CENTER OUTCOMES FORUM WORK GROUP #2

OCTOBER 18, 2023

KEY QUESTIONS TO ADDRESS

- What additional information currently collected by the CIBMTR should be used for disease-based risk adjustment for AML, ALL, and MDS?

- What changes in data collection are recommended soon to improve risk adjustment for AML, ALL, and MDS in the future?

- Members included Kwang Ahn, Yi-Ben Chen, Stella Davies, Firas El Chaer, Selina Lugar, Kristin Page, Wael Saber, Bart Scott

OVERVIEW OF WHAT WE CURRENTLY COLLECT FOR AML

- Disease subtype based on WHO (2016) ** ELN risk category (2017)
- Transform from MDS (Y/N) **
- Therapy related (Y/N) **
- Predisposing conditions (Bloom/Down/Fanconi/DKC/Other)
- Disease-specific labs (FISH, Karyo, Flow, PCR)
  - Three time points: diagnosis, in between, before prep
  - Used to confirm disease classification and MRD status
- CNS leukemia (Y/N)
- Disease status (PIF, CR1, CR2, CR3+, in relapse (#)) **
- How many induction cycles were required to achieve 1st CR? **
  - Time from CR1 to HCT for patients in CR2+ or relapse (AML/ALL) ** (surrogate for time in CR1)
- Measurable Residual Disease (MRD) questions

Recommendations:

- Transition to WHO 2022/ELN 2022, ICC when possible
- Update forms to collect needed data
- Update MRD questions
- Likely that several variables will be less relevant in future:
  - Transformation/Therapy-related (per WHO 2022)
  - # Induction cycles

** In CSA Model

ELN 2022 CLASSIFICATION

Table 6. 2022 ELN risk classification by genetics at initial diagnosis*

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM*(*EVI1*) • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*§

Including these baseline characteristics would help classify AML in a clinically relevant categories

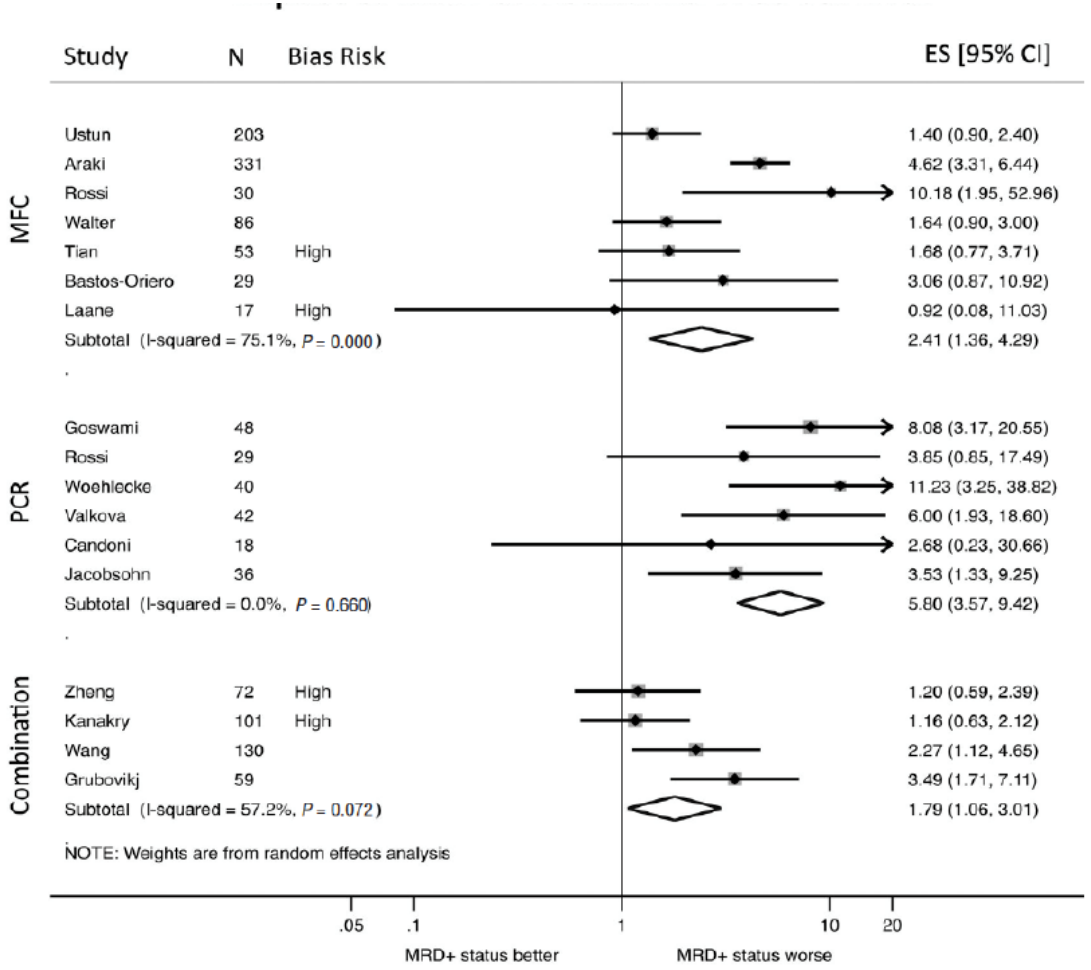
Dohner H. et al. Blood 2022

Table 7. Acute myeloid leukaemia.

