# The Foundation for the National Institutes of Health (FNIH) initiative on AML MRD

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**Cancer Drug Development Forum (CDDF)**
**Monday 25th April 2022**

National Heart, Lung, and Blood Institute

# Disclosures

- **Research Funding:**

  NIH Collaborative Research And Development Agreement
  - Sellas Life Sciences AG (laboratory funding)

  FNIH Biomarkers Consortium in AML MRD (laboratory funding).

- **Research collaborations:** Qiagen, Archer, Twinstrand, Mission Bio.

- **Advisory Boards:** Janssen, Novartis, BMS, Merck, Amgen (Official Duties)

- **Other Employment:** Johns Hopkins School of Medicine (Part-time: Clinical)

# Disclaimer

Any views expressed here represent personal opinion and do not necessarily reflect those of the U.S. Department of Health and Human Services, the United States federal government or the Foundation for the NIH

# AML MRD

- MRD in AML
- The FNIH AML MRD Consortium

# AML MRD

- **MRD in AML**
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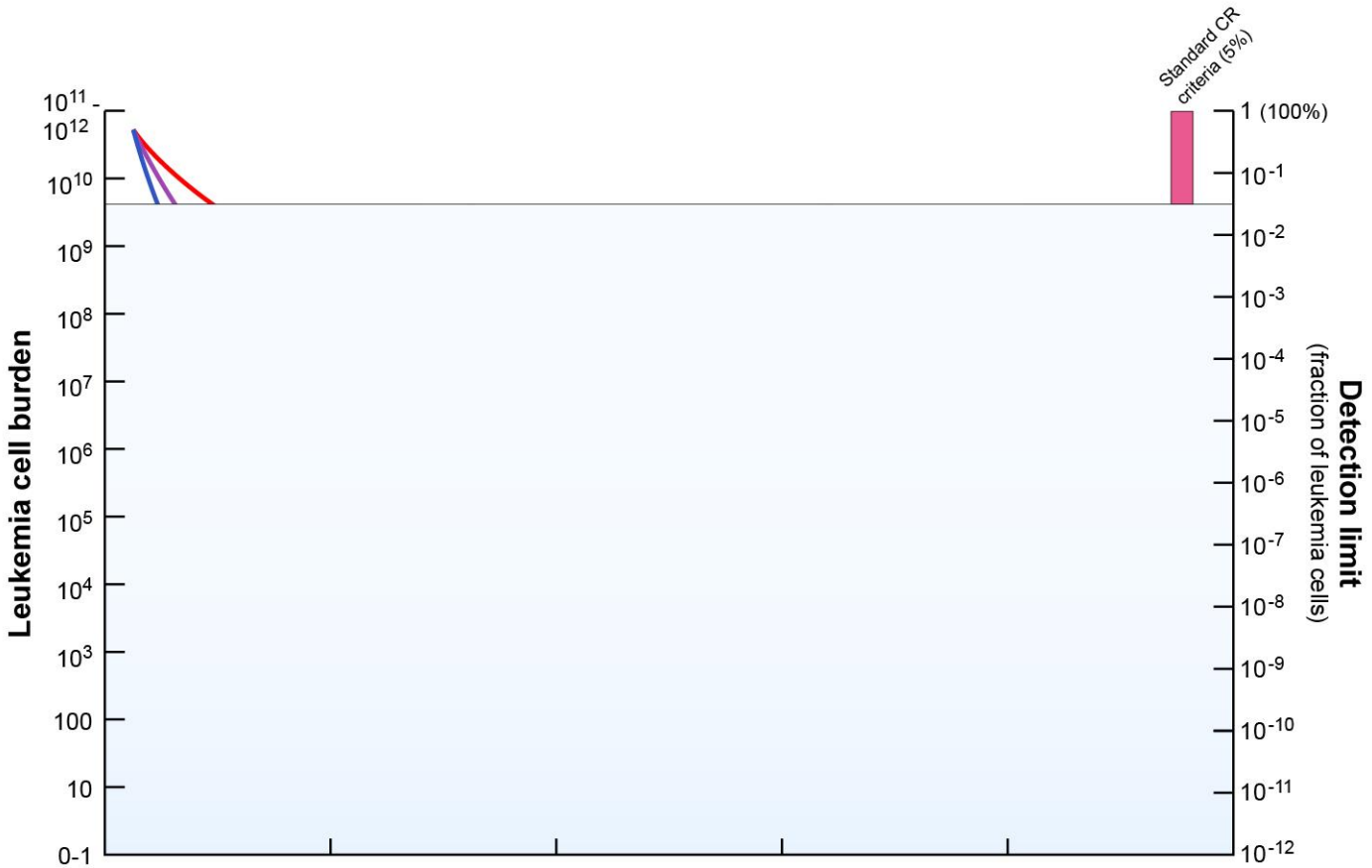
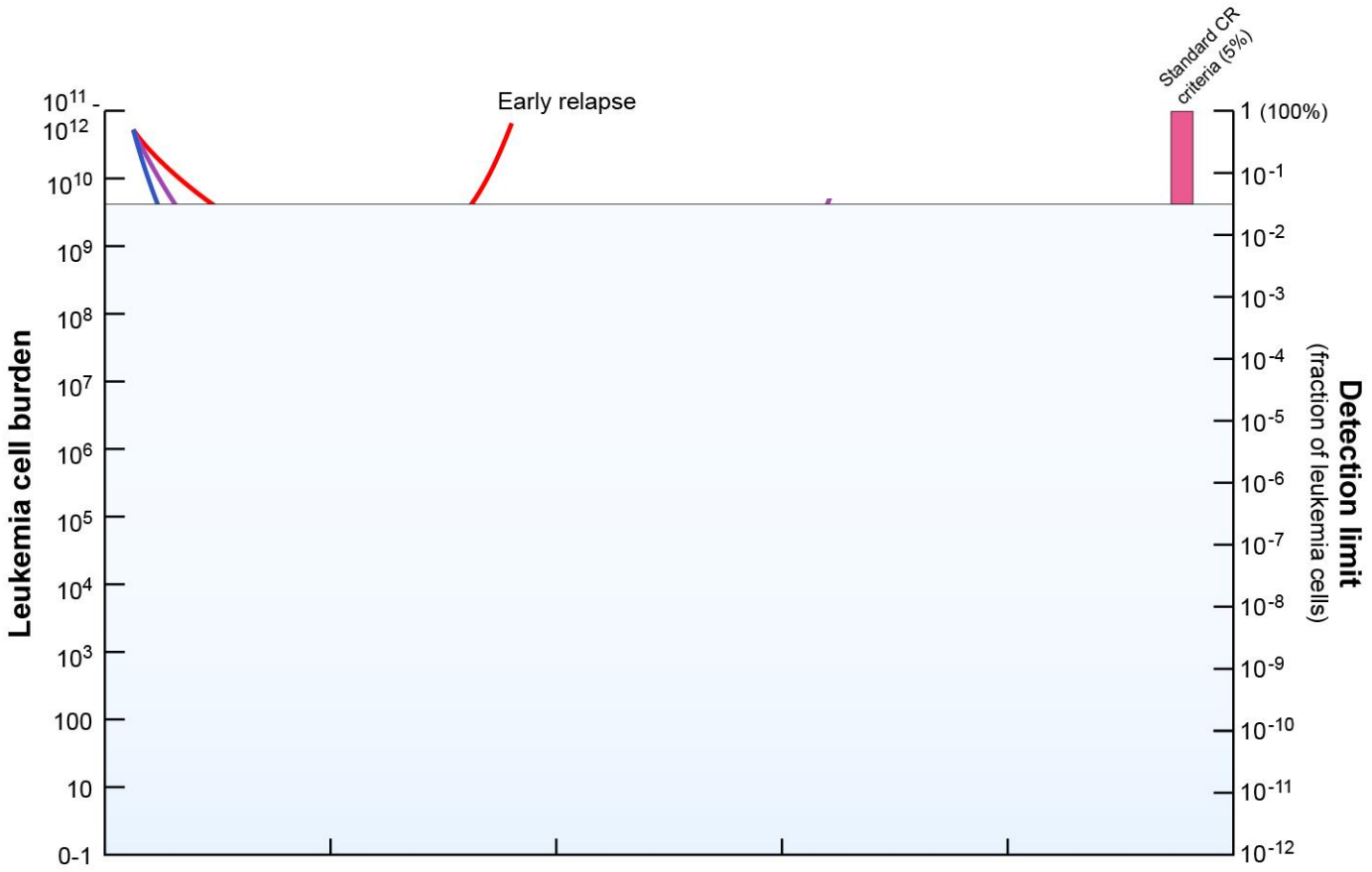
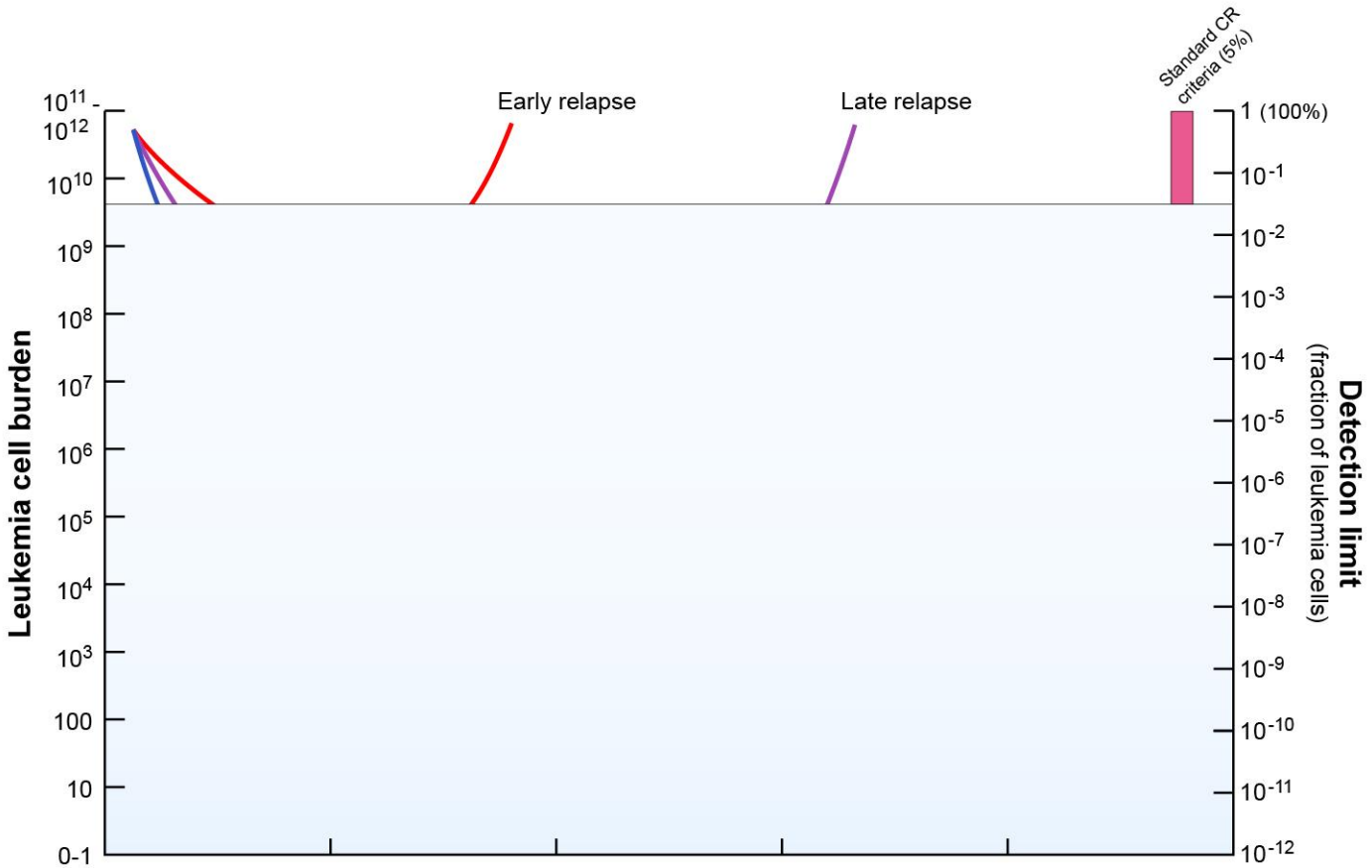



