

#### Multiple Myeloma

- All patients after initiation of therapy
- At first progression
### Other Malignant Diseases

#### Germ cell tumors
- Short initial remission
- Poor initial response

#### Myeloproliferative Disorders (including BCR-ABL-negative myeloproliferative neoplasms, myelofibrosis and later stages of polycythemia vera and essential thrombocythosis)

Intermediate or high-risk disease including:
- High-risk cytogenetics
- Poor initial response or at progression

#### Neuroblastoma
- Short initial remission
- Poor initial response or at progression

### Non-Malignant Disorders

#### Immune Deficiency Diseases (including Severe Combined Immunodeficiency syndromes, Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, Kostmann syndrome)

- At diagnosis

#### Inherited Metabolic Disorders (including Hurler’s syndrome, adrenoleukodystrophy, and others)

- At diagnosis

#### Hemoglobinopathies

- **Transfusion-Dependent Thalassemias**
  - At diagnosis

- **Sickle Cell Disease**
  - With aggressive course (end-organ complications, frequent pain crises)

#### Hemophagocytic Lymphohistiocytosis (HLH)

- At diagnosis

#### Severe Aplastic Anemia and other marrow failure syndromes (including Fanconi anemia, Diamond-Blackfan anemia, and others)

- At diagnosis
The referral guidelines were developed jointly by the National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation and are based on current clinical practice, medical literature, and evidence-based reviews.

Supported by an unrestricted educational grant from Otsuka America Pharmaceutical, Inc., provided to the National Marrow Donor Program through Be The Match Foundation®
Survival is improving. Allogeneic transplant outcomes have improved due to advances in clinical practice and human leukocyte antigen (HLA) typing and matching.

Patient eligibility is expanding. Improved outcomes now allow for more patients to be considered for transplant, resulting in growth in transplants for older patients and those in first complete remission (CR1).

Molecular markers influence therapy choices. New classifications based on cytogenetic and molecular abnormalities in AML allow physicians to better stratify patients into risk groups and select appropriate therapies.
This summary provides clinicians with an overview of recent trends in allogeneic transplantation for acute myelogenous leukemia (AML) in adults and how the latest research affects clinical decision-making. Worldwide, more than 7,000 allogeneic hematopoietic cell transplants (HCT) are performed annually for AML, making it the most common and fastest growing indication for allogeneic transplantation. Several factors have led to new applications of HCT to treat AML, including improved outcomes, expanded patient selection and refined risk stratification.

Refined Patient Selection

Molecular Markers Influence Therapy Choices

In 2008, the World Health Organization (WHO) re-classified AML into eight distinct categories with 25 sub-classifications based on the underlying cytogenetic and molecular genetic abnormalities that characterize AML.

Based on these WHO classifications, clinicians are now better able to refine risk stratification of patients with AML into prognostic risk groups and selecting those patients most likely to benefit from allogeneic HCT.

Survival Benefit of HCT in Intermediate-Risk AML in CR1

A 2009 meta-analysis demonstrated the survival benefit of allogeneic HCT for intermediate-risk AML in first complete remission (CR1) over chemotherapy and autologous transplantation (see Table 1). Based on this research, transplant consultation guidelines have recently been updated (see Table 2).

<table>
<thead>
<tr>
<th>CYTOGENETIC RISK</th>
<th># OF TRIALS</th>
<th>HAZARD RATIO (95% CI)</th>
<th>P-VALUE</th>
<th>ALLOGENEIC BENEFIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good-risk</td>
<td>10</td>
<td>1.06 (0.80–1.42)</td>
<td>0.68</td>
<td>No</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>14</td>
<td>0.76 (0.68–0.85)</td>
<td>&lt;0.01</td>
<td>Yes</td>
</tr>
<tr>
<td>Poor-risk</td>
<td>14</td>
<td>0.69 (0.57–0.84)</td>
<td>&lt;0.01</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Table 1: Allogeneic HCT in patients with intermediate- and poor-risk AML in CR1 have significantly better relapse-free survival compared to consolidation chemotherapy and autologous transplantation.

Transplant Guidelines Updated

Based on the new research, transplant consultation guidelines from the National Marrow Donor Program (NMDP) and the American Society for Blood and Marrow Transplantation (ASBMT) were updated to recommend that intermediate-risk AML patients in CR1 be referred for transplant consultation (see Table 2).

The intent of these guidelines, based on evidence-based reviews, is to identify patients at risk of disease progression and, therefore, which patients should be evaluated for transplantation.

Recommended Timing for Transplant Consultation

<table>
<thead>
<tr>
<th>ADULT ACUTE MYELOGENOUS LEUKEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk AML including:</td>
</tr>
<tr>
<td>• Antecedent hematological disease (e.g., myelodysplasia (MDS))</td>
</tr>
<tr>
<td>• Treatment-related leukemia</td>
</tr>
<tr>
<td>• Induction failure</td>
</tr>
<tr>
<td>CR1 with intermediate- or poor-risk cytogenetics or molecular markers</td>
</tr>
<tr>
<td>AML after relapse</td>
</tr>
<tr>
<td>CR2 and beyond</td>
</tr>
</tbody>
</table>