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

Khoury JD. et al. Leukemia 2022

IMPACT OF MRD ON LEUKEMIA-FREE SURVIVAL



Regardless of test used:

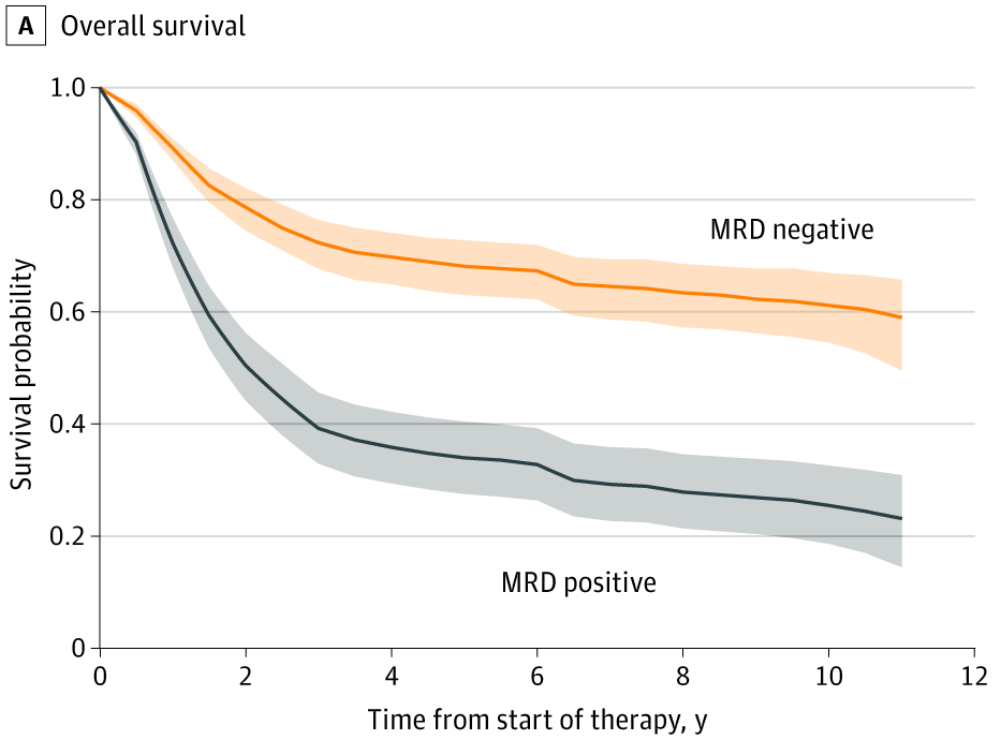
AML MRD in CR *before* Allo-HCT

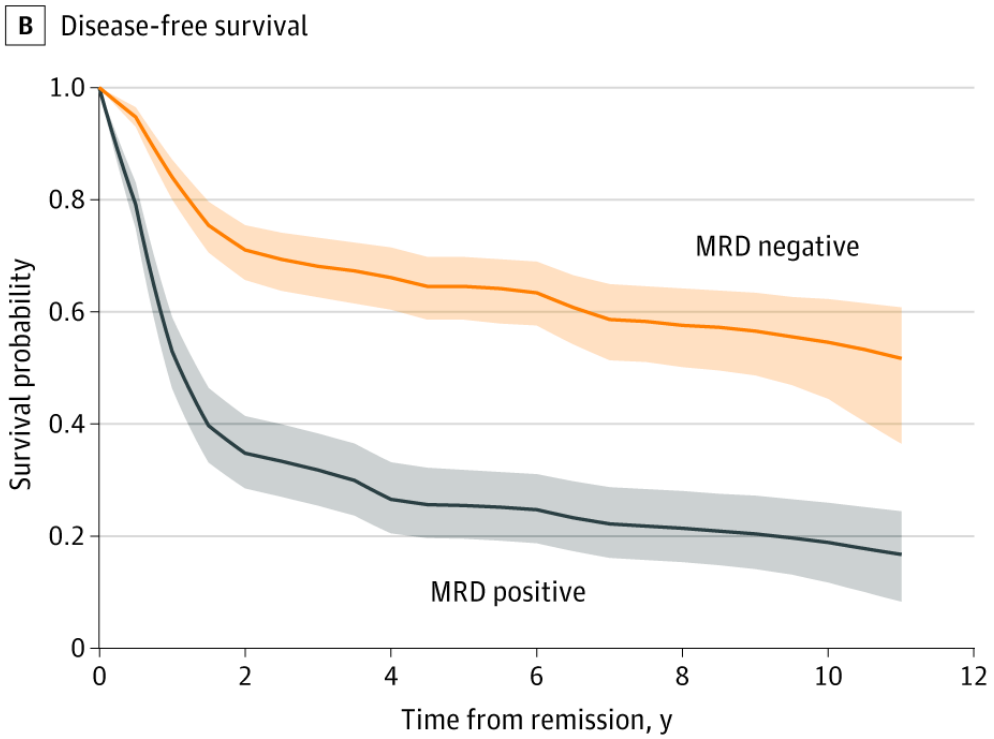
=

worse survival *after* transplant.