**Hourigan and Karp, Nature Rev Clin Oncology 2013**




**Hourigan and Karp, Nature Rev Clin Oncology 2013**




**Hourigan and Karp, Nature Rev Clin Oncology 2013**

**Table 1** | Evolution of criteria for complete remission in adult patients with AML

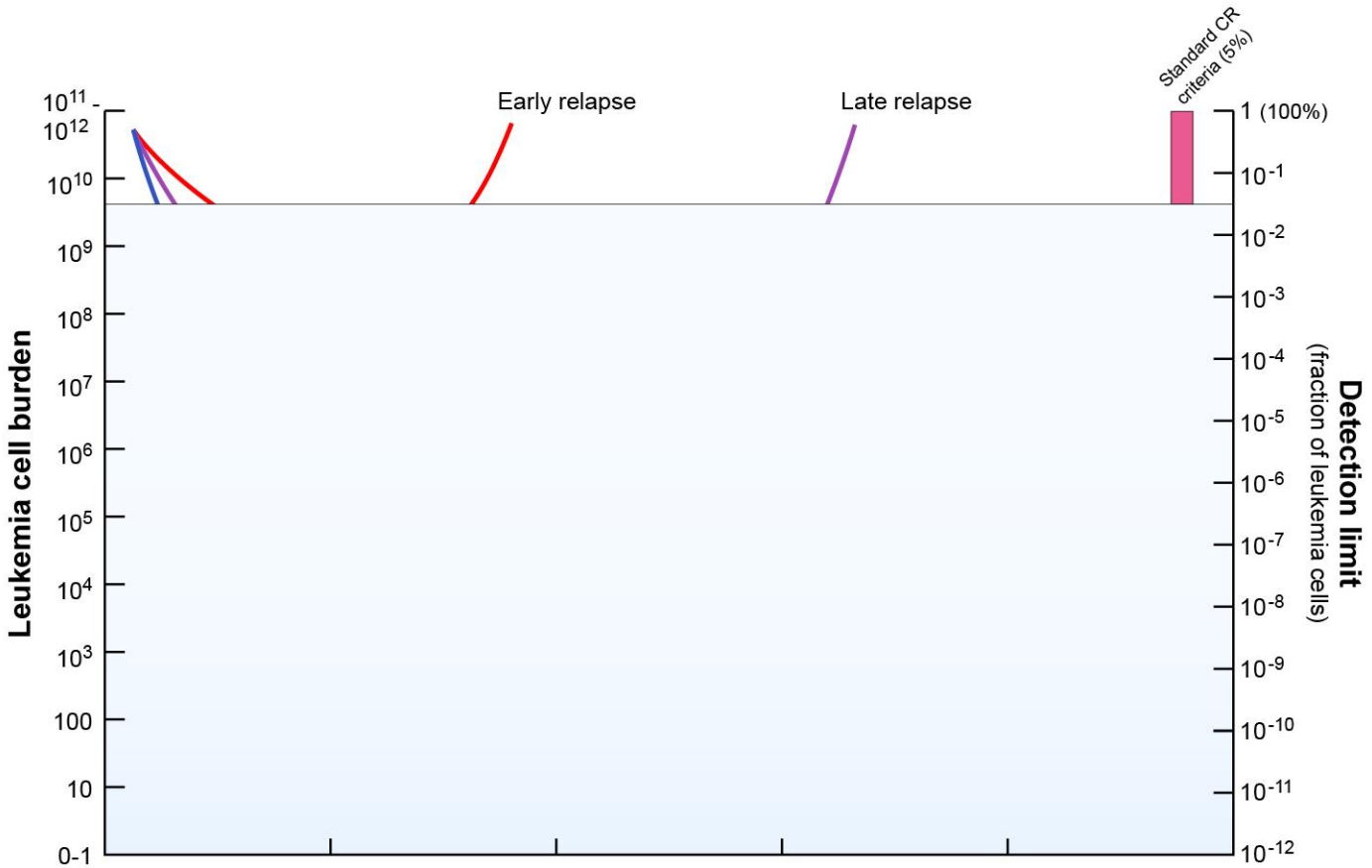
| Response criteria | 1956 | 2016 |
|---|---|---|
| Bone marrow | Less than 5% blasts and absence of cells that can be individually identified as leukaemic | Less than 5% blasts including no blasts with Auer rods |
| Extramedullary disease | Subsidence of all evidence of leukaemic infiltration | No residual evidence of extramedullary disease |
| Platelets | >100,000 | >100,000 |
| Neutrophil count | >200/$mm^3$ | >1,000/mcL |
| Haemoglobin | >12 gm/dl for 1 month | Transfusion-free |
| Clinical | No symptoms attributable to leukaemia | No criteria |

An additional category of 'cytogenetics normal in those with previously abnormal cytogenetics' is listed, but not required for a morphological complete response in the complete remission category of 2012 National Comprehensive Cancer Network guidelines[10] and is "commended primarily for use in clinical research studies" in the current International Working Group criteria[137] that those guidelines are based on. There is evidence, however, that persistence of cytogenetic abnormalities in patients with AML in complete remission is associated with a worse prognosis.[138] Abbreviation: AML, acute myeloid leukaemia.