Table 2: Excerpt from NMDP/ASBMT guidelines, which recommend transplant consultation for adult AML patients with: 1) high-risk disease, 2) CR1 with intermediate or poor-risk cytogenetics or molecular markers, and 3) CR2 and beyond.
Increased Use in Older Patients

Reduced-Intensity HCT Expands Eligibility

Reduced-intensity conditioning regimens have expanded HCT to older patients and those with comorbidities unable to undergo myeloablative HCT. Studies show that reduced-intensity HCT can have comparable outcomes to myeloablative transplants using both related and unrelated donors.6,7,8,9

Effect of Age on Survival

A multicenter study of 545 adults age 40–79 years with AML undergoing reduced-intensity transplantation did not identify age as a significant factor affecting overall survival.10 Other clinical studies have also shown that HCT can be appropriate therapy for older patients with AML.6,9

Improved Survival

Several factors have led to the steady improvement in overall survival after HCT, including:

Clinical Practice Advances

• Improved ability to manage post-transplant complications12
• Preparative regimens, such as reduced-intensity conditioning, tailored to the patient’s disease and condition5

HLA Matching Advances

• DNA-based patient and donor tissue typing13,14
• Identification of which HLA loci are most significant to outcomes13–15

Several recently published studies show that unrelated donor transplant outcomes in AML are now comparable to related donor transplant results.7,14–18 Table 3 shows the improvement over time for unrelated transplants facilitated by the NMDP.19 These improved outcomes have been achieved even as a greater number of older patients are being transplanted.

<table>
<thead>
<tr>
<th>YEAR OF HCT</th>
<th>NUMBER OF CASES</th>
<th>ONE-YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008–2010</td>
<td>2,837</td>
<td>58%</td>
</tr>
<tr>
<td>2004–2007</td>
<td>2,362</td>
<td>52%</td>
</tr>
<tr>
<td>1999–2003</td>
<td>1,287</td>
<td>41%</td>
</tr>
<tr>
<td>1987–1998</td>
<td>919</td>
<td>26%</td>
</tr>
</tbody>
</table>

Table 3. One-year survival of adults with AML after unrelated HCT is significantly better for patients transplanted during 2004–2007 and 2008–2010 (p<0.001) compared to patients transplanted during 1987–1998 and 1999–2003 (p<0.001).20

ACCESS AML RESOURCES

When considering AML as a treatment for patients with AML, quickly access:

• clinical resources
• education
• latest research to help guide decision-making

Visit marrow.org/md-AML
CLINICAL ACTION POINTS

1. Use molecular markers to stratify patients with AML into prognostic risk groups and identify those most likely to benefit from allogeneic HCT.

2. Recommend transplant consultation for patients in CR1 with intermediate- or poor-risk AML.

3. Review current protocols and consider HCT as a treatment option for older patients with AML.

References:


11. NMDP 2011 fiscal year reports.


20. CIBMTR Analysis of NMDP Facilitated Transplants 2012.

The National Marrow Donor Program (NMDP) is the global leader in providing marrow and umbilical cord blood transplants to patients with leukemia, lymphoma and other diseases. The nonprofit organization matches patients with donors, educates healthcare professionals and conducts research so more lives can be saved. The NMDP also operates Be The Match®, which provides support for patients, and enlists others in the community to join the Be The Match® Registry® – the world’s largest listing of potential marrow donors and donated cord blood units – contribute financially and volunteer. Learn more at marrow.org/md.
AML and MDS in Older Patients

Access education course
(Medscape requires a one-time free registration to access)

Description
Explore practical applications of classification and research data to compare treatment choices for older AML and MDS patients, including:

- How diagnostic testing has changed the timing of therapeutic choices and if age should be considered
- Applying data to mitigate risk and optimize the benefit among new drugs, transplantation, and combination approaches
- What coverage options are available for Medicare-eligible patients

Target Audience
This activity is intended for hematologists, oncologists, and other health care professionals who treat patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML).

Learning Objectives
1. Identify disease- and patient-related factors that predict outcomes of hematopoietic cell transplantation (HCT), new drugs, or combination therapy in older patients with MDS and AML
2. Explain recent clinical trial results that have influenced the selection of patients in trials for treatment of MDS and AML
3. Compare the risks and benefits of treatment options and how timing of therapy choices affects outcomes
Acute Myelogenous Leukemia (AML) - Adult

Worldwide, physicians perform more than 7,000 allogeneic transplants for AML, making it the most common and fastest growing indication for allogeneic hematopoietic cell transplantation (HCT). [1] In contrast, autologous transplants for AML are relatively rare.

Figure 1. AML Unrelated HCT, by Age

Download slide
Worldwide, more than 7,000 allogeneic hematopoietic cell transplants (HCT) are performed annually for acute myeloid leukemia (AML), making it the most common and fastest-growing indication for allogeneic transplantation.

In AML, research has clarified the role of transplant, resulting in improved outcomes. In addition, non-myeloablative and reduced-intensity conditioning regimens have expanded this therapy to more patients who would previously have been ineligible.

Table 1 shows National Marrow Donor Program (NMDP) data demonstrating steadily increasing one-year survival in adults undergoing allogeneic HCT for AML.

