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Widespread Use of Measurable Residual Disease in Acute Myeloid Leukemia Practice Running head: Minimal Residual Disease in Acute Myeloid Leukemia Survey

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Abstract

Purpose—Measurable residual disease (MRD) has prognostic importance for patients with acute myeloid leukemia (AML). How leukemia providers incorporate MRD into routine practice remains undefined.

Patients and methods—A survey was developed and distributed to a large sample of leukemia physicians. Demographic information was collected along with details concerning MRD practices. A multivariable logistic regression model evaluated provider characteristics predictive of MRD utilization.

Results—268 responses were received (response rate of 41%). 69% of providers reported routine use of MRD in management of AML, most commonly (90%) for its role in guiding therapy; providers who did not use MRD routinely most frequently cited inadequate resources (58%). Providers utilized flow cytometry- more than polymerase chain reaction-based assays with nucleophosmin-1 being the most common target with the latter. We found substantial variability in how MRD affected clinical decision making, particularly in pre- and post-transplant scenarios.

Conclusions—MRD was frequently used in making treatment decisions and in estimating prognosis. However, there was lack of uniformity in these practices. Standardization of assays,

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adoption of requisite technology, and dissemination of data about the value of MRD use would likely increase usage of MRD in the care of patients with AML.

Keywords

Minimal residual disease; Practice patterns; Acute myeloid leukemia; Prognostication

1. Introduction

Patients undergoing treatment for acute myeloid leukemia (AML) are considered to be in a complete remission (CR) if no morphologic disease is detectable in the presence of complete count recovery. Newer detection methods including multiparametric flow cytometry (MFC), polymerase chain reaction (PCR), next-generation sequencing (NGS), fluorescence *in situ* hybridization (FISH), and donor chimerism analysis for post-allogeneic transplant patients have enabled recognition of previously undetectable low-level residual leukemia, termed “measurable residual disease” (MRD). Although well-established in the treatment of patients with acute lymphoblastic leukemia, MRD has not been routinely incorporated into the care of patients with AML.

Emerging data suggest that the presence of MRD has important prognostic implications in AML, whether evaluated after induction chemotherapy[1], after consolidation therapy[2], or pre- and post-allogeneic transplantation[3]. Some of the most studied methods are MFC, molecular tests for nucleophosmin 1 (NPM1, gene mutation and overexpression), t(8;21) and inv(16), and FMS-like tyrosine kinase 3 – internal tandem domain (*FLT3*-ITD)[4]. However, the assays used, and the extent to which information about MRD influences everyday clinical practice remains uncertain; the lack of standardization for MRD detection may play a role.

This uncertainty prompted the following international survey of AML-focused physicians to delineate their use of MRD. In particular, we sought to evaluate physician characteristics predictive of MRD use in clinical decision-making relative to more conventional tests (e.g. marrow morphology), its timing, and the specific tests used. We also asked physicians to consider hypothetical cases involving MRD. Given the lack of standardization of MRD protocols and the technical and scientific infrastructure required for MRD implementation, we hypothesized that adoption of MRD would be incomplete and vary among physicians.

2. Methods

2.1 Survey Design, Participants

We obtained e-mail addresses for potential participants from those known to the Eastern Cooperative Oncology Group (ECOG) and the Leukemia and Lymphoma Society (LLS) as managing patients with leukemia. Additionally, physicians with a clearly stated clinical interest in AML or allogeneic transplantation related to AML were identified from the websites of all 69 National Cancer Institute-designated cancer centers[5] (accessed 6/22/16). An online survey to collect and collate data was created using REDCap software[6]. Participants were emailed a link to the survey item along with consent for participation; up

to three reminder e-mails were sent to those participants who had not yet responded. This study was deemed exempt from full institutional review board (IRB) review based on 45 CFR 46.101 (b)(2) by the Memorial Sloan Kettering Cancer Center IRB.

2.2 Measures

The survey is attached as a supplement. Responses to prior questions prompted subsequent questions: for example, physicians reporting a transplant-focused or combined (transplant and non-transplant) practice received transplant-specific questions (in addition to non-transplant-specific questions if combined practice). Demographic information collected was age, gender, practice characteristics (academic, private, combined, or other; transplant, non-transplant, combination), practice country (USA, other), and number of years in practice. Physicians were queried regarding the approximate yearly number of patients with AML seen at initial presentation, with relapsed or refractory disease, or for allogeneic transplant (<5, 5–9, 10–24, 25–50, or >50 patients for each category).