**Hourigan and Karp, Nature Rev Clin Oncology 2013**

“*Oh honey, there ain’t nothing complete about a complete remission*”

Professor Judy Karp
Head of Leukemia Program, Johns Hopkins
Heard on ward-round, ~2008

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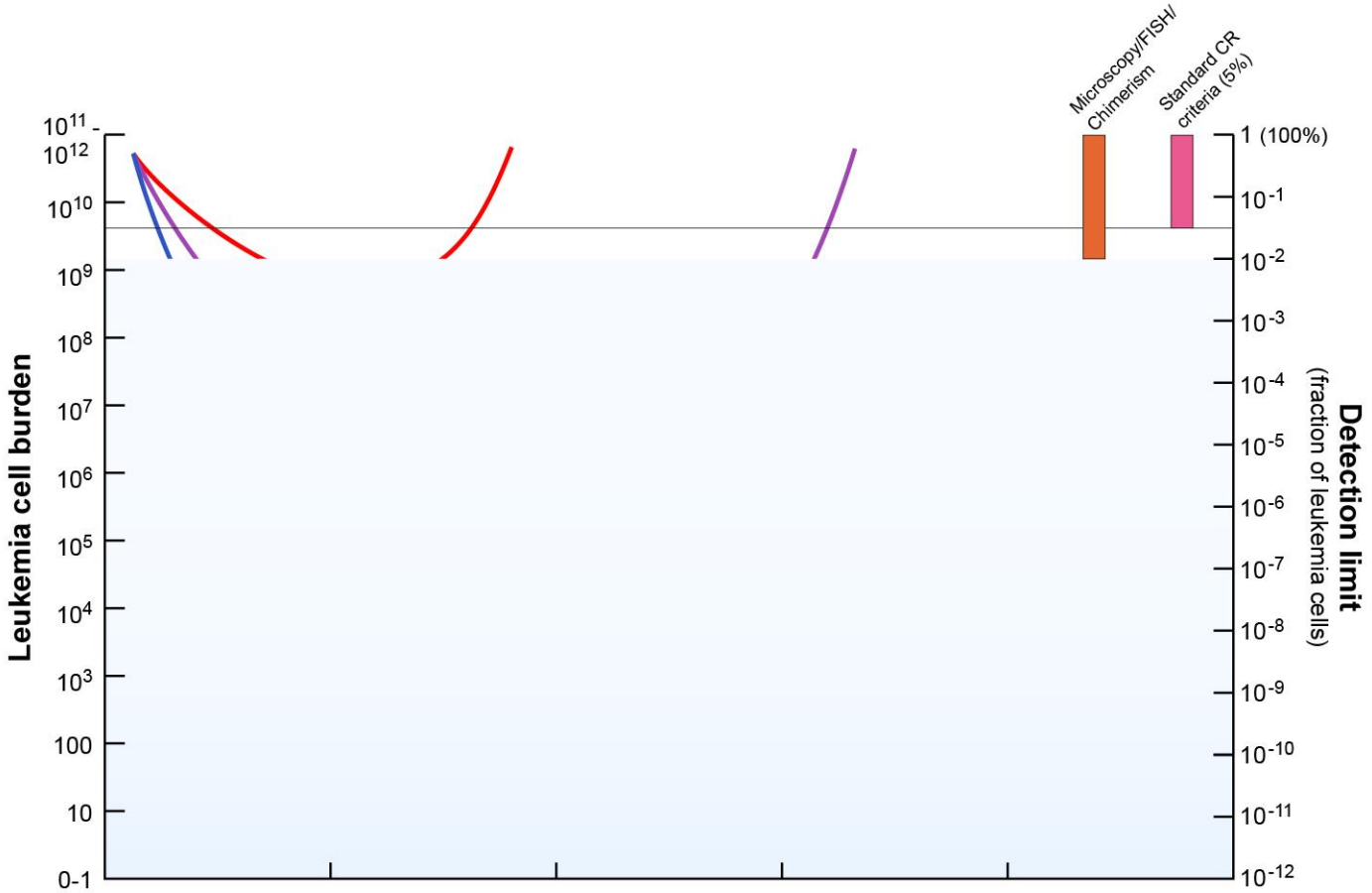
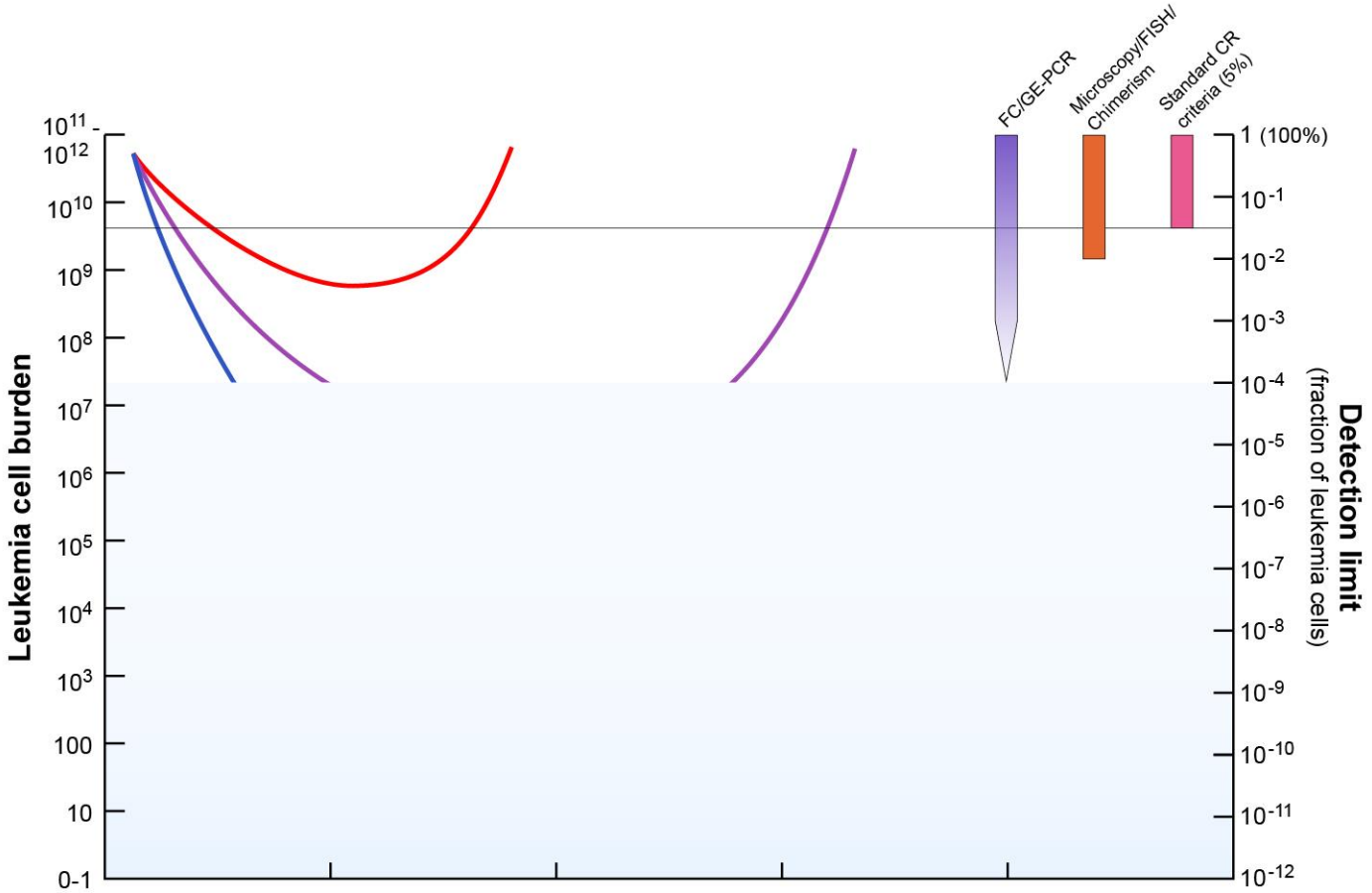
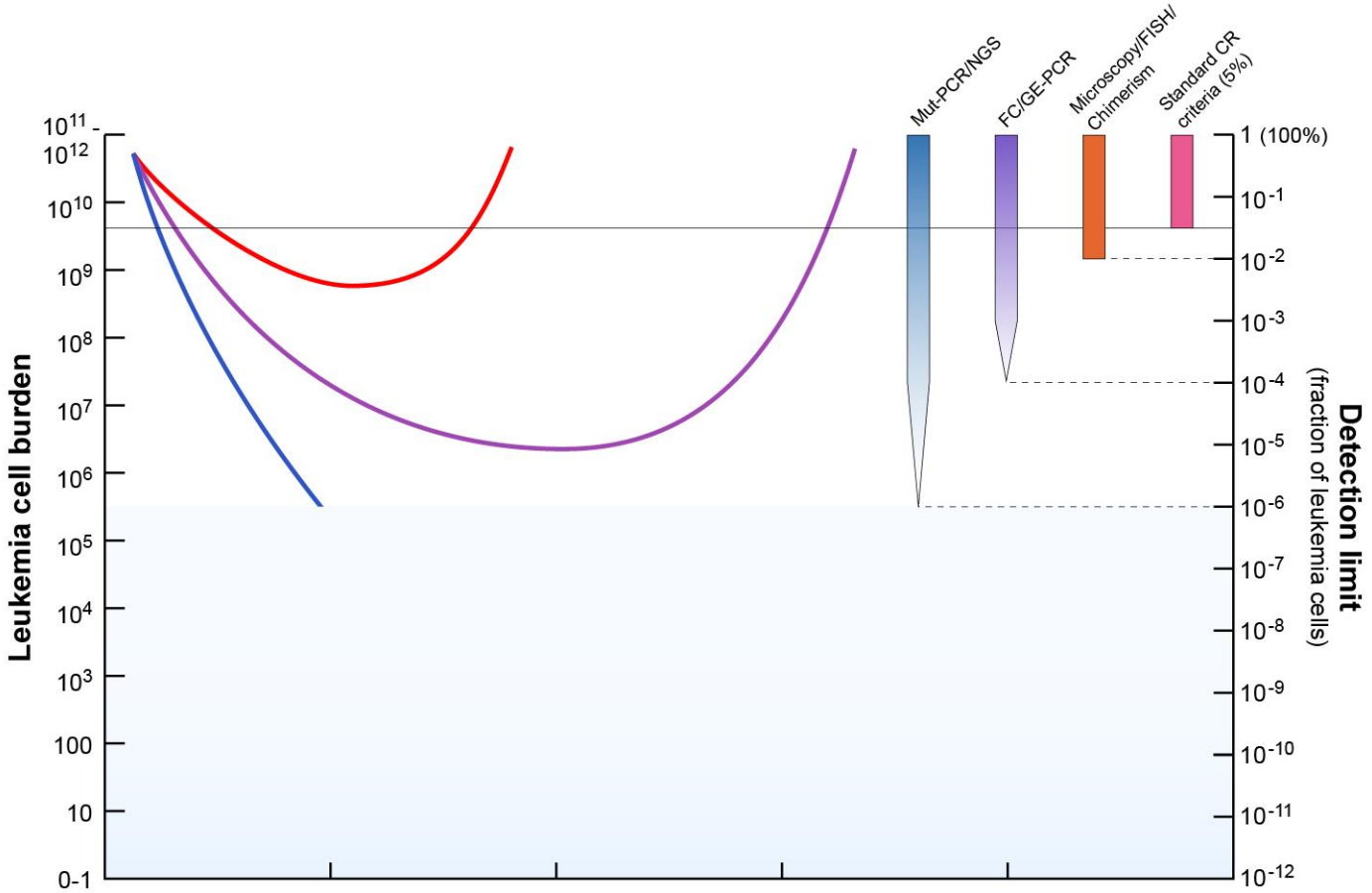



