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MRD Assessment in Acute Leukemias: How, When, and Really?

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Consultant/ Advisory Board

Kymera

ProRavel

No information discussed in this presentation overlaps with these relationships

Objectives

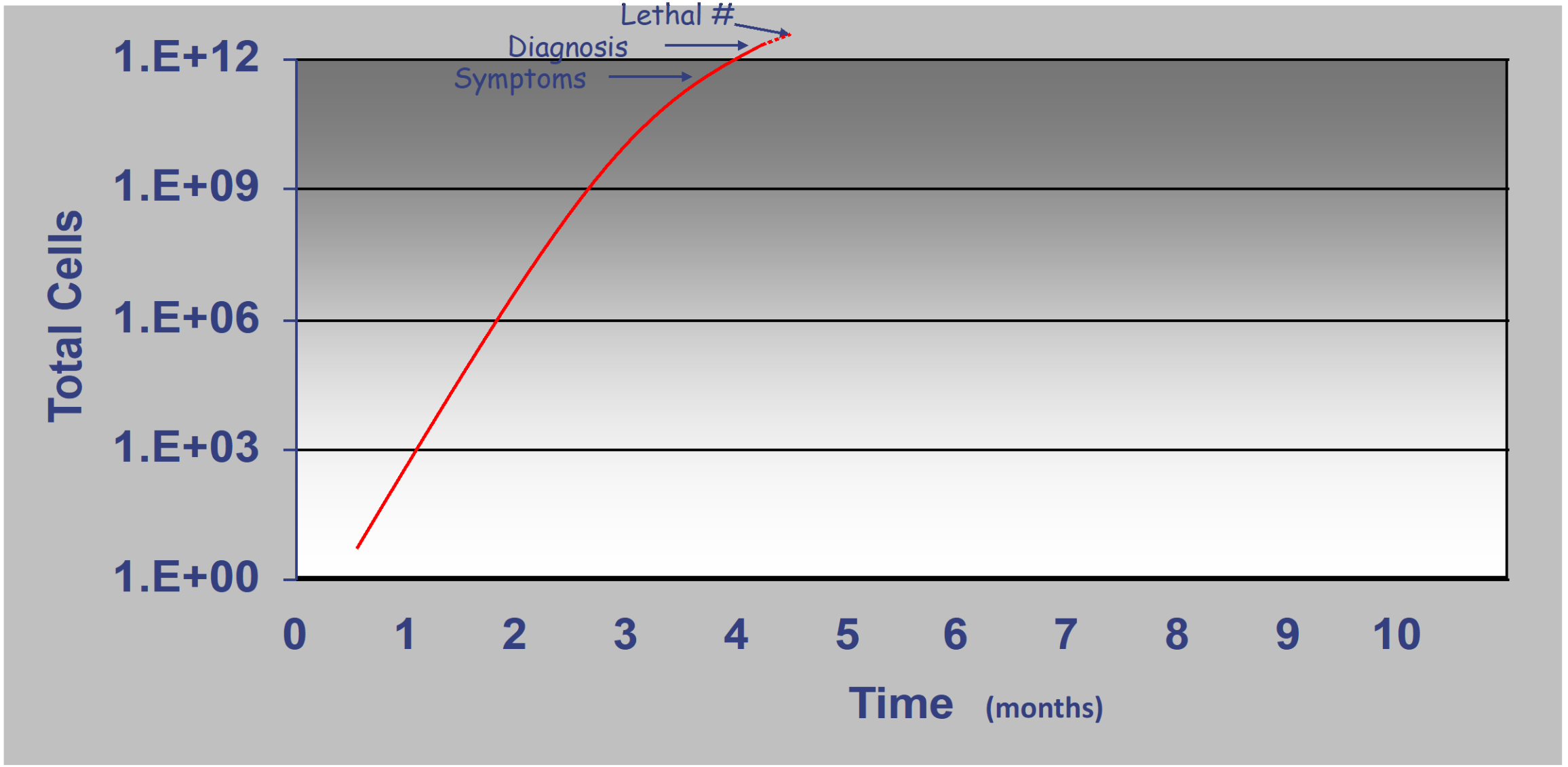
- What is measurable residual disease (MRD), and why is it important?
- How is it measured?
- How can it be used in AML?
- How can it be used in ALL?