Buckley et al. Haematologica, 2017

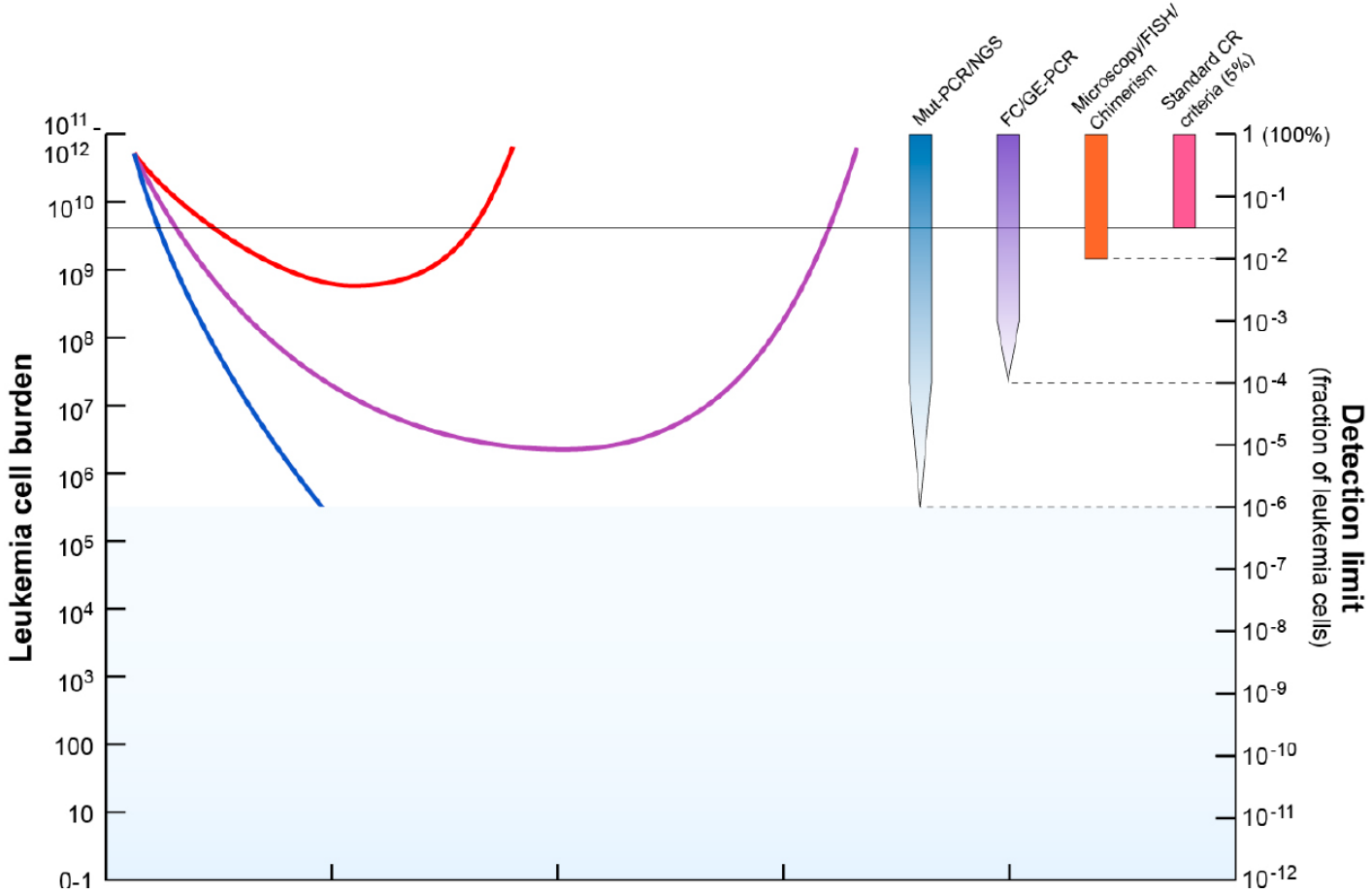
ESTIMATED SURVIVAL CURVES IN AML STRATIFIED BY MRD STATUS





Short N. et al. JAMA Onc 2020

MRD TESTING MODALITIES



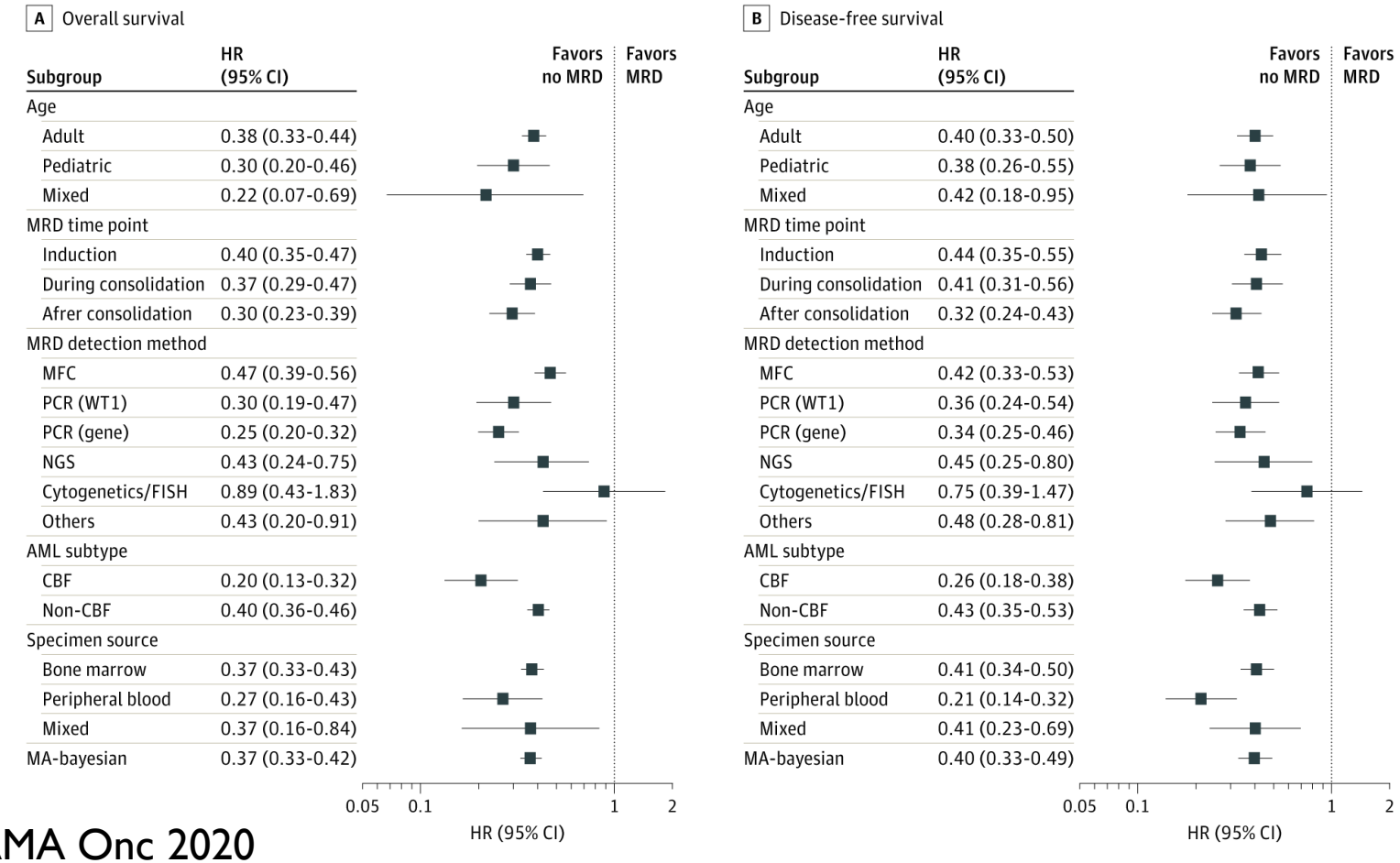
Hourigan and Karp, Nature Reviews Clinical Oncology, 2013