**Hourigan and Karp, Nature Rev Clin Oncology. 2013**

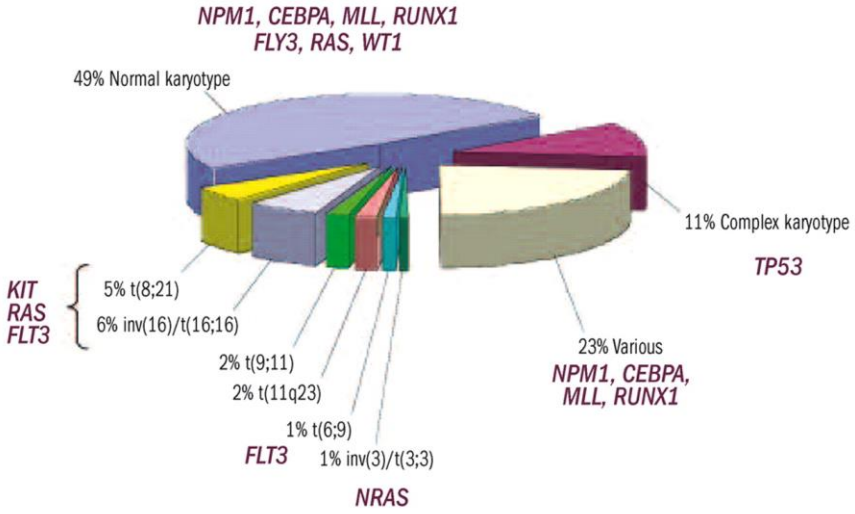


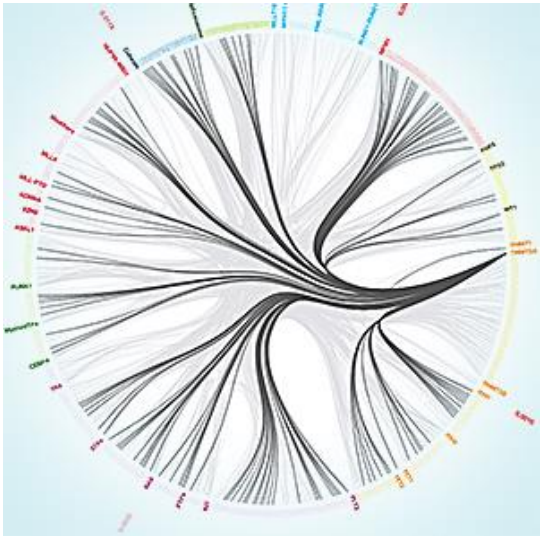

**Hourigan and Karp, Nature Rev Clin Oncology. 2013**

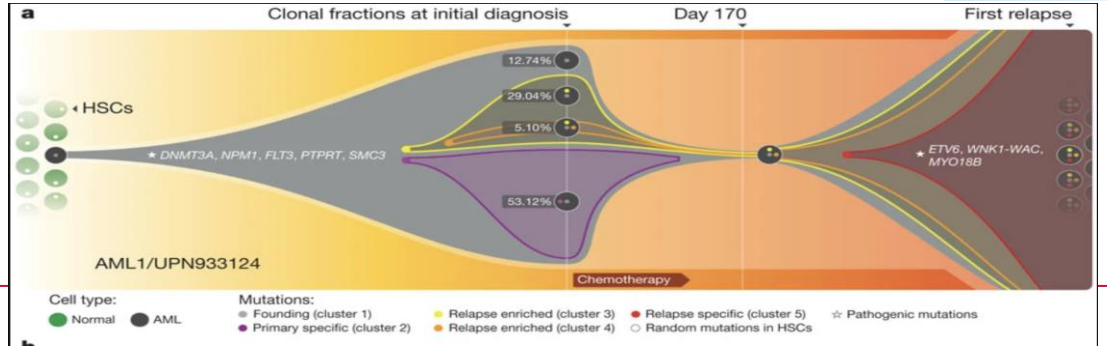



**Hourigan and Karp, Nature Rev Clin Oncology. 2013**

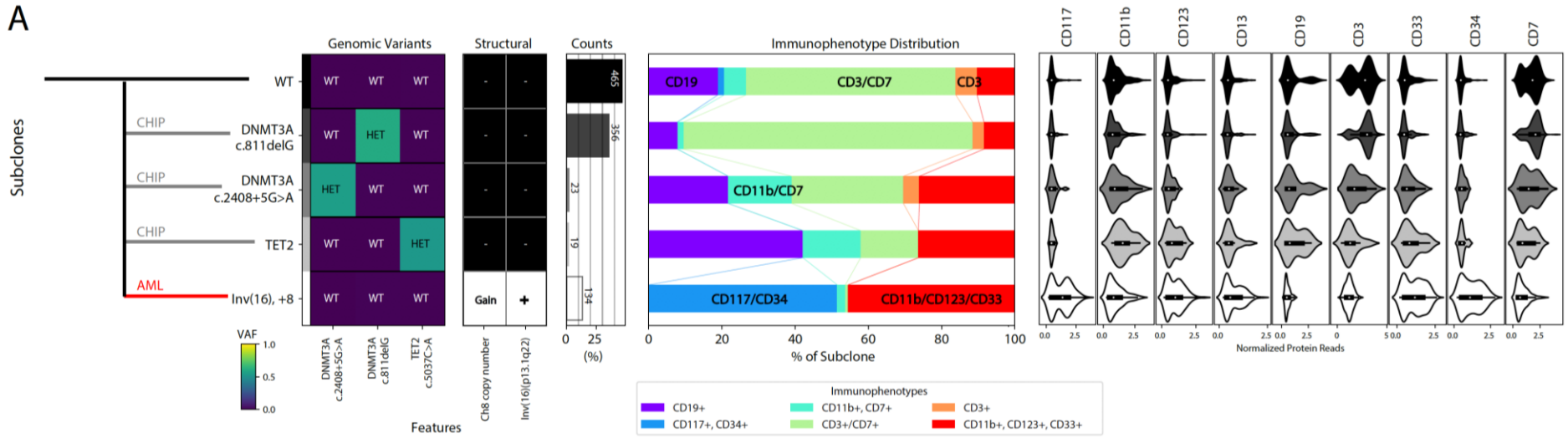
# Why MRD is hard in AML…





# Mutations ≠ Cancer



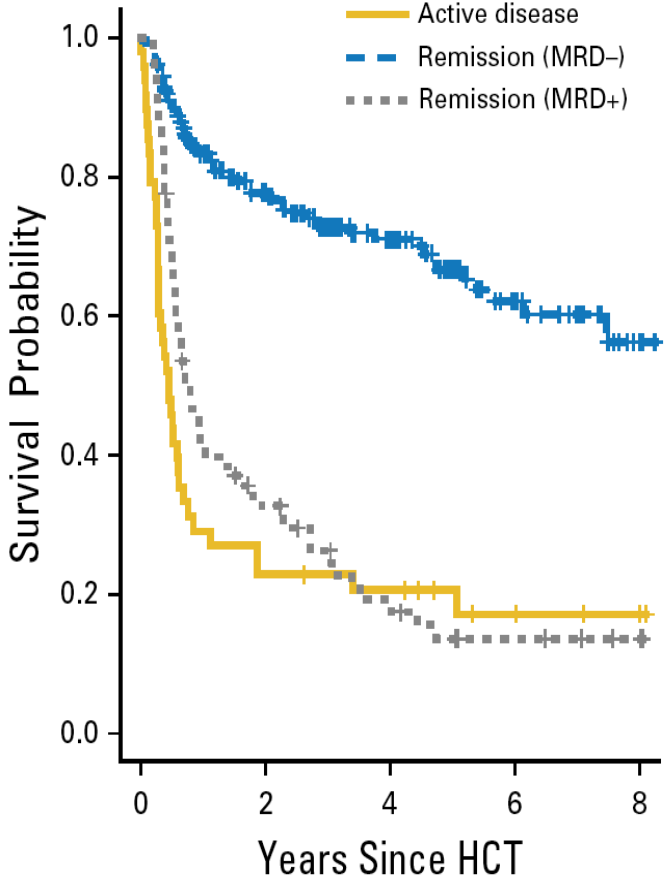

Dillon…Hourigan **Blood Cancer Discovery** (2021)