Participants were then asked whether they routinely utilized MRD in the care of patients with AML; the rationale for those for those stating ‘yes’ was assessed by listing potential reasons, including an option to list an answer not listed; the same was done for those stating “no”. Physicians indicating routine MRD use were asked situations in which they would not test for MRD.

We then asked participants who had indicated incorporating MRD into their practice about the frequency of MRD assessment and the frequency with which MRD assessment changes management (nearly 100% of the time, more than half of the time, roughly half of the time, less than half of the time, or virtually never for both). Additionally, we elicited the relative weight of MRD as compared to other clinical factors (age, performance status, baseline white blood cell count, karyotype, molecular genetics, and marrow morphology), the methodology (MFC versus PCR, peripheral blood vs. bone marrow, and the specific assays used), and timing in assessing MRD. Finally, we presented hypothetical clinical scenarios involving potential use of MRD to understand management decisions; providers were asked to select their most likely management choice, with the option to fill in any answer choice not listed. Due to an error within the survey instrument, one hypothetical scenario question was discarded.

2.3 Data analysis

All data analyses were conducted using the R statistical software (R version 3.3.2). T-tests, and chi-square or Fisher’s exact tests evaluated the association between provider demographic factors and MRD use. A multivariable logistic regression model was built to examine associations of MRD use adjusted for other factors identified as significant in univariate analysis. A Fisher’s exact test assessed the relative weight of the importance of MRD compared to other disease attributes based on provider type (transplant, non-transplant, or combined). Free-text responses concerning assay targets and sensitivity were jointly coded by Z.E-P, M.S.T., and a researcher independent of this study.

3. Results

3.1 Participant Information

Table 1 contains demographic and practice information for participants. The survey was mailed to 651 physicians of whom 268 responded (41%, including 9 with partial responses). The mean age of respondents was 49 years (SD 10.4, median = 47 years), 73% were men, and the mean years in practice was 15 (SD = 10.8, median = 12). 99% worked in an academic practice and 99% practiced in the U.S. Physicians most commonly reported seeing 10–24 patients of all types per year.

3.2 Frequency, Predictors, and Timing of MRD Use

Among non-transplant and combined physicians, 55 (47%) assessed for MRD following induction chemotherapy, including on day 14 (17%), day 28 (15%), and at the time of count recovery (15%); 60% of providers assessed for MRD after consolidation, when given (Table 1). 69% of physicians reported routine use of MRD in their practice (Table 2). This was most common (81%) in those dealing exclusively with transplant versus 59% among non-transplant providers, and 67% for those with a combined practice (p=0.009). The most common reasons for MRD use were its perceived value in guiding therapy (90%) and in estimating prognosis (80%), whereas the two most commonly cited reasons for not utilizing MRD were lack of resources (52%) and uncertainty regarding the use of MRD results (40%). Among non-transplant providers who indicated they routinely use MRD, 58% felt that doing so changed management at least half the time, contrasted with 32% who reported that MRD assessment affected management less than half of the time or never. Covariates significantly associated with MRD use among all providers included female gender, more years in practice, and transplant-based practice (Table 3). All three remained significant in a multivariable logistic regression model. There was a strong association of female gender for non-transplant practice (p = 0.011), and years in practice was significant for combined practice (p = 0.02). No association was found between provider age nor number of patients seen and MRD utilization.

3.3 Weight of MRD

Table 4 displays the relative weight ascribed to MRD as compared to other clinical factors. Majorities considered MRD more important than WBC (60% of respondents), and equally important as age (51%), pre-treatment karyotype (62%), and pre-treatment molecular genetics (60%); a plurality (40% of respondents) considered MRD to be less important than performance status. The majority of providers (64%) did not consider gradations of MRD (rather than the binary presence or absence), nor the distinction between morphologic residual disease and MRD (86%) to be clinically important.