METHODS FOR DETECTION OF MRD IN AML

	Method	Target	Sensitivity	Applicable in % of AML	Turn-around time (days)	Limitations/ problems
Established	Multi-parameter flow cytometry (MFC)	Leukemia-associated immunophenotype (LAIP) or different from normal (DfN)	10^{-3} to 10^{-4}	85-90	2	Less sensitive, more subjective analysis
Established	Real-time quantitative PCR (RT-qPCR)	Robust data: *NPM1*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1* Less validated: *KMT2A*::*MLLT3*, *DEK*::*NUP214*, *BCR*::*ABL1*, *WT1*	10^{-4} to 10^{-5}	40-50*	3-5	Limited applicability
Exploratory	Next-generation sequencing (NGS)†,‡	Potentially any somatic mutation†	10^{-2} to 10^{-4}	~100	5-10	Less sensitive, costly, technically challenging
Exploratory	Digital PCR (dPCR)	Specific targeted mutations	10^{-3} to 10^{-4}	~70	3-5	Specific assay necessary for every mutation, limited sensitivity

Dohner H. et al. Blood 2022

HR FOR AML MRD-TESTING SUBTYPES



Short N. et al. JAMA Onc 2020

OVERVIEW OF WHAT WE CURRENTLY COLLECT FOR AML

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Recommendations:

- Transition to WHO 2022/ELN 2022, ICC when possible
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  - # Induction cycles

** In CSA Model

OVERVIEW OF WHAT WE CURRENTLY COLLECT FOR ALL

- Disease subtype using WHO 2016 ** Risk stratification (Lazaryan)

  T-cell and Ph+ status
- Predisposing conditions (SAA, Bloom, Down, Fanconi, Other)
- Prior TKI use (Y/N)
- Disease-specific labs (FISH, Karyo, Flow, PCR)
  - Three time points: diagnosis, in between, before prep
  - Used to confirm disease classification and MRD status
- CNS leukemia (Y/N)
- Disease status (PIF, CR1, CR2, CR3+, in relapse (#)) **
- How many induction cycles were required to achieve 1st CR? **
  - Time from CR1 to HCT (if AML/ALL and in CR2+ or relapse) **
- MRD questions

Recommendations:

- Transition to WHO 2022
- Update forms to collect needed data including expanding Ph-like ALL and Early T-cell precursor
- Update MRD questions, role in ALL is clear

** In CSA Model

CLINICAL RISK STRATIFICATION FOR ALL

HIGH-RISK FEATURES[g]		
	B-ALL	**T-ALL**
Age	**>35 years**	**>35 years**
White blood cell (WBC) count	**>30 x 10^9/L**	**>100 x 10^9/L**
Phenotype	**N/A**	**ETP-ALL**
Cytogenetics/Molecular risk group	**See Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (ALL-3)**	***RAS/PTEN* mutation and/or *NOTCH1/FBXW7* wild type**