<table>
<thead>
<tr>
<th>Year of HCT</th>
<th>Number of Cases</th>
<th>One-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008-2010</td>
<td>2,837</td>
<td>58%</td>
</tr>
<tr>
<td>2004-2007</td>
<td>2,362</td>
<td>52%</td>
</tr>
<tr>
<td>1999-2003</td>
<td>1,287</td>
<td>41%</td>
</tr>
<tr>
<td>1987-1998</td>
<td>919</td>
<td>26%</td>
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</table>

### Improved survival over time–AML

#### Research defines optimal transplant timing and advances

The improvement in HCT outcomes in AML mirrors the trend for improved survival in nearly all diseases treated by allogeneic transplantation. [1,2] A key reason for improved survival is a better understanding of optimal timing for HCT. Research has shown, for example, that transplanting AML patients with high-risk cytogenetics while in first complete remission (CR1) improves outcomes compared with chemotherapy or delayed transplant. [3]

Other important reasons for improved survival include:

- Improved patient/donor human leukocyte antigen (HLA) matching using DNA-based tissue typing
- Better understanding of which HLA loci are most significant to outcomes
- Improved ability to manage post-transplant complications

Improved clinical outcomes from HCT for AML are driven by advances in the biology of AML which help identify patients at higher risk of relapse from chemotherapy alone. These biological markers provide clinicians with personalized information to guide the decision process for each patient.

### Transplant consultation guidelines in AML

NMDP/Be The Match and the American Society for Blood and Marrow Transplantation (ASBMT) have jointly developed transplant consultation guidelines based on current clinical practice, medical literature and evidence-based reviews. According to the guidelines for AML, shown in Figure 1, patients with the following subtypes of AML should be HLA-typed and referred for transplantation consultation as soon as disease risk is known.

**Acute Myelogenous Leukemia (AML)**

- High-risk AML including:
  - Antecedent hematological disease (e.g., myelodysplasia (MDS))
  - Treatment-related leukemia
  - Induction failure
- CR1 with intermediate- or poor-risk cytogenetic or molecular markers
- AML after relapse
- CR2 and beyond

Figure 1. NMDP/ASBMT guidelines for adults with AML

### Spotlight on AML: Transplant outcomes improving

To help guide patient treatment choices, we have developed transplant consultation guidelines in support of our Network partnership with The University of Kansas Hospital. These guidelines are designed to help clinicians with personalized information to guide the decision process for each patient.

**BMT program highlights**

- Region’s largest BMT and acute leukemia program: The widest range of treatment options, including photopheresis and clinical trials
- Region’s first BMT program accredited by the Foundation for Accreditation of Cellular Therapy, or FACT
- More than 1,800 successful transplants
- Designated as a BMT-CTN core center
- Designated as a Center of Excellence for all payers that utilize this distinction
- Network member of the National Marrow Donor Program since 1995
- Medicare-approved since 1977

### Dear Colleague

This issue of Transplant Connection focuses on acute myeloid leukemia (AML) including recent transplant outcomes, advances in the understanding of AML genetic mutations and the impact of age on transplant outcomes.

In addition, I’d like to invite you to attend our Advances in Blood and Marrow Transplantation CME-certified symposium on April 27, 2013. I’m excited to discuss the latest in optimal pathways of care for patients with complex hematological malignancies. Details about this free event are on page 3.

**Joseph P. McQuirk, DO**

Director, Blood and Marrow Transplant (BMT) Program

The University of Kansas Cancer Center

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Prognostic utility of genetic markers in intermediate-risk AML

Unlike patients with AML who have low- and high-risk cytogenetic risk factors, AML patients in the intermediate-risk group have heterogeneous clinical outcomes and require a more individualized treatment plan. The majority of AML patients fall into this intermediate-risk group, and between 40% and 50% of these will have normal cytogenetics. In order to devise a personalized treatment plan for these patients, clinicians must understand and incorporate a growing number of molecular markers of prognosis.

Although research on genetic mutations in AML has yielded dozens of genetic biomarkers with potential prognostic value, there are challenges to incorporating this fast-moving data in everyday patient care. For example, some genetic mutations only exert their influence when coexisting with other mutations or chromosomal translocations. Also, most of these recently identified markers have been isolated in small patient subsets, making it difficult to know how generalizable the results may be.

Recent research, however, has identified three molecular markers in AML that have now also been integrated into clinical practice guidelines developed by the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) consortium. [1,2]

Three markers define genetic risk groups

The NCCN and ELN guidelines incorporate the FLT3-ITD, NPM1 and CEBPA molecular markers/genetic abnormalities, which were included in the World Health Organization (WHO) classification for AML in 2008. [3] Based on the mutational status of these markers, AML patients can be classified into four genetic risk groups: favorable, intermediate-I, intermediate-II, and adverse. In order to better stratify patients with normal cytogenetics, particularly given the difficulty of achieving a second remission for patients with relapsed AML, [5] given the significantly worse outcomes for patients with AML in the intermediate-I, II and adverse risk categories, allogeneic stem cell transplantation is recommended for all intermediate-adverse risk AML patients in first complete remission, depending upon donor availability.

Timely referral to a transplant center immediately after completion of induction chemotherapy is critically important in moving quickly to HCT while in remission.