3.4 Method of MRD assessment

The majority of providers reported using BM rather than PB (95% vs. 5%) for MRD assessment, and MFC rather than PCR (77% vs. 23%). Only 21% used serial PCR measurements to track disease response. Supplement Table1 characterizes the results of a free-text question regarding institutional assays around MRD, with a focus on specific AML

targets and the sensitivity of these various assays; NPM1 was the most commonly mentioned target among responses (19).

3.5 Clinical Scenarios

Table 5 displays the clinical scenario prompts given to participants, and the relative frequencies of management responses chosen. A majority (91%) of providers recommended allogeneic transplant for an adverse-risk patient who was MRD-negative after induction. Among providers who reported testing for MRD after consolidation, only 50% would recommend transplant for MRD-positive AML, whereas 26% would incorporate other factors and 19% would recommend for clinical trial. Among transplant or combined providers, for a patient who was otherwise going to be considered to undergo transplant but who was MRD positive after induction, responses were similar between recommending against transplant (27%), giving further chemotherapy (25%), and altering the conditioning regimen used (24%). Regarding post-transplant MRD positivity, the most common management was administration of hypomethylating agents or targeted agents (46%) followed by expectant monitoring (19%).

4. Discussion

Although National Comprehensive Cancer Network (NCCN) guidelines[7] do not yet recommend MRD monitoring or its incorporation into clinical decision-making, our survey of 268 leukemia physicians found that 69% reported used MRD in routine care of AML patients, particularly with regard to therapeutic decision-making and prognostication.

Our data reflect the growing body of evidence showing the importance of MRD assessment post-induction, post-consolidation, and pre- and post-transplant. Indeed, European LeukemiaNet (ELN) guidelines now recognize CR without MRD as a distinct response category[8]. The most commonly cited reasons for not using MRD were the absence of requisite technologies or systems at one’s own institution. This is consistent with the need for improved scientific and technical infrastructure, as well as increased assay standardization and reproducibility, if MRD is to be more widely adopted. That more years of practice experience predicted MRD use suggests that less experienced providers feel less comfortable incorporating MRD into practice; future educational activities could therefore target more junior clinicians in this regard. Our finding that the large majority of providers ascribe equivalence to MRD and morphologic residual disease is consistent with findings from Araki et al.[3], demonstrating equivalent outcomes among MRD-positive and persistent disease patients undergoing allogeneic transplant, although those results may have been influenced by selection bias given that a minority of patients with >5% blasts undergo transplant for relapsed/refractory AML.

Effective risk stratification is fundamental to caring for patients with AML; established factors strongly predictive of relapse and/or shortened survival include adverse karyotype, therapy-related AML, and deleterious molecular genetic mutations such as *FLT3*-ITD; older age, elevated white blood cell count (WBC), and poor performance status (PS) are also associated with decreased survival[9] and novel prognostic markers continue to emerge[10–12]. In this study, MRD was considered more important than only baseline WBC (60%),

whereas a minority felt MRD was more important than PS (21%), molecular genetics (15%), age (27%), and karyotype (12%); determining the relative contributions of these factors in estimating prognosis and planning treatment is difficult.

Regarding the methodology and assessment of MRD, numerous studies have performed direct comparisons to evaluate the characteristics of PB versus BM as sampling sites[13–16]; in our study, BM sampling was strongly favored. Shayegi et al. [17] used Nucleophosmin 1 (NPM1) and found strong overall concordance between BM and PB PCR-based testing (83%), but a relatively high false negative rate (23%) for PB sampling as compared to BM. Conflicting results were found in Stahl et al.[13] in an exclusively post-transplant AML population, with a concordance of only 60%. Our survey results suggest that the vast majority of physicians use BM sampling rather than PB in their practice.