NCCN Guidelines version 3.2023

CYTOGENETIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL

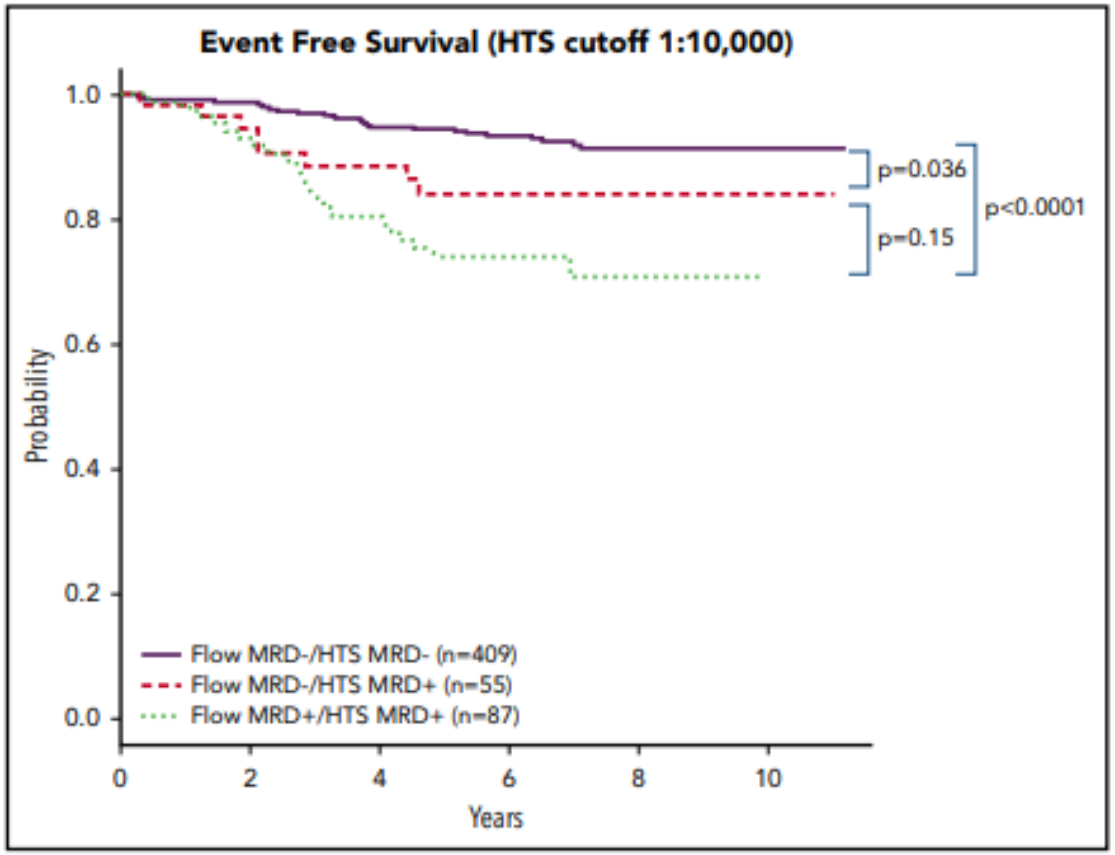
RISK GROUPS	CYTOGENETIC AND MOLECULAR ALTERATIONS
Standard risk	• Hyperdiploidy (51–65 chromosomes) ▸ Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome • t(12;21)(p13;q22): *ETV6::RUNX1*[i] • t(1;19)(q23;p13.3): *TCF3::PBX1* • *DUX4* rearranged • *PAX5* P80R • t(9;22)(q34;q11.2): *BCR::ABL1*[j] without *IKZF1* plus[k] and without antecedent chronic myeloid leukemia (CML)
Poor risk	• Hypodiploidy[l,m] (<44 chromosomes) • *TP53* mutation • *KMT2A* rearranged (t[4;11] or others) • *IgH* rearranged[n] • *HLF* rearranged • *ZNF384* rearranged • *MEF2D* rearranged • *MYC* rearranged • *BCR::ABL1*-like (Philadelphia chromosome [Ph]-like) ALL ▸ JAK-STAT (*CRLF2r*,[o] *EPORr*, *JAK1/2/3r*, *TYK2r*, mutations of *SH2B3*, *IL7R*, *JAK1/2/3*) ▸ ABL class (rearrangements of *ABL1*, *ABL2*, *PDGFRA*, *PDGFRB*, *FGFR*) ▸ Other (*NTRKr*, *FLT3r*, *LYNr*, *PTK2Br*) • *PAX5alt* • t(9;22)(q34;q11.2): *BCR::ABL1*[j] with *IKZF1* plus[k] and/or antecedent CML • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of *IKZF1*[k,p,q] • Complex karyotype (5 or more chromosomal abnormalities)

NCCN Guidelines version 3.2023

CLONOSEQ, THE ONLY FDA AUTHORIZED NGS-BASED MRD TESTING IN ALL

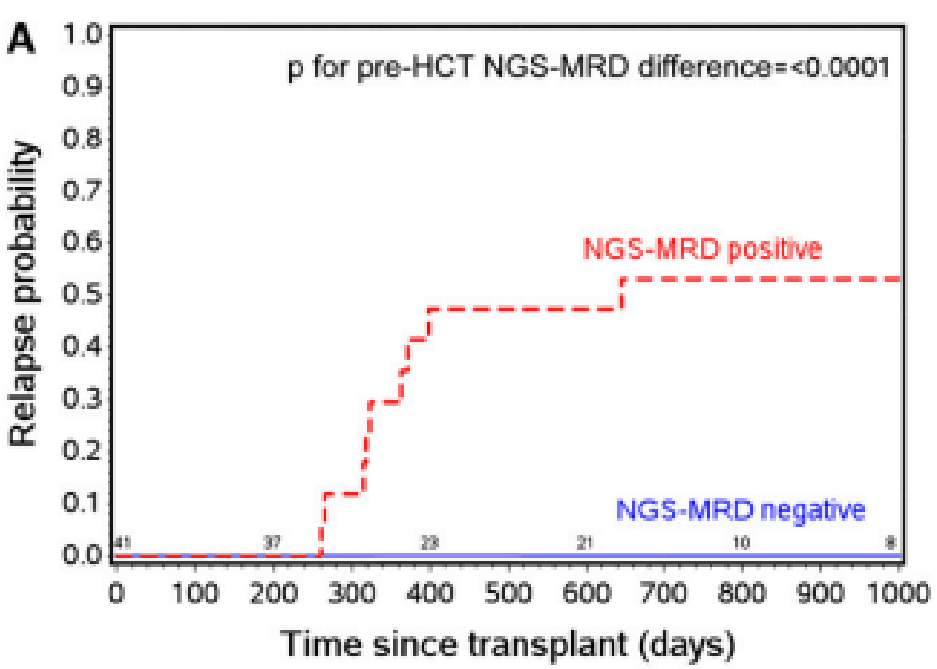
- The ClonoSEQ assay is an in vitro diagnostic that uses multiplex PCR and NGS to identify and quantify certain gene sequences in DNA extracted from bone marrow from patients with ALL or multiple myeloma.