HCT outcomes by genetic risk group

These guidelines have recently been validated for their prognostic value in a study of 1,550 adult AML patients treated between 1985 and 2006. [4] Eligible patients had cytogenetically normal AML with known mutational status of NPM1, CEBPA, and FLT3-ITD. Primary end points included complete remission (CR), disease-free survival (DFS), and overall survival (OS) among patients classified into the four ELN risk groups. Outcomes were studied separately for patients age >60 years (<181) and those ≥60 years (n=732).

Table 2 shows outcomes of the younger (age <60 years) patients according to ELN genetic risk groups. Patients in the favorable group had significantly better CR, DFS, and OS compared to patients in the adverse classification (p<0.001). Results were similar in patients ≥60, with patients in the favorable group also having significantly better CR, DFS, and OS rates compared to patients in the adverse group.

Early consideration of transplant recommended

A recent review by two international experts in AML and stem cell transplantation, Drs. Stephen Forman and Jacob Rowe, highlights the need for consideration for transplantation for patients with AML, particularly given the difficulty of achieving a second remission for patients with relapsed AML. [5] Given the significantly worse outcomes for patients with AML in the intermediate-I, II and adverse risk category, allogeneic stem cell transplantation is recommended for all intermediate-adverse risk AML patients in first complete remission, depending upon donor availability.

Timely referral to a transplant center immediately after completion of induction chemotherapy is critically important in moving quickly to HCT while in remission.

In this study of MDS (n=535) and AML (n=545) patients reported to the CIBMTR (Center for International Blood and Marrow Transplant Research) between 1995-2005, patients were studied in four age groups: 40-54, 55-59, 60-64 and ≥65 years. Median follow-up time for the four age cohorts ranged from 25 to 37 months.

Most patients received peripheral blood stem cells (n=896) versus bone marrow (n=184), and most received unrelated donor grafts (n=611) versus identical sibling grafts (n=469). The following variables were well balanced within the different age groups: sex, interval from diagnosis to transplantation, performance status, donor/recipient cytogenetics and degree of unrelated donor/recipient HLA match.

Two-year overall survival is shown in Table 3. Multivariate analysis found no significant impact of age on non-relapse mortality, disease-free survival or overall survival (all p<0.3). Day-100 incidence of grade II-IV acute graft-versus-host disease was similar across all groups for both diseases (AML: 33% - 35%, p=0.96; MDS: 31% - 36%, p=0.89).

Impact of age on outcomes

No significant impact of age on transplant outcomes in AML/MDS

A study of reduced intensity transplantation in 1,080 adults older than 40 years of age with AML in first complete remission or myelodysplastic syndromes (MDS) has shown that age has no effect on outcomes. [1]

Older age alone should not be considered a contraindication to HCT.

In this study of MDS (n=535) and AML (n=545) patients reported to CIBMTR (Center for International Blood and Marrow Transplant Research) between 1995-2005, patients were studied in four age groups: 40-54, 55-59, 60-64 and ≥65 years. Median follow-up time for the four age cohorts ranged from 25 to 37 months.

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Table 3. Two-year overall survival of patients >40 years transplanted for MDS or AML in first complete remission.

<table>
<thead>
<tr>
<th>AML AGE RANGE (years)</th>
<th>55-59</th>
<th>60-64</th>
<th>≥65</th>
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<tbody>
<tr>
<td>MDS</td>
<td>44%</td>
<td>50%</td>
<td>54%</td>
</tr>
<tr>
<td>AML</td>
<td>45%</td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td>MDS</td>
<td>42%</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>AML</td>
<td>38%</td>
<td></td>
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</tbody>
</table>

Older age was not associated with higher relapse rates, despite the higher percentage of patients with high-risk disease in the older patient groups. The researchers noted that HCT resulted in 2-year survival rates of >70% in all age groups, “whereas conventional chemotherapy offers almost no chance of extended survival for older patients with AML or MDS.” The researchers concluded that “older age alone should not be considered a contraindication to HCT.”

Phase II trial of a lenalidomide regimen or a sequential azacitidine plus lenalidomide regimen in older subjects with AML. Patients age 65 and older with newly diagnosed or secondary AML are eligible. Stem cell transplant candidates are excluded.

Visit kuccancercenter.org/campaigns to learn about these and other additional BMT and hematologic malignancy clinical trials. Refer a patient

We invite you to attend our upcoming Advances in Blood and Marrow Transplantation Symposium. This CME-certified program will review the latest advances in the field of autologous and allogeneic transplantation and supportive care:

- Date: Saturday, April 27, 2013
- Time: 8:45 a.m.-5 p.m.
- Location: Robert E. Hemenway Life Sciences Innovation Center, Kansas City, Kan.

View program details

The full conference brochure is available at continued.ku.edu/kumc/bmt

Register

Registration is free of charge.
Call 877-404-5823 or visit continued.ku.edu/kumc/bmt

AML CLINICAL TRIALS SPOTLIGHT

Currently, The University of Kansas Cancer Center clinical trials for patients with AML include:

- Phase III randomized trial of CPX-351 or “1+3” as induction for patients ages 60-75 with secondary AML or AML with high risk cytogenetics. CPX-351 is a novel, liposomal formulation of daunorubicin and cytarabine with phase II data demonstrating improved CR rates and overall survival in patients with AML. Transplant candidates are eligible.