MFC has the advantage of wider applicability (>90–95% of AML patients), faster return times, and cost reductions as compared to PCR evaluations[18]. Greater use of MFC as compared to PCR techniques (77% vs. 23%) was found in this study, and the primary reasons were availability of resources (34%) and patient characteristics (33%). There is a paucity of data directly comparing the two methods. Perea and colleagues[19] studied core-binding factor (CBF) AML patients harboring either t(8;21) or inv(16); 74 post-induction samples were assayed for MFC and PCR simultaneously, and the overall concordance rate between methods was 67%. MFC was solely positive in 5 samples, versus 19 samples that were negative for MFC and positive for PCR, suggesting a higher sensitivity for PCR assays. A similar analysis by Ouyang et al.[20], also in CBF AML patients, showed good agreeability between MFC and PCR only at extreme levels of disease in the quantitative PCR assay (<0.1% and >10%). As described above, the predominant reasons cited in our study for favoring MFC over PCR were factors related to an institution (availability of resources) or the patient (targetable sequence or mutation). Data from free text responses describe common use of NPM1 and *FLT3* (both ITD and TKD) as targeted mutations within AML, and varying usage of MFC-, PCR-, and NGS-based assays, with a wide range in reported sensitivities across and within testing modalities, collectively suggesting heterogeneity in practice in this area.

The clinical scenario for which physician opinion was least variable was scenario 1, in which 91% of non-transplant or combined practice physicians favored transplant in a patient with poor-risk AML, even though the patient was MRD negative after induction chemotherapy. This suggests, as further evidenced by the relative weights in Table 4, that physicians view pre-treatment cytogenetics as more prognostic of poor outcome (e.g. relapse) than post-treatment MRD, despite suggestions to the contrary[21]. In the post-consolidation setting, 50% of physicians who reported assessing for MRD recommended transplant in MRD-positive patients. In general, data from these scenarios suggest considerable uncertainty as to how MRD data should be used in practice; for few case scenarios was there clear uniformity of practice, whereas most confirmed our theory that variation in practice exists.

Case scenario #5, was intended to evaluate transplant physicians' management of MRD positivity after transplant; 46% chose hypomethylating (HMA) or targeted agents as their

most common management, but responses varied. Although the phase II RELAZA study[22] suggested the benefit of azacitidine in this setting, the results have yet to be confirmed in a randomized study; such a study might prove difficult to perform given the low toxicity of azacitidine relative to the high risk of relapse. It warrants noting as a general point that there is not yet proof that treating patients whose only evidence of disease is MRD yields better clinical outcomes than waiting until morphologic disease relapse has been observed; an ongoing randomized study in the United Kingdom (AML 18) is addressing this question.

Our survey-based study involved 268 participants and is the first to provide a perspective on use of MRD. However, there were limitations. Lacking a link between survey responses and demographic information or center affiliation, no conclusions can be drawn about possible inter-center variations. Consequently our results may be skewed towards reflecting the practices of centers with a higher number of respondents. For practical reasons the hypothetical case scenarios presented were necessarily simplistic, and did not allow for the complexity frequently inherent in management of AML. We did not provide a concrete definition for “routine”, instead leaving it to individual providers to deem for themselves whether the frequency with which they use MRD reaches this descriptive threshold. Finally, although it is likely that most AML patients are cared for at academic medical centers, our results do not capture practice patterns for those patients treated in community or private practices.

Despite these limitations and our survey’s finding a lack of general consensus on how to best apply MRD-based data, the survey leaves little doubt the majority of physicians in academic practice now use information derived from testing for MRD in some way; it seems likely that use of MRD assessment will increase. Our survey indicates the biggest impediments to such growth are a perceived lack of standardization and uncertainty as to the most appropriate use of MRD testing results. Accordingly, it is incumbent on us to both further standardize MRD assessment, thereby increasing the reproducibility of a given assay and to conduct more trials to define the practical clinical role of MRD monitoring, especially the question over treating MRD in the absence of morphologic evidence of relapsed or refractory disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Use of MRD among leukemia care providers in acute myeloid leukemia is common
- MRD is used frequently in estimating prognosis and in making treatment decisions
- More years of experience, female gender, and transplant practice predicted MRD use
- Nucleophosmin 1 was the most common target utilized in MRD testing
- Variations in MRD testing and management exist in contemporary practice

Table 1:

Participant Demographics

Characteristic	Provider Type	All (N = 268)	Transplant (N = 85)	Non-transplant (N = 74)	Combined (N =109)
Mean age, years (SD)		49.2 (10.4)	49.7 (10.7)	48 (10.3)	49.5 (10.2)
Gender, N (%)	Male	195 (73%)	58 (68%)	58 (78%)	79 (72%)
	Female	73 (27%)	27 (32%)	16 (22%)	30 (28%)
Country, N (%)	United States	264 (99%)	85 (100%)	71 (96%)	108 (99%)
	Other	4 (1%)	0 (0%)	3 (4%)	1 (1%)
Practice setting, N (%)	Academic	265 (99%)	84 (99%)	74 (100%)	107 (98%)
	Community	2 (1%)	1 (1%)	0 (0%)	1 (1%)
	Other	1 (0%)	0 (0%)	0 (0%)	1 (1%)
Mean years of practice (SD)		15.1 (10.8)	15.7 (10.6)	13.9 (11.2)	15.4 (10.8)
Patients seen at initial presentation *	<5	60 (22%)	46 (54%)	8 (11%)	6 (6%)
	5–9	38 (14%)	11 (13%)	9 (12%)	18 (17%)
	10–24	91 (34%)	18 (21%)	23 (31%)	50 (46%)
	25–50	46 (17%)	8 (9%)	17 (23%)	21 (19%)
	>50	33 (12%)	2 (2%)	17 (23%)	14 (13%)
Patients seen with relapsed/ refractory disease *	<5	29 (11%)	15 (18%)	10 (14%)	4 (4%)
	5–9	49 (18%)	23 (27%)	8 (11%)	18 (17%)
	10–24	107 (40%)	31 (36%)	24 (32%)	52 (48%)
	25–50	62 (23%)	13 (15%)	23 (31%)	26 (24%)
	>50	21 (8%)	3 (4%)	9 (12%)	9 (8%)
Patients treated with allogeneic transplant *	<5	53 (20%)	2 (2%)	41 (55%)	10 (9%)
	5–9	41 (15%)	10 (12%)	7 (9%)	24 (22%)
	10–24	112 (42%)	43 (51%)	17 (23%)	52 (48%)
	25–50	46 (17%)	21 (25%)	8 (11%)	17 (16%)
	>50	16 (6)%	9 (11%)	1 (1%)	6 (6%)

* All values refer to patient volume on a yearly basis

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Table 2:

Use of MRD

Variable		All, N (%)	Transplant, N (%)	Non-Transplant, N (%)	Combined, N (%)
Providers Routinely Use MRD		186 (69%)	69 (81%)	44 (59%)	73 (67%)
Reasons for MRD Utilization	MRD use could change management	168 (90%)	63 (91%)	42 (95%)	63 (86%)
	MRD use is a policy or practice at my institution	98 (53%)	36 (52%)	24 (55%)	38 (52%)
	Patient inquiry into MRD use	17 (9%)	10 (14%)	0 (0%)	7 (10%)
	MRD use in estimating prognosis	148 (80%)	56 (81%)	34 (77%)	58 (79%)
	MRD use is the standard of care	115 (60%)	47 (68%)	29 (66%)	39 (53%)
	MRD use in research	64 (34%)	21 (30%)	23 (52%)	20 (27%)
	Other	1 (1%)	0 (0%)	1 (2%)	0 (0%)
Reasons for Lack of MRD Utilization	MRD technology/systems unavailable at my institution	43 (52%)	10 (62%)	17 (57%)	16 (44%)
	Uncertainty over management of MRD results	33 (40%)	4 (25%)	12 (40%)	17 (47%)
	MRD not the practice of my institution	29 (35%)	8 (50%)	12 (40%)	9 (25%)
	Practices concerning MRD use are unstandardized *	5 (6%)	1 (6%)	2 (7%)	2 (6%)
	Do not believe MRD has a role in AML	2 (2%)	0 (0%)	0 (0%)	1 (3%)
	Unfamiliarity with MRD-related research	1 (1%)	0 (0%)	0 (0%)	2 (6%)
	Other	14 (17%)	3 (19%)	6 (20%)	5 (14%)
Timing of MRD Assessment ^	After induction, day 14			10 (23%)	10 (14%)
	After induction, day 28 *			4 (9%)	14 (19%)
	After induction, at recovery of counts *			7 (16%)	10 (14%)
	After consolidation			27 (61%)	43 (59%)
	Before transplant			25 (57%)	47 (64%)
	After transplant			14 (32%)	35 (48%)
	Other			3 (7%)	2 (3%)