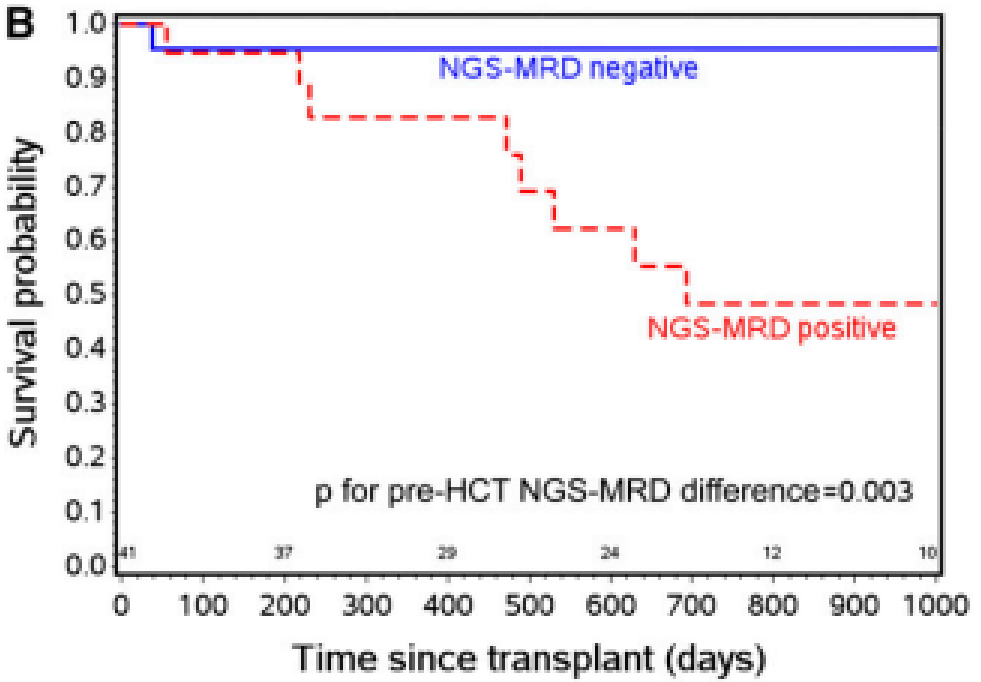
- The ClonoSEQ assay measures the amount of MRD and is capable of detecting MRD at levels below 1 in 1 million cells.



Wood B. et al. Blood 2018

NGS-MRD PRE- AND EARLY POST-ALLO-BMT FOR ALL





Pulsipher et al. Blood 2015

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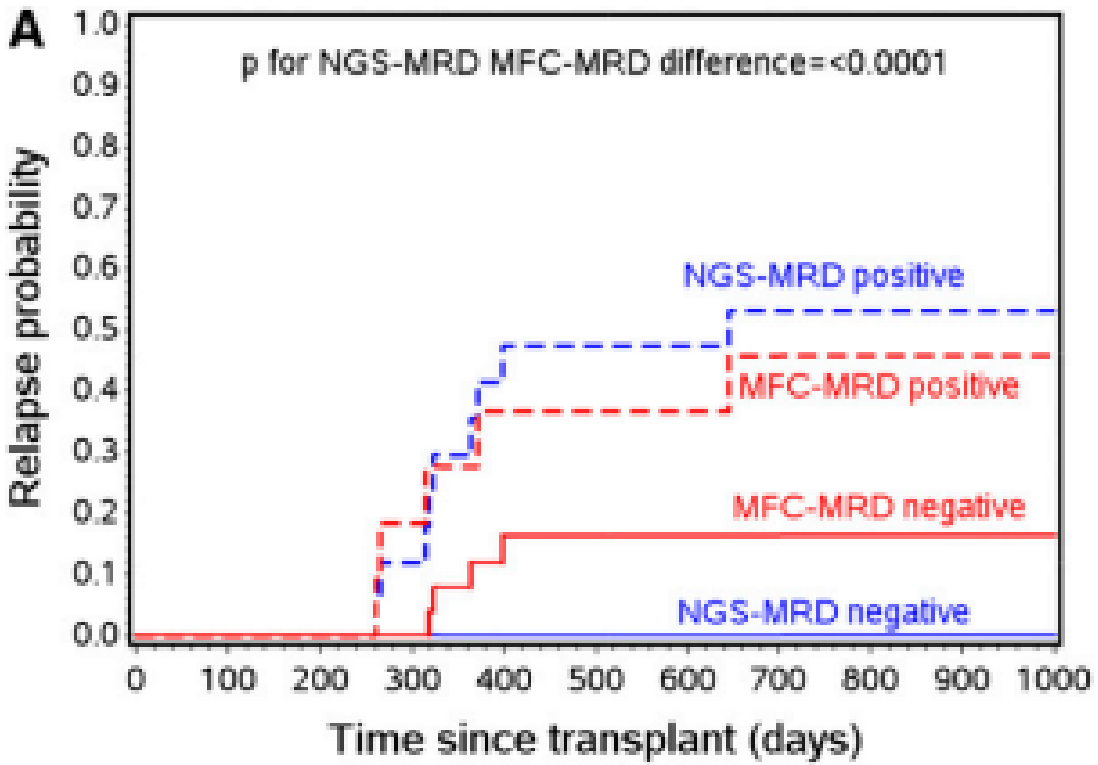