What is MRD?

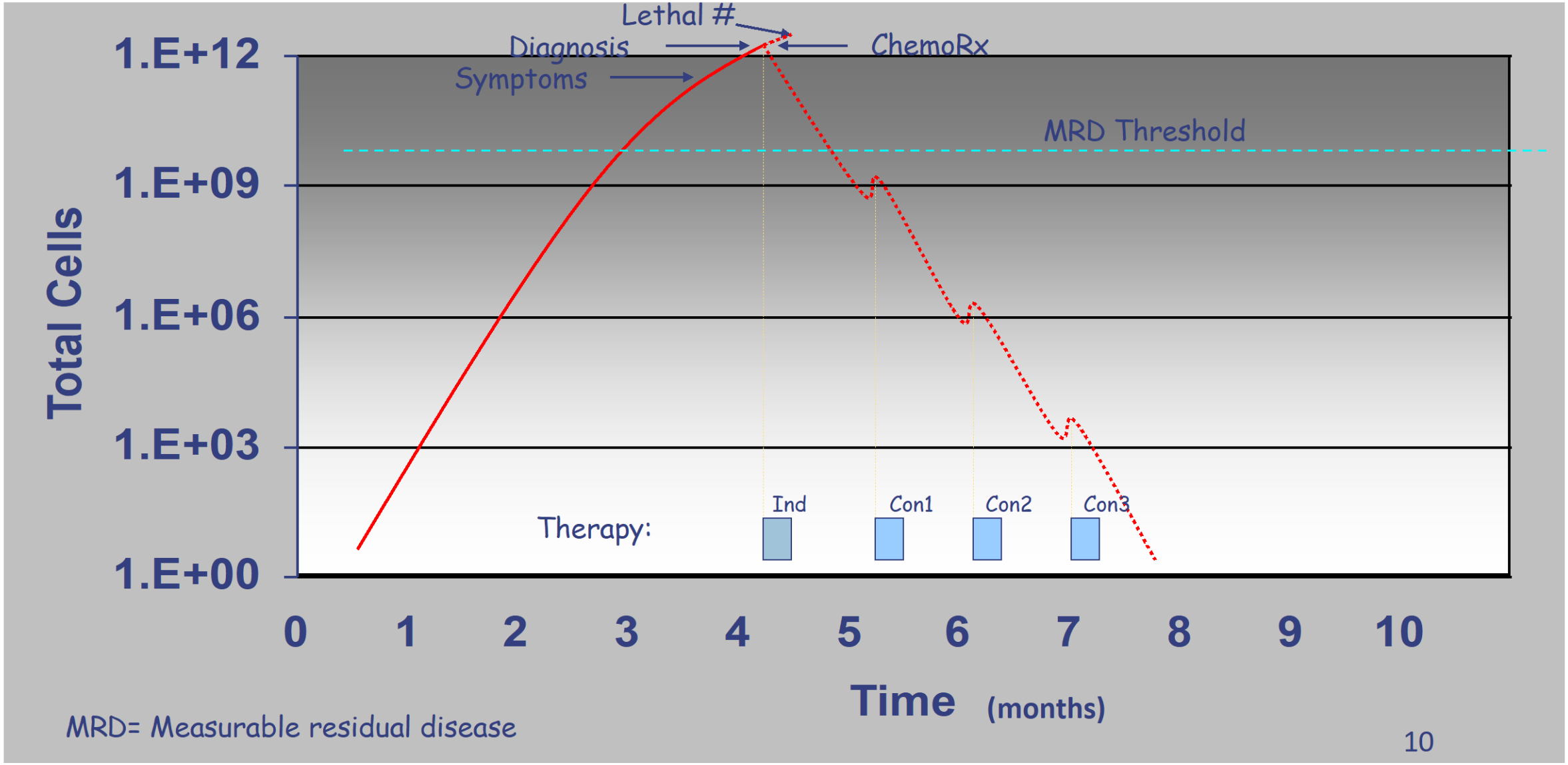
Measurable residual disease (MRD)

- Detection of leukemia cells down to levels of $1:10^4$ to $1:10^6$ of WBCs
  - Compare with 1:20 (5%) in morphology-based assessments