NIH National Heart, Lung, and Blood Institute

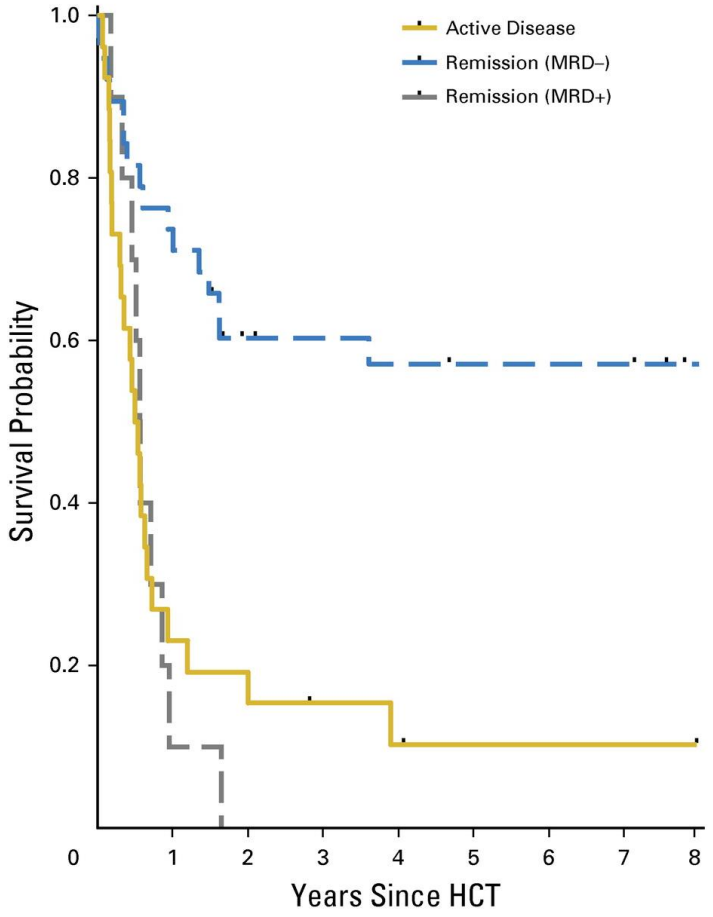
REVIEW ARTICLE | NOVEMBER 1, 2021

# 2021 Update Measurable Residual Disease in Acute Myeloid Leukemia: European LeukemiaNet Working Party Consensus Document

Michael Heuser, Sylvie D Freeman, Gert J Ossenkoppele, Francesco Buccisano, Christopher S Hourigan, Lok Lam Ngai, Jesse Marc Tettero, Costa Bachas, Constance Baer, Marie C Béné, Veit Buecklein, Anna Czyz, Barbara Denys, Richard Dillon, Michaela Feuring-Buske, Monica L Guzman, Torsten Haferlach, Lina Han, Julia K Herzig, Jeffrey L Jorgensen, Wolfgang Kern, Marina Y. Konopleva, Francis Lacombe, Marta Libura, Agata Majchrzak, Luca Maurillo, Yishai Ofran, Jan Philippé, Adriana Plesa, Claude Preudhomme, Farhad Ravandi, Christophe Roumier, Marion Subklewe, Felicitas Thol, Arjan A van de Loosdrecht, Bert A. van der Reijden, Adriano Venditti, Agnieszka Wierzbowska, Peter J.M. Valk, Brent L. Wood, Roland B Walter, Christian Thiede, Konstanze Döhner, Gail J. Roboz, Jacqueline Cloos ✉

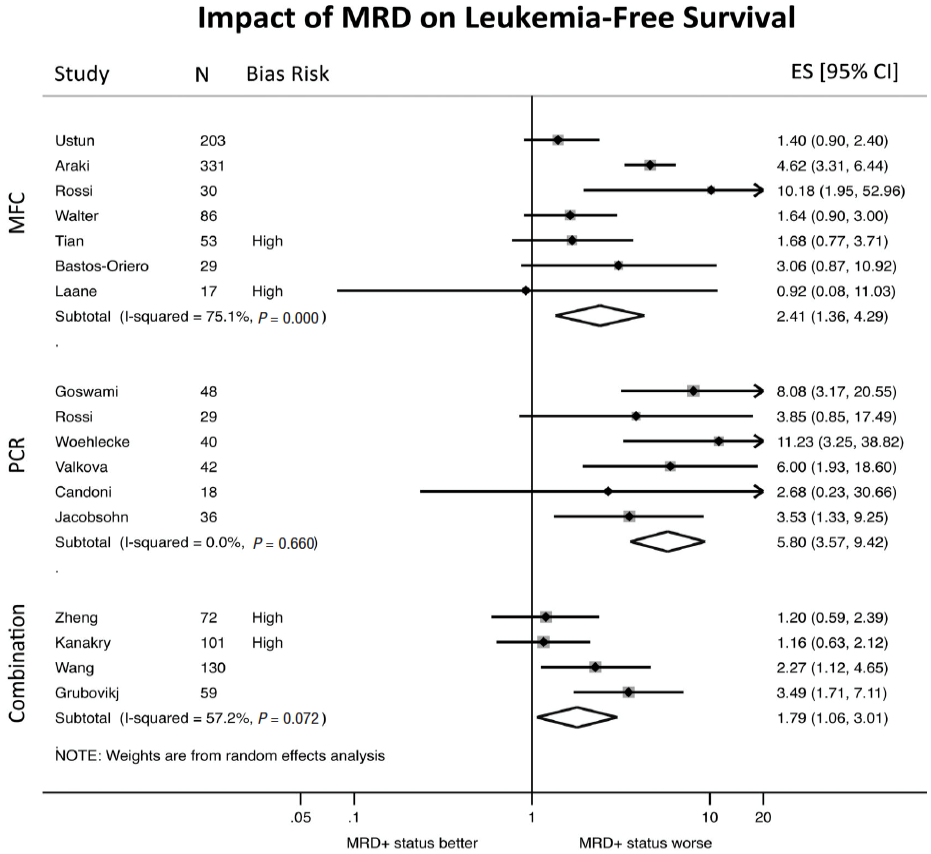



Araki *et. al.*, JCO 2016




Hourigan *et. al.*, JCO 2016

# Poor survival if AML MRD+ prior to Allo-HCT




*Regardless of test used:*

AML MRD in CR *before* Allo-HCT = worse survival *after* transplant.