- Phase Ib/II trial of PF-0449913, a Hedgehog inhibitor, in combination with low-dose Ara-C or decitabine in patients under conventional induction chemotherapy. Hedgehog inhibitors have shown promise in targeting the leukemia stem cells in pre-clinical models, and this early phase study is designed to find the maximum tolerated dose and efficacy of the PF-0449913 in combination with traditional AML therapy.

- Phase II study of a lenalidomide regimen or a sequential azacitidine plus lenalidomide regimen in older subjects with AML. Patients age 65 and older with newly diagnosed or secondary AML are eligible. Stem cell transplant candidates are excluded.

Visit kuccancercenter.org/campaigns to learn about these and other additional BMT and hematologic malignancy clinical trials.

Refer a patient

Contact us at 913-588-1227 or toll free at 800-332-6048.
Learning more about your disease and treatment options can help you make informed decisions about your health care. Be The Match® can help you understand how transplant may be used to treat AML.

To get started, read on to learn about:
- How transplant can treat AML
- If transplant helps your type of AML
- If transplant is right for you
- Questions to ask your doctor
- Transplant outcomes for AML
- Initial treatment of AML
- Making treatment decisions

About Acute Myelogenous Leukemia (AML)

Acute myelogenous leukemia (AML) is a fast-growing cancer of the blood and bone marrow. It is also sometimes called acute myeloid leukemia. In AML, the bone marrow makes many cancerous cells called leukemic blasts. Normal blasts develop into white blood cells that fight infection. In AML, the leukemic blasts do not develop properly and cannot fight infections. These leukemic blasts grow quickly and crowd out the bone marrow, preventing it from making the normal red blood cells, white blood cells, and platelets that the body needs.

Nearly 15,000 people in the United States are diagnosed with AML each year.¹ AML can affect people of any age, but it is most common in adults. The cause of AML is unknown.

How transplant can treat AML

A bone marrow or cord blood transplant begins with chemotherapy, with or without radiation, to destroy the diseased cells and marrow. The transplant replaces diseased blood-forming cells with healthy ones. There are two types of transplants: allogeneic and autologous. An allogeneic transplant uses healthy blood-forming cells from a family member, unrelated donor, or umbilical cord blood unit. An autologous transplant uses the patient’s own blood-forming cells, which are collected and stored.

In both types, a patient gets chemotherapy, with or without radiation, prior to transplant to prepare his or her body for the treatment. Then the replacement cells are infused into the patient’s blood stream. From there, the cells find their way into the bone marrow, where they start making healthy red blood cells, white blood cells, and platelets. The entire process, from the start of chemotherapy or radiation, until hospital discharge, can last weeks to months, followed by many months of recovery at home.

For some patients with AML, chemotherapy alone may bring long-term remission. Remission means that tests cannot find any leukemia cells and a patient is symptom-free. But for others, the disease is more aggressive and chemotherapy alone may not be enough. For these patients, getting a referral to a transplant doctor early in their disease may offer the best route to a cure or a long-term remission.

Most transplants for AML are allogeneic. Autologous transplant isn’t usually used for AML because the risk of relapse (a return of the disease) is higher than with allogeneic transplant.

Key points:
- Chemotherapy alone may be the best treatment for some patients, while for others, early referral to a transplant doctor is the best route to a cure or long-term remission
- If transplant is needed, getting a transplant early in the disease may offer the best outcome
- Most transplants for AML are allogeneic
Understanding if transplant would help your AML

Whether a transplant is right for you depends on how likely the disease is to return. This is based on certain features of the leukemia, called risk factors, and your general health. A transplant doctor will weigh the risk of the leukemia coming back against getting a transplant that may cure the leukemia, but may also cause other problems. The doctor also considers whether your specific risk factors are a sign that chemotherapy is not likely to lead to a cure or long-term remission.

One way a doctor determines how likely the leukemia is to return is through cytogenetic testing. This means looking at the chromosomes in the leukemia cells. Chromosomes are thread-like strands of DNA that carry genetic information about your body. Certain changes in the chromosomes predict a lower risk of the disease returning. Others predict a higher risk.

If your disease has a high chance of returning and you are a good candidate for transplant, delaying a transplant may lower your likelihood of long-term remission or cure.

There are medical guidelines for when someone should be referred for a transplant consultation, whether or not you might be need a transplant at that time. Talking to a transplant doctor is especially recommended if your disease has any of the following features:

For AML in adults:
- You had a disease such as myelodysplastic syndrome (MDS) that became AML
- Your AML was caused by another treatment, such as chemotherapy for another disease
- Your initial chemotherapy doesn’t lead to remission
- Your initial chemotherapy leads to a remission, but cytogenetic or molecular testing shows high risk disease
- You relapse one or more times after chemotherapy

For AML in children:
- Your child has high-risk cytogenetics such as monosomy 5 or 7
- Your child is under the age of two when diagnosed
- Your child’s AML was caused by another treatment, such as chemotherapy for another disease
- Your child’s initial chemotherapy doesn’t lead to remission
- Your child’s initial chemotherapy leads to remission, but cytogenetic or molecular testing shows high risk disease
- Your child relapses one or more times after chemotherapy

Key points:
- Ask your doctor about your specific risk factors and the possibility of remission or cure with or without a transplant
- If cytogenetic testing shows that your disease has a high risk of returning, ask for a referral to a transplant doctor to find out if transplant is right for you

How a transplant doctor helps you decide if transplant is right for you

To find out if transplant is right for you, you will need a physical check-up by your transplant doctor. During the check-up, your lungs, heart, liver, kidneys, and nervous system will be checked. The transplant doctor will also review your health history and current status of your disease.