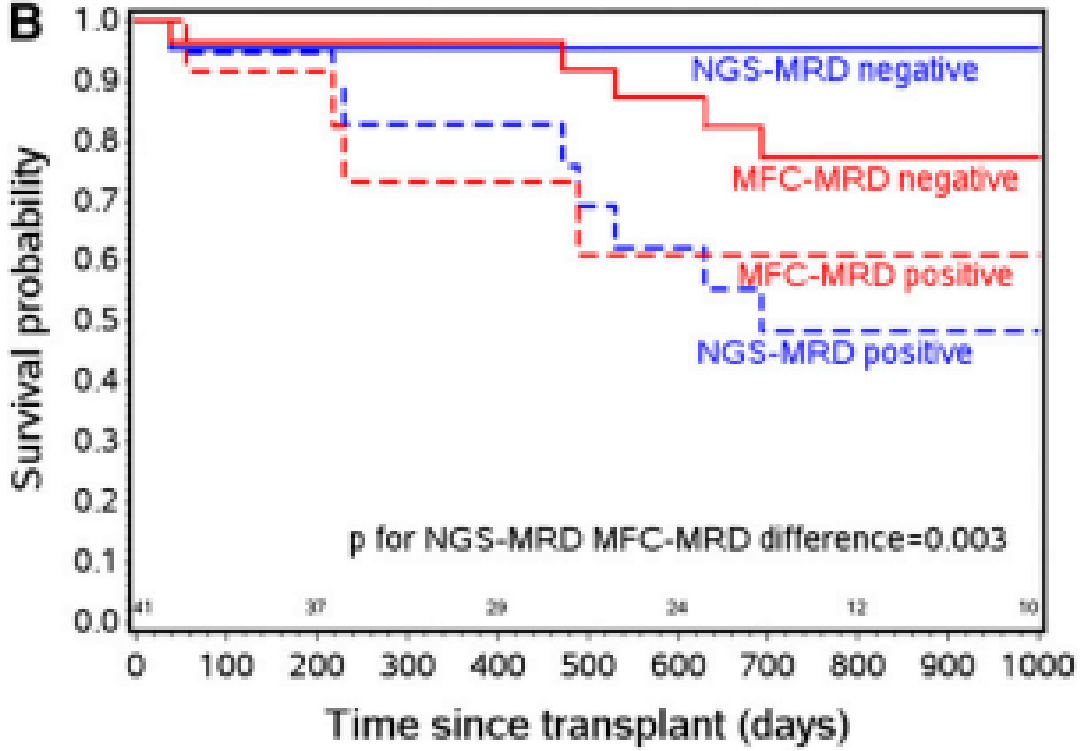

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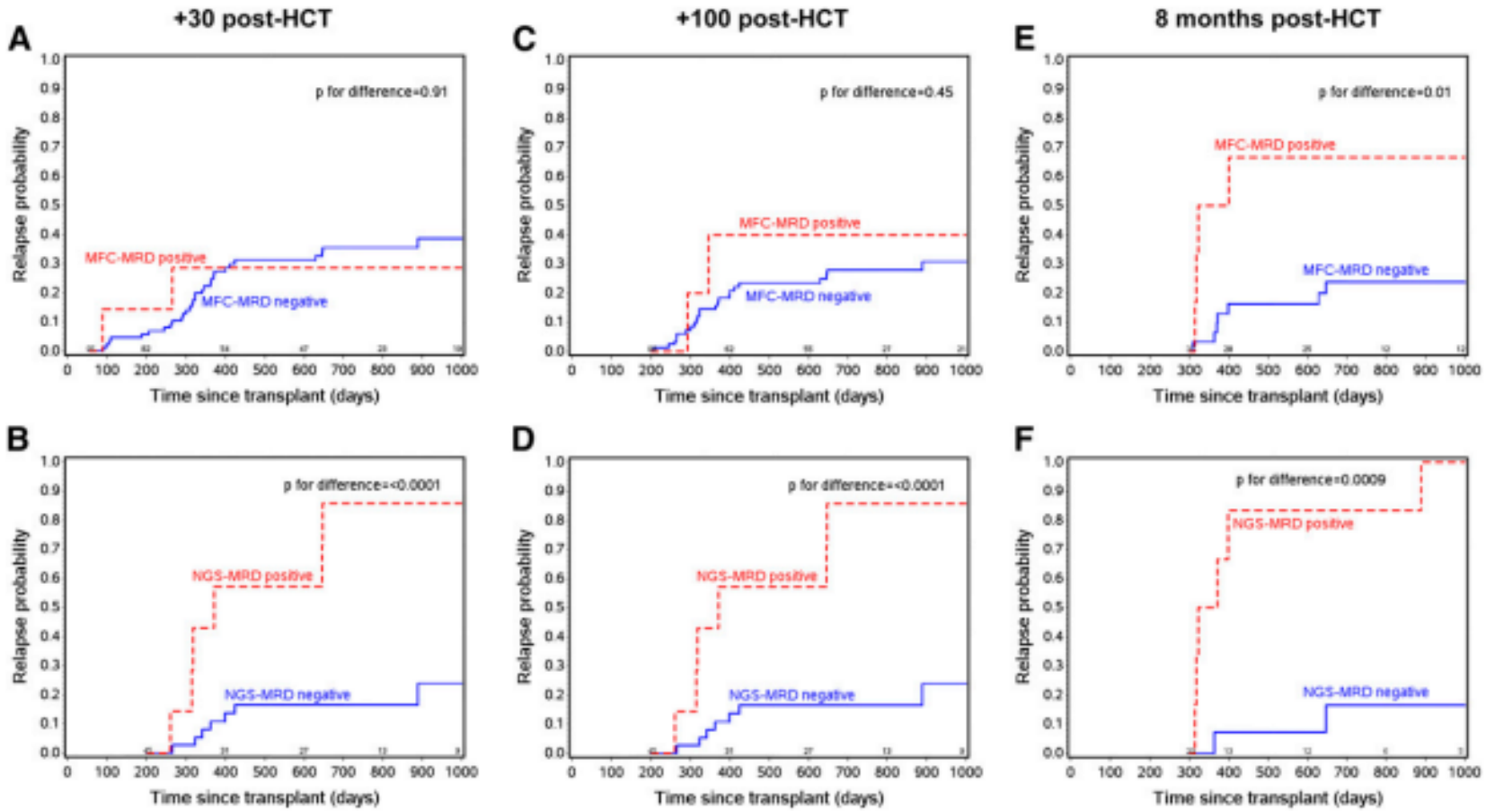

Pulsipher et al. Blood 2015

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Recommendations:

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** In CSA Model

OVERVIEW OF DATA WE CURRENTLY COLLECT FOR MDS

- Disease subtype at diagnosis using WHO 2016 **
  - Therapy related (Y/N)
  - Predisposing condition
    - SAA/DDX41/Diamond Blackfan/ Fanconi/ GATA2/

    Li-Fraumeni/ PNH/ RUNX1/ SAMD9/ Shwachman/ Telomere/Other
- CBC results
- Disease specific labs (FISH, Karyo):
  - Two time points
- Did the recipient transform to a different subtype or AML?
- IPSS-R risk score at HCT

Recommendations:
- Transition to WHO 2022
- Update forms to collect needed data
- Consider IPSS-M