**Buckley…Hourigan…Walter**
**Haematologica 2017**

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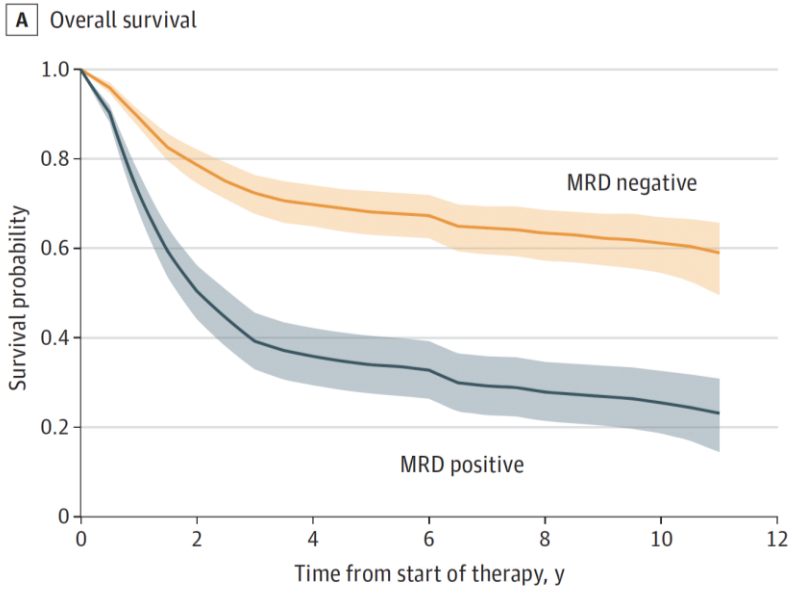
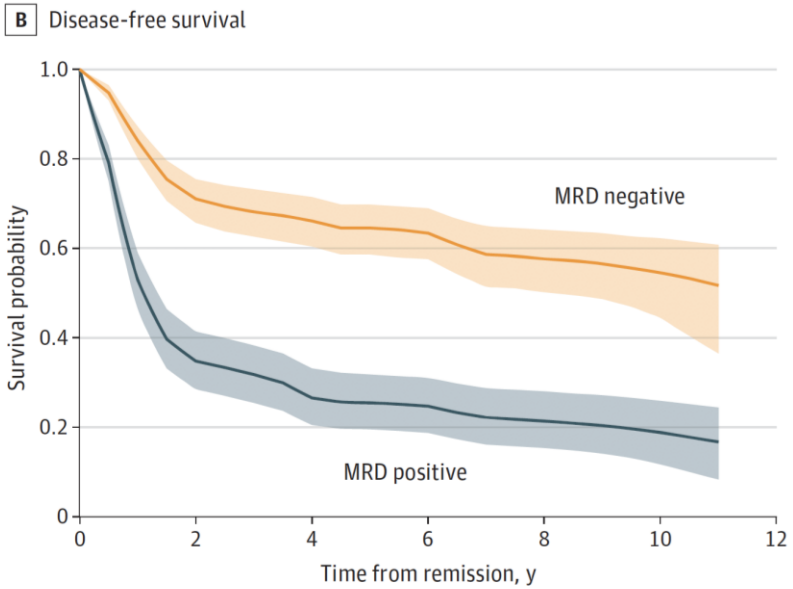
# Association of MRD with Survival in AML




**Short…Hourigan…Ravandi**
**JAMA Oncology 2020**

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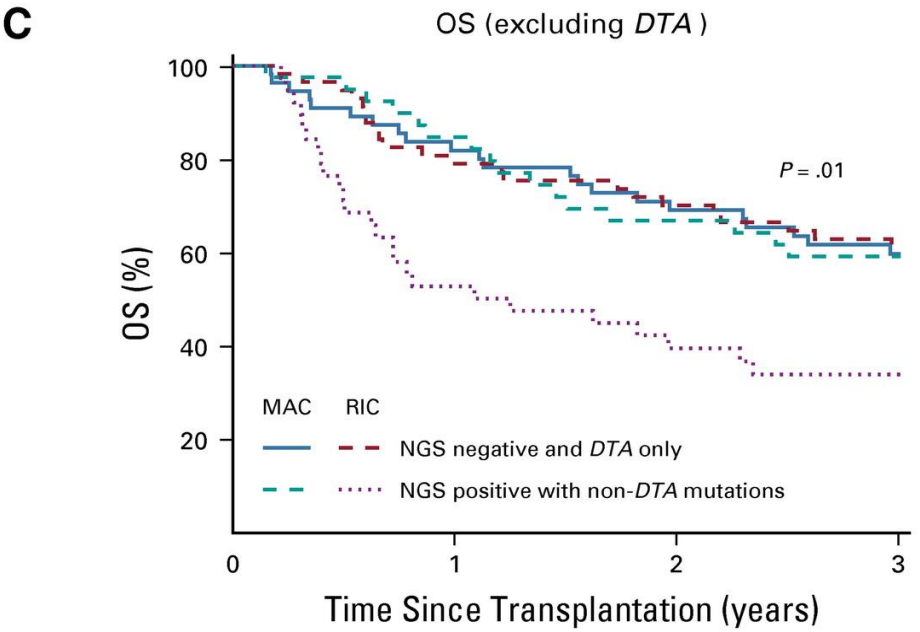
# Genomic evidence of AML MRD pre-alloHCT is associated with higher relapse and worse survival in those randomized to RIC rather than MAC




No. at risk

| | | | | |
|---|---|---|---|---|
| NGS negative and *DTA* only | | | | |
| MAC | 55 | 45 | 37 | 30 |
| RIC | 57 | 45 | 39 | 34 |
| NGS positive with non-*DTA* mutations | | | | |
| MAC | 40 | 33 | 26 | 21 |
| RIC | 38 | 20 | 14 | 12 |

Hourigan *et al.*

**JCO** 2020

| MRD Test Use Case | Notes |
|---|---|
| **Patient Selection/ Eligibility Criteria** | *Example:* Stratification of AML patients in first complete remission (CR1) enrolled post-transplant maintenance therapy clinical trial based on expected risk of relapse (prognosis). Typically, **landmark assessment** (e.g.: end of two cycles, pre-transplant, or end of treatment) based on a **threshold level** (eg: 0.1%) assigning patients with AML in CR to **higher or lower risk cohorts**. May also be used to identify patients most likely to respond to an additional intervention (predictive). |
| **Early relapse detection** | *Example:* Monitoring of **individual patients** with AML in cytomorphological remission after completion of treatment for early detection of impending clinical relapse. Clinical utility depends on both limit of detection of assay, nature of MRD target tracked, testing frequency, sample source and frequency of testing. Typically, **serial measurements** to assess for conversion from **negative to positive** MRD test or a confirmed 1 log increase after prior low copy number molecular persistence. |
| **Anti-leukemic efficacy quantification** | *Example:* Determination of “deep” vs “shallow” remissions in **individual patients** after therapy. Typically, disease clearance expressed as **log reduction** (ie: **paired assessments** from before and after treatment), but thresholds have also been used. May be used to compare (with greater dynamic range than conventional cytomorphological assessments) efficacy of different therapies. May be used as a surrogate biomarker in new drug development and, if association with survival proven, new drug approvals. |

**Gui and Hourigan Cancer J. 2022**

# Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment

## Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2020
Clinical/Medical


MRD3000


MRD3000

PubMed.gov

aml residual disease

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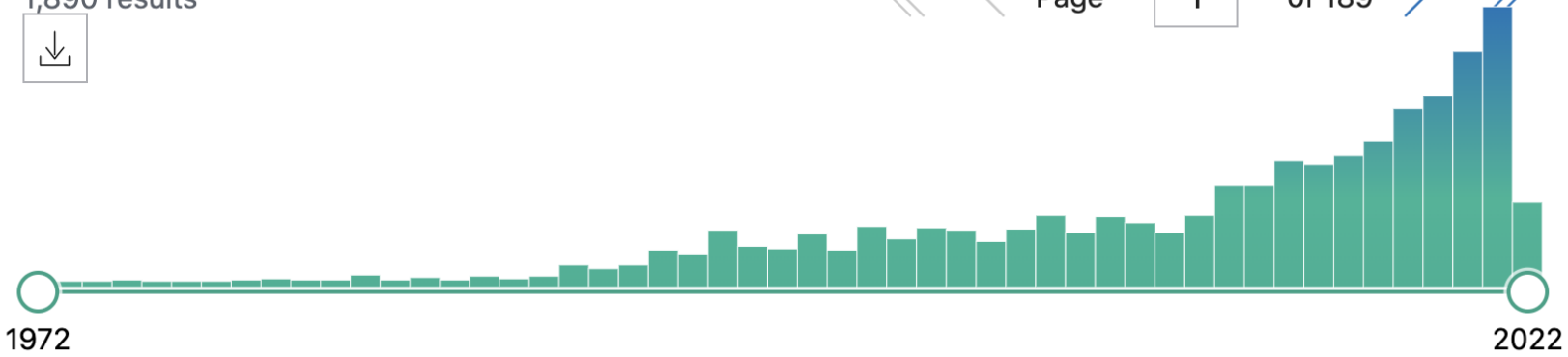


# AML MRD

- MRD in AML
- **The FNIH AML MRD Consortium**

# Measurable residual disease (MRD) in acute myeloid leukemia (AML)

BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

FNIH
Foundation for the National Institutes of Health

# Co-PIs

Dana-Farber Cancer Institute

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH National Heart, Lung, and Blood Institute