You will also meet with other members of the health care team. A social worker or other professional will meet with you to talk about your concerns related to transplant (for example: emotional, financial, travel, lodging, work and/or school). The social worker can help you find resources to support you during your transplant journey. Most transplant centers (hospitals that do
transplants) require you to have a dedicated caregiver to help you through the recovery process.

**Key points:**
- A transplant doctor will look at many things including your health history, disease status and the risks and benefits of transplant before recommending a transplant
- A transplant social worker is available to help you and your family with emotional and practical support

**Questions to ask your doctor**

It is important to ask questions so you are comfortable with the treatments that your doctors recommend and so you can make decisions about your treatment. Questions you may want to ask your doctor include:
- What are my chances of living disease-free if I get a transplant? If I don’t get a transplant?
- What are the risks of waiting or trying other treatments before a transplant?
- Do I have any risk factors that might affect my transplant outcomes?
- How much does my age influence my risk?
- What are the possible side effects of transplant? How can they be reduced?
- What can you tell me about my quality of life if I get a transplant? If I don’t?
- How might my quality of life change over time, with or without transplant?

**Key point:**
- Don’t be afraid to ask questions so you understand which treatments are right for you

**Transplant outcomes for AML**

Outcomes data (information on how patients have done after their transplant) is used to estimate transplant outcomes. Outcomes data only show how other patients have done as a group. This information can’t tell how you will do for sure. It can only give you an idea of how other patients have done with a similar disease and treatment. No two people are exactly the same, and you may respond differently to your transplant than someone else. Talk to your transplant doctor about how outcomes data may apply to your specific situation. Fortunately, transplant outcomes have continued to improve over time.

**Key point:**
- Transplant outcomes overall are useful but only your transplant team can tell you what your chances are of doing well

**Initial treatment of AML**

Some form of chemotherapy will be part of the treatment plan for almost all patients with AML, whether or not they go on to receive a transplant. Chemotherapy is a treatment that uses a group of medicines that destroy cancer cells or stop them from growing.

There are typically two phases of chemotherapy for AML: induction and consolidation.

**Induction chemotherapy**

Most patients with AML are given induction chemotherapy. The goal is to bring the disease into remission. Induction therapy is usually intense. Though the chemotherapy typically lasts about one week, it may take three or more weeks in the hospital to recover from the treatment. After induction chemotherapy, the next step may be a transplant or consolidation chemotherapy, depending on the treatment plan.

**Consolidation chemotherapy**

Consolidation therapy is the standard treatment at first remission, and it is also intense. The goal of this therapy is to lower the number of or eliminate diseased cells left in the body. It consists of monthly treatments with recovery time in between. The whole series of treatment may last several months.
**Relapsed disease**

Induction therapy brings about a remission in most patients, but over time some patients will relapse (return of the disease). Patients who relapse after chemotherapy may be treated with different chemotherapy drugs and/or more intense doses. Patients who relapse soon after remission or who fail to have a remission after initial induction treatment have high-risk disease. For these patients, a referral to a transplant doctor is necessary because a second round of chemotherapy is less likely to bring about long-term remission. A bone marrow or cord blood transplant may be the best option for a cure or long-term remission.

**Making treatment decisions**

It is important to know your treatment options so you can make the best decision for yourself. Soon after your diagnosis, ask your doctor if a consultation with a transplant doctor is right for you. When you meet with a transplant doctor, there are two main decisions to make. The first decision is whether to have a transplant. A transplant doctor can help you understand the risks and benefits of transplant for your specific situation.

The second decision is when to have a transplant. Getting a transplant at the right time in the course of your disease may offer the best chance of a cure. The transplant doctor will work with you to decide what timing for the transplant is best for you.

**Other resources to help you learn more**

Be The Match has a variety of free resources to help you learn about transplant. Visit BeTheMatch.org/patient-learn and choose the resources that best meet your needs. Here are just a few that you might find helpful:

- Webcast: *An Introduction to Marrow and Cord Blood Transplant*
- Booklet: *An Introduction to Marrow and Cord Blood Transplant*
- Brochure: *Understanding Transplant Outcomes Data*

Be The Match has a team dedicated to providing information and support to you before, during, and after transplant. You can contact us to ask questions you may have about transplant, to request professional or peer support, or to receive free patient education materials.

**Call: 1-888-999-6743**

**Email:** patientinfo@nmdp.org

**Web:** BeTheMatch.org/patient-learn
Reference


2. Recommended Timing for Transplant Consultation. Guidelines developed jointly by National Marrow Donor Program/Be The Match and the American Society for Blood and Marrow Transplantation (ASBMT). Available at: marrow.org/md-guidelines

Most recent medical review completed 6/2013
Recommended Timing for Transplant Consultation

Published jointly by the National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation
Recommended Timing for Transplant Consultation

Intent of guidelines

These guidelines highlight disease categories that include patients at risk for disease progression and who should be referred for a consultation for autologous or allogeneic hematopoietic cell transplant (HCT).