IPSS-M RISK SCORE CONSTRUCTION FROM AN ADJUSTED COX MULTIVARIABLE REGRESSION FOR LEUKEMIA-FREE SURVIVAL

Table 1. IPSS-M Risk Score Construction from an Adjusted Cox Multivariable Regression for Leukemia-Free Survival.*

Category and Variable	Adjusted Hazard Ratio (95% CI)†	Model Weight‡
Clinical		
Bone marrow blasts — %	1.07 (1.05–1.09)	0.0704
min(Platelets,250) — x10^9/l	0.998 (0.997–0.999)	–0.00222
Hemoglobin — g/dl	0.84 (0.81–0.88)	–0.171
Cytogenetic		
IPSS-R cytogenetic category§	1.33 (1.21–1.47)	0.287
Gene main effects (17 variables, 16 genes)¶		
TP53^{multihit}	3.27 (2.38–4.48)	1.18
MLL^{PTD}	2.22 (1.49–3.32)	0.798
FLT3$^{ITD+TKD}$	2.22 (1.11–4.45)	0.798
SF3B1^{5q}	1.66 (1.03–2.66)	0.504
NPM1	1.54 (0.78–3.02)	0.430
RUNX1	1.53 (1.23–1.89)	0.423
NRAS	1.52 (1.05–2.20)	0.417
ETV6	1.48 (0.98–2.23)	0.391
IDH2	1.46 (1.05–2.02)	0.379
CBL	1.34 (0.99–1.82)	0.295
EZH2	1.31 (0.98–1.75)	0.270
U2AF1	1.28 (1.01–1.61)	0.247
SRSF2	1.27 (1.03–1.56)	0.239
DNMT3A	1.25 (1.02–1.53)	0.221
ASXL1	1.24 (1.02–1.51)	0.213
KRAS	1.22 (0.84–1.77)	0.202
SF3B1$^{\alpha}$	0.92 (0.74 1.16)	–0.0794
Gene residuals (1 variable, 15 genes; possible values of 0, 1, or 2)‖		
min(Nres,2)	1.26 (1.12–1.42)	0.231

* CI denotes confidence interval; IPSS-M, International Prognostic Scoring System–Molecular; IPSS-R, International Prognostic Scoring System–Revised; ITD, internal tandem duplication; min, minimum; PTD, partial tandem duplication; and TKD tyrosine kinase domain.

† Hazard ratio is for the risk of leukemic transformation or death, adjusted for age, sex, and secondary/therapy-related versus primary myelodysplastic syndrome. Cox regression was performed for 2428 patients with available covariables and leukemia-free survival data.

‡ Model weights were derived from the logarithm of the raw hazard ratios up to three significant digits. The following formula applies: IPSS-M score = $1.15467 + (\sum_{\text{variables } j} w_j x_j)/\log(2)$, where w_j denotes the weight of variable j, and x_j the value of the variable j observed in a given patient.

§ IPSS-R cytogenetic categories were as follows: 0 denotes very good, 1 good, 2 intermediate, 3 poor, and 4 very poor.

¶ *SF3B1*^{5q} is the *SF3B1* mutation in the presence of isolated del(5q) —that is, del(5q) only or with one additional aberration excluding -7/del(7q). *SF3B1*$^{\alpha}$ is the *SF3B1* mutation without comutations in *BCOR*, *BCORL1*, *RUNX1*, *NRAS*, *STAG2*, *SRSF2*, and del(5q).

‖ Nres is defined as the number of mutated genes within the following list: *BCOR*, *BCORL1*, *CEBPA*, *ETNK1*, *GATA2*, *GNB1*, *IDH1*, *NF1*, *PHF6*, *PPM1D*, *PRPF8*, *PTPN11*, *SETBP1*, *STAG2*, and *WT1*. The variable min(Nres,2) can therefore take the value 0, 1, or 2.

Bernard E et al. NEJM Evid2022;1:EVIDoa2200008

OVERVIEW OF DATA WE CURRENTLY COLLECT FOR MDS

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  - Therapy related (Y/N)
  - Predisposing condition
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- CBC results
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Recommendations:
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MRD QUESTIONS FOR AML / ALL (TED LEVEL DATA)

- Forms currently ask the following MRD questions:
  - Specify method(s) that was used to assess measurable residual disease status (check all that apply)
    - FISH/Karyotyping/Flow/PCR/NGS/Not assessed
  - Was measurable residual disease detected by…
    - FISH (Y/N)
    - Karyo (Y/N)
    - Flow (Y/N)
    - NGS (Y/N)

Concerns raised that:

1. Cytogenetic data likely represents gross levels of disease as opposed to MRD
2. Consider capturing VAF
3. What do we need for research purposes?
4. What are data managers accurately able to report?

WHEN CONSIDERING MRD TESTING, SEVERAL KEY QUESTIONS NEED TO BE ADDRESSED:

- **Patient's Disease Status**:
  - Was the patient's disease considered to be MRD positive, MRD negative, or was it not assessed? This question helps establish the baseline MRD status and informs subsequent monitoring strategies.
- **Testing Methods and Practices**:
  - What MRD testing methods were employed? Different laboratories and institutions may use varying techniques, such as flow cytometry, polymerase chain reaction (PCR), or next-generation sequencing (NGS). Understanding the specific method is crucial for comparing results.
  - Are these tests performed at fixed intervals or triggered by specific clinical events? Defining the frequency of MRD testing is important for tracking disease progression.
- **Sensitivity of MRD Testing**:
  - What is the sensitivity of the MRD testing used at each center? Sensitivity refers to the ability of a test to detect very low levels of disease. Sensitivity can vary widely, from 1 in 1,000 cells to 1 in 1,000,000 cells.
  - How do we reconcile differences in sensitivity between academic center A and community center B, which detects 1 in 10,000 cells? It's crucial to acknowledge these variations and consider them when interpreting results.