FRED HUTCH CURES START HERE™

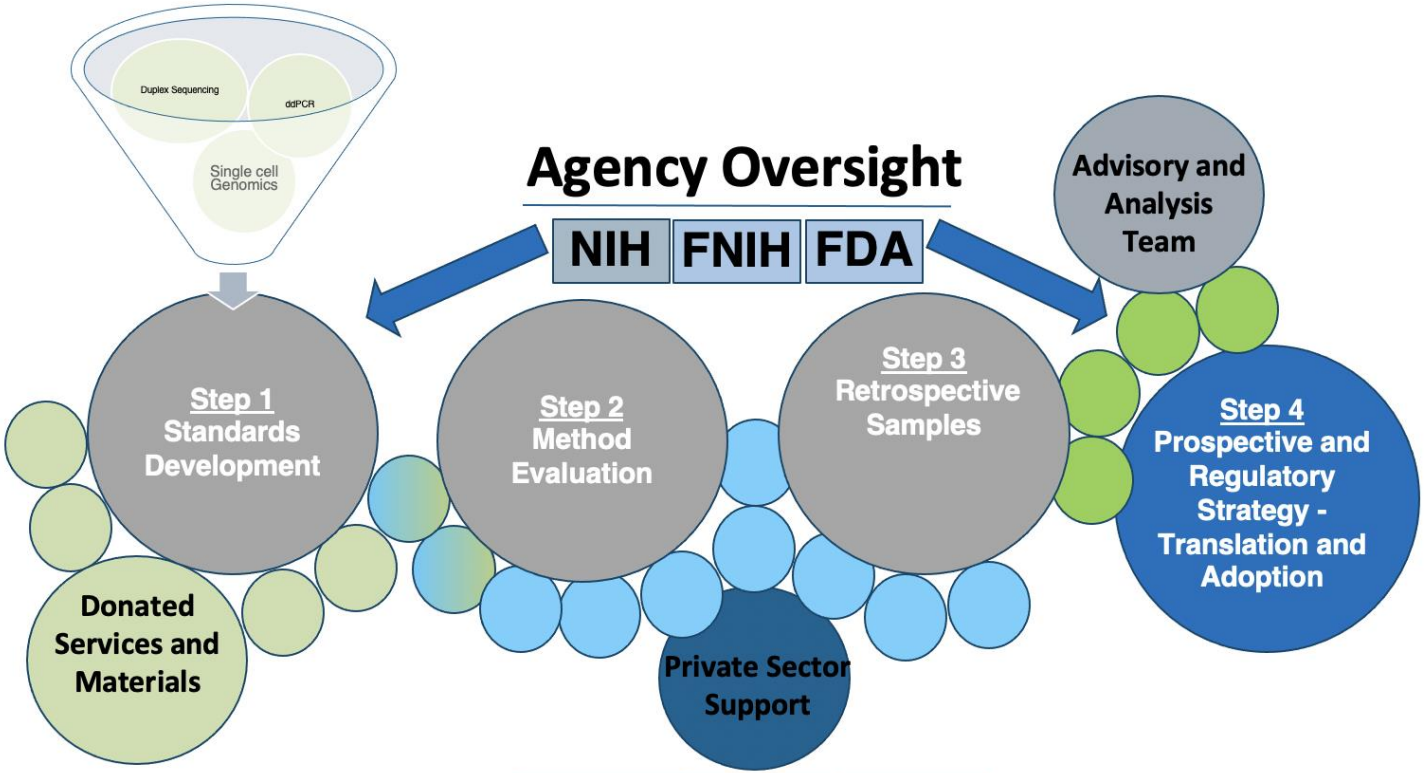
**Coleman Lindsley MD PhD**

**Chris Hourigan DM DPhil**

**Jerry Radich MD**

# MRD in AML Project Team

Year 1 Milestone > Year 2 Milestone > Year 3 Milestone > Year 4 Completion




## Project Leadership

BIOMARKERS CONSORTIUM FNIH

# Pharmaceutical Industry Partners





GlaxoSmithKline




**Plus others hoping to join…**

# Research/Diagnostic Company Partners







**Plus others hoping to join…**

U.S. FOOD & DRUG ADMINISTRATION

**CDER**

Nicole Gormley

Angelo de Claro

Emily Jen

Donna Przepiorka

**CDRH**

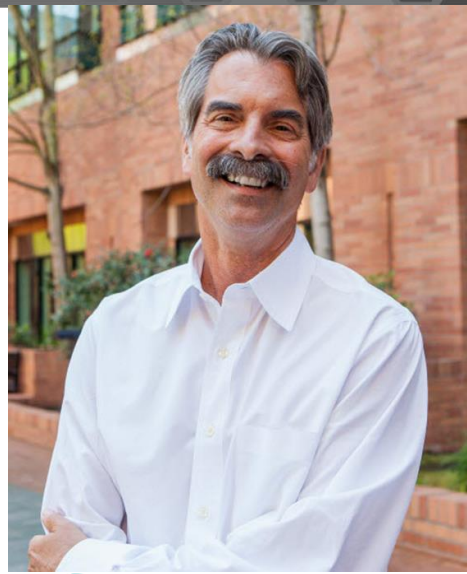
Karen Bijwaard

Chris Trindade

# Standards Subgroup

"*Determining the types of samples (cell lines, artificial cell-like material, DNA mixes, etc.), procurement, and deciding the complexity and the range of mutation levels in the mixes*". Enables methods comparisons and multi-site testing.

Representation from 14 of 21 partners



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**Jerry Radich**

NIH National Heart, Lung, and Blood Institute

# Methods Subgroup

Focus on molecular methodologies – with parallel workstreams focusing on ultra-deep DNA variant detection and novel single cell technologies. "*Finding new methods, testing, developing analytic plans to compare new methods*"

Representation from 19 of 21 partners incl:

| | | |
|---|---|---|
| 10X Genomics | NuProbe | Thermo Fisher |
| Bio-Rad | Sysmex Inostics | Twinstrand Biosciences |

National Heart, Lung, and Blood Institute

**Chris Hourigan**

National Heart, Lung, and Blood Institute

# Retrospective Subgroup

"*Obtaining samples and clinical outcome data from past clinical studies that can used to test new methods*".

Focus on three treatment scenarios:

- Intensive cytotoxic therapy
- Less-intensive hypomethylating agent based therapy
- Allogeneic transplantation

Representation from 12 of 21 partners incl:

AstraZeneca FDA Novartis

Dana-Farber Cancer Institute

**Coleman Lindsley**

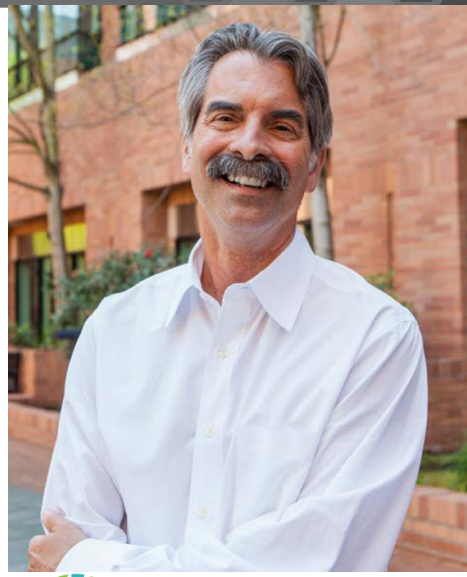
NIH National Heart, Lung, and Blood Institute

# Prospective and Regulatory Subgroup

"*Outreach to U.S. Intergroup (eg: NCI: MyeloMATCH), bone marrow transplant community (eg: CIBMTR/NMDP: MEASURE) and the biopharmaceutical industry " to translate findings and best practices from the fNIH consortium work into the prospective generation of new evidence for AML MRD*".

Representation from 15 of 21 partners incl:

Abbvie FDA GlaxoSmithKline Jazz



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NATIONAL CANCER INSTITUTE

# PRECISION MEDICINE IN CANCER TREATMENT

Discovering unique therapies that treat an individual's cancer based on the specific genetic abnormalities of that person's tumor.

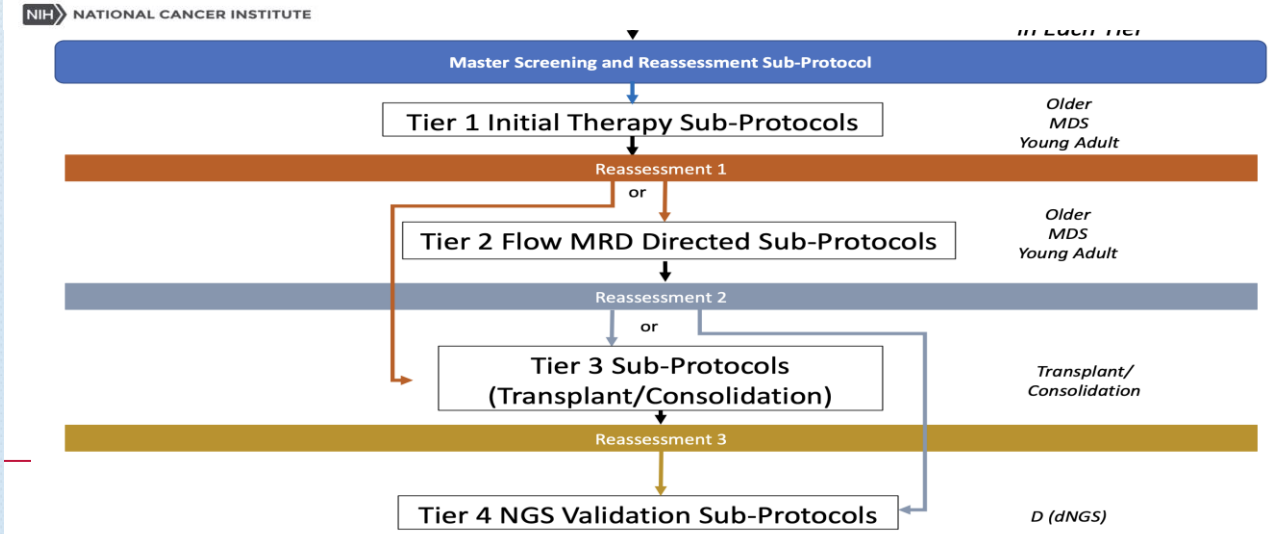
www.cancer.gov

# MyeloMATCH

Umbrella trial to test treatments for acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) and to evaluate early endpoint efficacy signals in specific molecular and clinical risk groups