For some patients, early transplant may be indicated; for others, transplant may be needed later or not at all. Because appropriate planning and early donor identification are critical for optimal outcomes, early consultation is appropriate, even for patients who may never need HCT.

If allogeneic transplant is an option, high-resolution HLA typing of the patient and potential family donors should be completed early after diagnosis, and if no matches are found, a preliminary unrelated donor search of the Be The Match Registry® should be done.

These 2013 guidelines were developed jointly by the National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation and are based on current clinical practice, medical literature, and evidence-based reviews.¹

¹ Evidence-based Reviews, developed by the American Society for Blood and Marrow Transplantation, 2003–2012. Published in Biology of Blood and Marrow Transplantation and available online at the “Guidelines, Policy Statements and Reviews” page of ASBMT.org
<table>
<thead>
<tr>
<th><strong>Acute Myelogenous Leukemia (AML)</strong></th>
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<tbody>
<tr>
<td><strong>High resolution HLA typing is recommended at diagnosis for all patients</strong></td>
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<tr>
<td>Early after initial diagnosis, all AML patients including:</td>
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<tr>
<td>• CR1—except favorable risk AML [defined as: t(16;16); inv 16; t(8;21); t(15;17); normal cytogenetics with NPM1 or biallelic CEBPA mutation and without FLT3-ITD]</td>
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<tr>
<td>• Antecedent hematological disease (e.g., myelodysplastic syndrome (MDS))</td>
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<td>• Treatment-related leukemia</td>
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<td>• Primary induction failure or relapse</td>
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<tr>
<td>• Presence of minimal residual disease after initial or subsequent therapy</td>
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<td>• CR2 and beyond, if not previously evaluated</td>
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<thead>
<tr>
<th><strong>Acute Lymphoblastic Leukemia (ALL)</strong></th>
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<td><strong>High resolution HLA typing is recommended at diagnosis for all patients</strong></td>
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<tr>
<td>Early after initial diagnosis, all ALL patients including:</td>
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<tr>
<td>• CR1</td>
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<tr>
<td>• Primary induction failure or relapse</td>
<td></td>
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<tr>
<td>• Presence of minimal residual disease after initial or subsequent therapy</td>
<td></td>
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<tr>
<td>• CR2 and beyond, if not previously evaluated</td>
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<thead>
<tr>
<th><strong>Myelodysplastic Syndromes (MDS)</strong></th>
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<tr>
<td>Any intermediate or high IPSS score</td>
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<tr>
<td>Any MDS with poor prognostic features, including:</td>
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<tr>
<td>• Treatment-related MDS</td>
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<tr>
<td>• Refractory cytopenias</td>
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<tr>
<td>• Adverse cytogenetics</td>
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<td>• Transfusion dependence</td>
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<thead>
<tr>
<th><strong>Chronic Myelogenous Leukemia (CML)</strong></th>
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<tbody>
<tr>
<td>• Inadequate hematologic or cytogenetic response after trial of tyrosine kinase inhibitor (TKI)</td>
<td></td>
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<tr>
<td>• Disease progression</td>
<td></td>
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<tr>
<td>• Intolerance to TKI</td>
<td></td>
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<tr>
<td>• Accelerated phase</td>
<td></td>
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<tr>
<td>• Blast crisis (myeloid or lymphoid)</td>
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<thead>
<tr>
<th><strong>Chronic Lymphocytic Leukemia (CLL)</strong></th>
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<tbody>
<tr>
<td>• High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p); ZAP70, CD38 positivity; unmutated Ig VH mutational status)</td>
<td></td>
</tr>
<tr>
<td>• Short initial remission</td>
<td></td>
</tr>
<tr>
<td>• Poor initial response</td>
<td></td>
</tr>
<tr>
<td>• Fludarabine-resistant</td>
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<tr>
<td>• Richter’s transformation</td>
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</table>
Acute Myelogenous Leukemia (AML)

High resolution HLA typing is recommended at diagnosis for all patients

Early after initial diagnosis, all AML patients including:
- CR1—except favorable risk AML [defined as: t(16;16); inv 16; t(8;21); t(15;17); normal cytogenetics with NPM1 or biallelic CEBPA mutation and without FLT3-ITD]
- Primary induction failure or relapse
- Monosomy 5 or 7
- Age <2 years at diagnosis
- Treatment-related leukemia
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

Acute Lymphoblastic Leukemia (ALL)

Infant at diagnosis
- High Risk CR1 including:
  - Philadelphia chromosome positive
  - WBC >100,000 at diagnosis
  - 11q23 rearrangement
  - Mature B-cell phenotype (Burkitt’s lymphoma)
- Primary induction failure or relapse
- Presence of minimal residual disease after initial or subsequent therapy
- CR2 and beyond, if not previously evaluated

Lymphomas

Non-Hodgkin Lymphoma

Follicular
- Poor response to initial treatment
- Initial remission duration <12 months
- First relapse
- Transformation to diffuse large B-cell lymphoma

Diffuse Large B-Cell or High-Grade Lymphoma
- At first or subsequent relapse
- CR1 for patients with high or high-intermediate IPI risk
- No CR with initial treatment
- Second or subsequent remission