* These responses were frequently mentioned in free-text for “other” and were therefore converted into separate question responses

^ Asked only of non-transplant and combined provider

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Table 3:

Predictors of MRD Use

Variable (Univariate)	MRD Use - All			MRD Use - Transplant			MRD Use - Non-Transplant			MRD Use - Combined		
	Yes (%)	No (%)	P	Yes (%)	No (%)	P	Yes (%)	No (%)	P	Yes (%)	No (%)	P
Age (yrs), mean (SD)	49.9 (10.5)	47.4 (10)	0.057	50.6 (10.8)	46 (9.6)	0.106	47.6 (9.8)	48.7 (11.1)	0.66	50.8 (10.4)	46.9 (9.2)	0.052
Years practicing, mean (SD)	16.1 (11.1)	12.9 (10)	0.021	16.6 (11)	11.8 (8.1)	0.057	13.7 (10.9)	14.3 (11.8)	0.83	17 (11.2)	12.2 (9.2)	0.02
Gender			0.037			0.080			0.011			0.653
Male	128 (66)	67 (34)		44 (76)	14 (24)		30 (52)	28 (48)		54 (68)	25 (32)	
Female	58 (79)	15 (21)		25 (93)	2 (7)		14 (88)	2 (12)		19 (63)	11 (37)	
Country												
United States	185 (70)	79 (30)		68 (81)	16 (19)		43 (61)	28 (39)		73 (68)	35 (32)	
Other	1 (25)	3 (75)					1 (33)	2 (67)		0 (0)	1 (100)	
Practice Setting												
Academic	184 (69)	81 (31)		68 (81)	16 (19)		44 (59)	30 (41)		72 (67)	35 (33)	
Combined	2 (100)	0 (0)		1 (100)	0 (0)					1 (100)	0 (0)	
Other	0 (0)	1 (100)								0 (0)	1 (100)	
Practice volume (estimated annually)												
Initial presentation			0.618			0.583			0.133			0.718
<5	45 (75)	15 (25)		39 (85)	7 (15)		3 (38)	5 (62)		3 (50)	3 (50)	
5–9	26 (68)	12 (32)		9 (82)	2 (18)		6 (67)	3 (33)		11 (61)	7 (39)	
10–24	58 (64)	33 (36)		14 (78)	4 (22)		10 (43)	13 (57)		34 (68)	16 (32)	
25–50	34 (74)	12 (26)		5 (62)	3 (38)		13 (76)	4 (24)		16 (76)	5 (24)	
>50	23 (70)	10 (30)		2 (100)	0 (0)		12 (71)	5 (29)		9 (64)	5 (36)	
Relapsed/refractory			0.860			0.438			0.128			0.857
<5	20 (69)	9 (31)		14 (93)	1 (7)		4 (40)	6 (60)		2 (50)	2 (50)	
5–9	35 (71)	14 (29)		19 (83)	4 (17)		5 (62)	3 (38)		11 (61)	7 (39)	
10–24	71 (66)	36 (34)		25 (81)	6 (19)		11 (46)	13 (54)		35 (67)	17 (33)	
25–50	46 74)	16 (26)		9 (69)	4 (31)		18 (78)	5 (22)		19 (73)	7 (27)	
>50	14 (67)	7 (33)		2 (67)	1 (33)		6 (67)	3 (33)		6 (67)	3 (33)	
Allogeneic transplant			0.208			0.965			0.429			0.984
<5	30 (57)	23 (43)		2 (100)	0 (0)		22 (54)	19 (46)		6 (60)	4 (40)	

5–9	29 (71)	12 (29)	9 (90)	1 (10)	4 (57)	3 (43)	16 (67)	8 (33)
10–24	79 (71)	33 (29)	34 (79	9 (21)	10 (59)	7 (41)	35 (67)	17 (33)
25–50	36 (78)	10 (22)	17 (81)	4 (19)	7 (88)	1 (12)	12 (71)	5 (29)
>50	12 (75)	4 (25)	7 (78)	2 (22)	1 (100)	0 (0)	4 (67)	2 (33)
Provider type			0.009					
Transplant	69 (81)	16 (19)						
Non-transplant	44 (59)	30 (41)						
Mixed	73 (67)	36 (33)						