**Overarching scientific rationale:**

- As tumor burden is reduced over the course of treatment, low-level residual disease can be identified by advanced assays and therapeutically targeted.
- These assays will require clinical utility validation and myeloMATCH is positioned to conduct the necessary trials to accomplish this.
- Estimated to launch mid-2021



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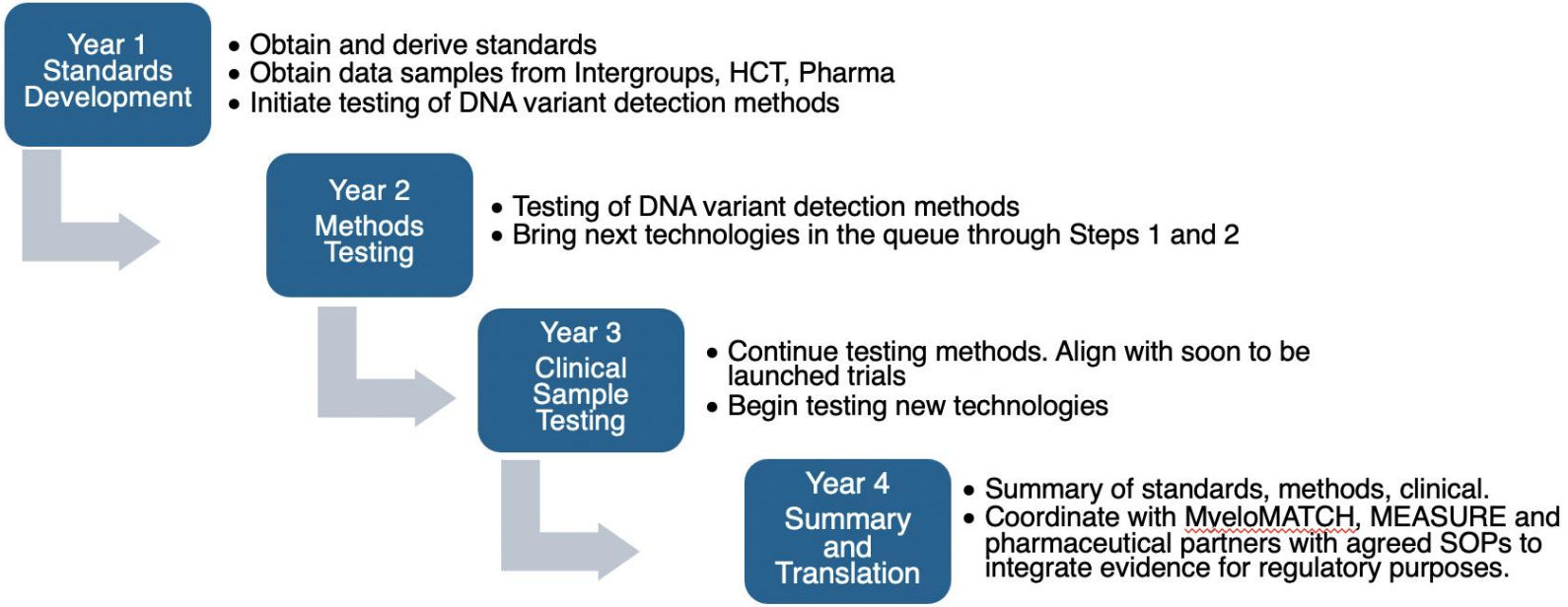
MOLECULAR EVALUATION OF AML PATIENTS AFTER STEM CELL TRANSPLANT TO UNDERSTAND RELAPSE EVENTS

# MEASURE: Molecular Evaluation of AML Patients After Stem Cell Transplant to Understand Relapse Events

**Resource for Clinical Investigation in Blood and Marrow Transplantation**

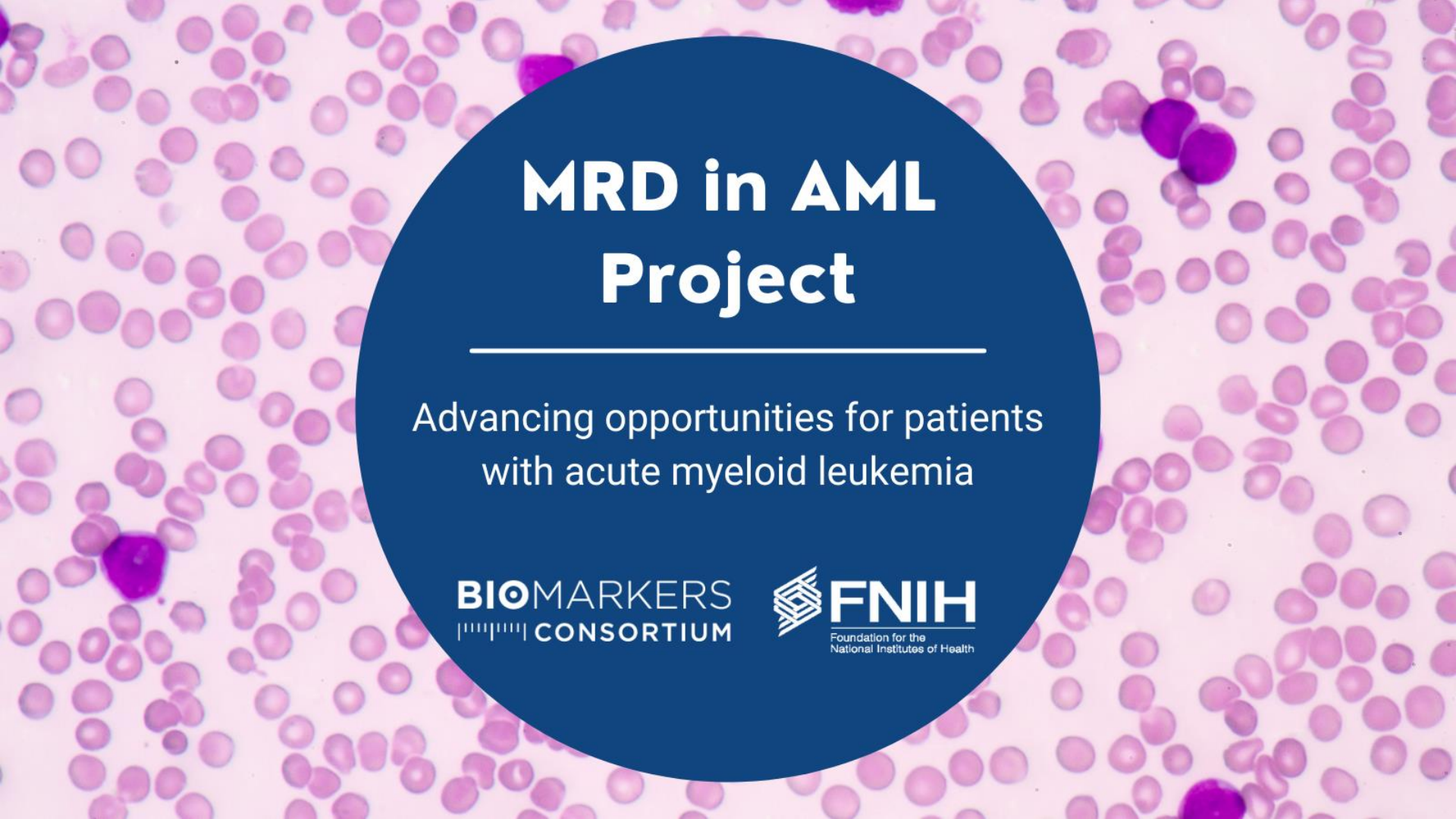
**NCT05224661**

# Project Timeline



# Unknown but answerable questions in AML MRD

- Do serial MRD measurements allow for better prognostication in individual patients than at a single key clinical landmark?
- In what circumstances does MRD testing add information beyond baseline characterization?
- Does MRD status have the same prognostic significance if achieved after intensive vs. non-intensive therapy?
- Can blood substitute for marrow for in AML MRD assessments?
- Are all/any detected non-DTA mutations appropriate for AML MRD tracking in remission? – or are some more pathognomonic than others?
- How often are subclones responsible for relapse found in remission and/or in the original diagnostic sample when using highly-sensitive MRD-depth NGS measurements? *ie: can we predict potential escape clones?*


MRD in AML Project
Advancing opportunities for patients with acute myeloid leukemia
BIOMARKERS CONSORTIUM
FNIH
Foundation for the National Institutes of Health

# Summary

- **Nothing complete about a complete remission** in AML, but higher sensitivity measurements can better risk stratify cohorts.
- **AML MRD good for papers, not yet for patients**. Incentives and resources have traditionally not been aligned to move field forward towards generation of robust evidence of clinical utility using harmonized validated assays – FNIH biomarkers consortium represents an opportunity to bridge the canyon.
- **Collaboration offers pathway to success** between research /diagnostic assay companies, academic physician-scientists, regulatory agencies, the pharmaceutical industry and ultimately patients – a “win-win-win-win-win”.


# Questions?

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