Mantle Cell
- After initiation of therapy

Other High Risk Lymphomas
- After initiation of therapy

Hodgkin Lymphoma

- Primary induction failure or relapse
- Second or subsequent remission

Multiple Myeloma

- All patients after initiation of therapy
- At first progression
<table>
<thead>
<tr>
<th>Other Malignant Diseases</th>
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<tbody>
<tr>
<td><strong>Germ cell tumors</strong></td>
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<tr>
<td>· Short initial remission</td>
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<tr>
<td>· Poor initial response</td>
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<thead>
<tr>
<th><strong>Myeloproliferative Disorders</strong> (including BCR-ABL-negative myeloproliferative neoplasms, myelofibrosis and later stages of polycythemia vera and essential thrombocytosis)</th>
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<tbody>
<tr>
<td>Intermediate or high-risk disease including:</td>
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<tr>
<td>· High-risk cytogenetics</td>
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<td>· Poor initial response or at progression</td>
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<tr>
<th><strong>Neuroblastoma</strong></th>
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<tr>
<td>· Short initial remission</td>
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<tr>
<th>Non-Malignant Disorders</th>
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<tbody>
<tr>
<td><strong>Immune Deficiency Diseases</strong> (including Severe Combined Immunodeficiency syndromes, Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, Kostmann syndrome)</td>
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<tr>
<td>· At diagnosis</td>
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<tr>
<th><strong>Inherited Metabolic Disorders</strong> (including Hurler's syndrome, adrenoleukodystrophy, and others)</th>
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<tr>
<th><strong>Hemoglobinopathies</strong></th>
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<tr>
<td>Transfusion-Dependent Thalassemias</td>
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<tr>
<th>Sickle Cell Disease</th>
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<td>· With aggressive course (end-organ complications, frequent pain crises)</td>
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<tr>
<th><strong>Hemophagocytic Lymphohistiocytosis (HLH)</strong></th>
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<td>· At diagnosis</td>
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<tr>
<th><strong>Severe Aplastic Anemia and other marrow failure syndromes</strong> (including Fanconi anemia, Diamond-Blackfan anemia, and others)</th>
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<td>· At diagnosis</td>
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</table>
The referral guidelines were developed jointly by the National Marrow Donor Program®/Be The Match® and the American Society for Blood and Marrow Transplantation and are based on current clinical practice, medical literature, and evidence-based reviews.

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About ASBMT
The American Society for Blood and Marrow Transplantation (ASBMT) is an international professional membership association of physicians, investigators and other health care professionals promoting blood and marrow transplantation and cellular therapy research, education, scholarly publication and clinical standards.

About the National Marrow Donor Program® (NMDP)
The National Marrow Donor Program (NMDP) is the global leader in providing a cure to patients with life-threatening blood and marrow cancers such as leukemia and lymphoma, as well as other diseases. The nonprofit organization manages the world’s largest registry of potential marrow donors and cord blood units, connects patients to their donor match for a life-saving marrow or umbilical cord blood transplant, educates health care professionals and conducts research so more lives can be saved.

The NMDP also operates Be The Match®, which provides patient support and enlists the community to join the Be The Match Registry®, contribute financially and volunteer. Learn more at marrow.org/md.
For patients and families

If you or a loved one is diagnosed with leukemia, lymphoma or other life-threatening disease, a bone marrow or cord blood transplant (BMT) may be your best or only hope for a cure. We are dedicated to helping you get the support and information you need to learn about your disease and treatment options, prepare for transplant and thrive after transplant. The information and resources here will help you navigate your transplant journey.

Learning about your disease

Read more about your disease, including symptoms, how transplant is used to treat your disease and survival outcomes.

Considering transplant & other treatment options

Learn about bone marrow transplant and other treatment options. Get tips for talking with your doctor and learn what to consider when making treatment decisions.

Finding a donor

The search for a donor takes time so it’s good to have your doctor start a search as soon as possible. Read more about the steps of the search process and how matches are made.

Getting a transplant

If you know you are having a transplant, learn about choosing a transplant center, planning for a transplant, what a transplant is and what to expect during the process.
Transplant Center Directory

Below is a complete list of all U.S. transplant centers that perform allogeneic transplants (transplants using related or unrelated donors).

Click on a transplant center's name for more information about the center, including the kinds of transplants performed, transplant outcomes, diseases treated, and general cost information.

All centers have contact information listed. You are encouraged to contact individual centers to learn more about their transplant programs.

The list on this page is sorted by state. To find individual transplant center information, you can also use the advanced search to search by details such as diagnoses and patient age groups treated (NMDP transplant centers only).

Alabama

University of Alabama at Birmingham
The Children's Hospital of Alabama (Secondary Location)
NMDP Transplant Center
Bone Marrow Transplant & Cell Therapy Program
619 South 19th Street
P302 West Pavilion
Advisory Group on Financial Barriers to Transplant
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Anthem BCBS/WellPoint, Inc.

**Vice Chair**
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Ruth Brentari  
Senior Director, Kaiser Foundation Health Plan

Ronald Potts, MD  
Quality Improvement Director, Kaiser Permanente National Transplant Services

Allan Chernov, MD  
Medical Director, Blue Cross Blue Shield Texas
Health Care Quality and Policy

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Vice President, Managed Care and Business Operations
City of Hope

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Senior Medical Director, Aetna

Deborah Rodriguez
Supervisor
UCSF Bone Marrow Transplant Program

Anthony Bonagura, MD
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Multiplan

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