Variable (Multivariable)	**Odds Ratio (95% CI)**	
Female gender	2.24 (1.17–4.48)	0.018
Provider type		
Transplant	Reference	
Non-transplant	0.38 (0.18–0.77)	0.008
Mixed	0.48 (0.24–0.94)	0.036
Years in practice	1.03 (1.01–1.06)	0.014

Table 4:

Relative Weight of MRD Compared to Other Clinical Variables

Variable (MRD compared to ____)		All, N (%)	Transplant, N (%)	Non-Transplant, N (%)	Combined, N (%)	P
	Less Important	19 (10%)	11 (16%)	5 (12%)	3 (4%)	0.111
WBC count	As Important	54 (30%)	20 (29%)	9 (21%)	25 (35%)	
	More Important	109 (60%)	37 (54%)	28 (67%)	44 (61%)	
	Less Important	48 (26%)	16 (24%)	14 (33%)	18 (25%)	0.079
Karyotype	As Important	113 (62%)	42 (62%)	20 (48%)	51 (70%)	
	More Important	22 (12%)	10 (15%)	8 (19%)	4 (5%)	
	Less Important	39 (21%)	7 (10%)	11 (26%)	21 (29%)	0.029
Age	As Important	93 (51%)	38 (56%)	18 (43%)	37 (51%)	
	More Important	50 (27%)	23 (34%)	13 (31%)	14 (19%)	
	Less Important	45 (25%)	13 (19%)	14 (33%)	18 (25%)	0.317
Molecular Genetics	As Important	109 (60%)	41 (60%)	22 (52%)	46 (64%)	
	More Important	28 (15%)	14 (21%)	6 (14%)	8 (11%)	
	Less Important	73 (40%)	25 (37%)	16 (38%)	32 (44%)	0.647
Performance Status	As Important	72 (39%)	31 (46%)	17 (40%)	24 (33%)	
	More Important	38 (21%)	12 (18%)	9 (21%)	17 (23%)	
Gradations of MRD are Important (yes, %)		66 (36%)	25 (36%)	13 (30%)	28 (38%)	0.697
Distinction between morphologic disease and MRD is important? (yes, %)		25 (14%)	10 (14%)	5 (12%)	10 (14%)	0.962

Table 5:

Hypothetical Case Scenarios

Setting	Clinical Scenario	Management Choice	N (%)
Non-transplant	(1) Poor-risk AML, MRD-negative CR after induction chemotherapy (asked of non-transplant and combined providers)	Recommend for transplant	74 (91%)
		Recommend for clinical trial	3 (4%)
		Other	3 (4%)
		Administer consolidation chemotherapy	1 (1%)
	(2) Poor-risk AML, MRD-positive CR after consolidation chemotherapy (asked of providers who indicated MRD testing following induction)	Recommend for transplant	35 (50%)
		Depends on other factors	18 (26%)
		Recommend for clinical trial participation	13 (19%)
		Administer maintenance therapy	2 (3%)
		Other	2 (3%)
	(3) Unspecified-risk AML, MRD positive after induction chemotherapy, MRD negative after consolidation chemotherapy	Depends on underlying risk	49 (70%)
		Recommend for transplant	11 (16%)
		Expectant management	8 (11%)
		Other	2 (3%)
Transplant	(4) Persistent MRD after induction chemotherapy, being considered for transplant	Recommend against transplant	38 (27%)
		Administer additional chemotherapy	35 (25%)
		Change conditioning regimen	34 (24%)
		None	11 (8%)
		Avoid use of T-cell depleted graft	10 (7%)
		Depends on other clinical factors *	7 (5%)
		Other	4 (3%)
		Change transplant donor type	1 (1%)
	(5) Poor-risk AML 60 days following allogeneic transplant, no morphologic evidence of disease, but MRD positive	Administer hypomethylating agents or targeted therapies	64 (46%)
		Expectant monitoring	26 (19%)
		Donor lymphocyte infusion	19 (14%)
		Taper immunosuppression *	15 (11%)
		Recommend for clinical trial	9 (6%)
		Other	6 (4%)
		Administer further chemotherapy	1 (1%)

* These responses were frequently mentioned in free-text for “other” and were therefore converted into separate question responses