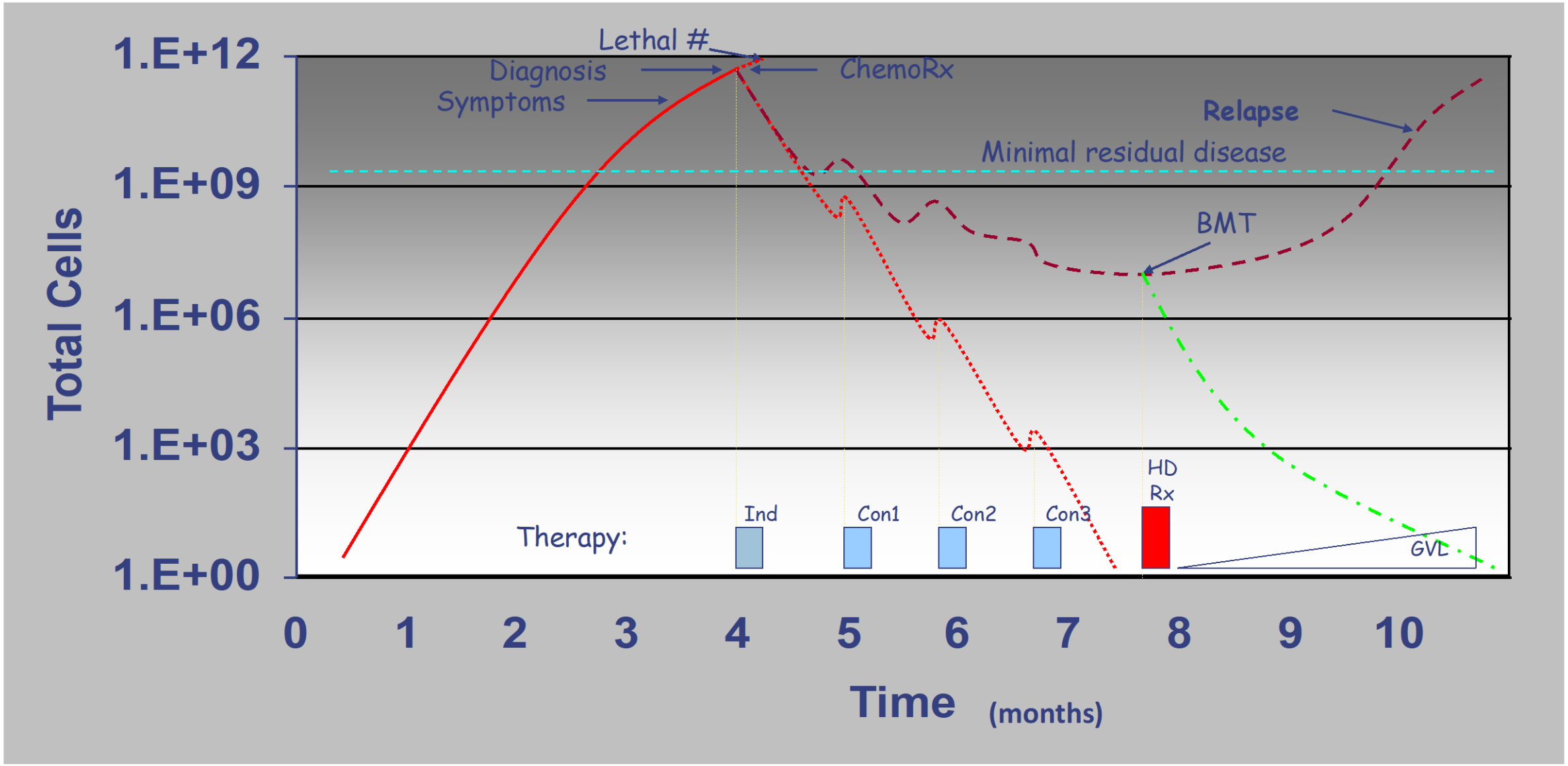
The kinetics of acute leukemia: Diagnosis



The kinetics of acute leukemia: Treatment



The kinetics of acute leukemia: Treatment



Why do patients have measurable residual disease after initial therapy?

Poor prognostic

- Greater starting leukemia cell number
- Intrinsic resistance to initial therapy

Neutral prognostic

- Inadequate treatment
  - Pharmacokinetic factors
  - Pharmacogenomic factors

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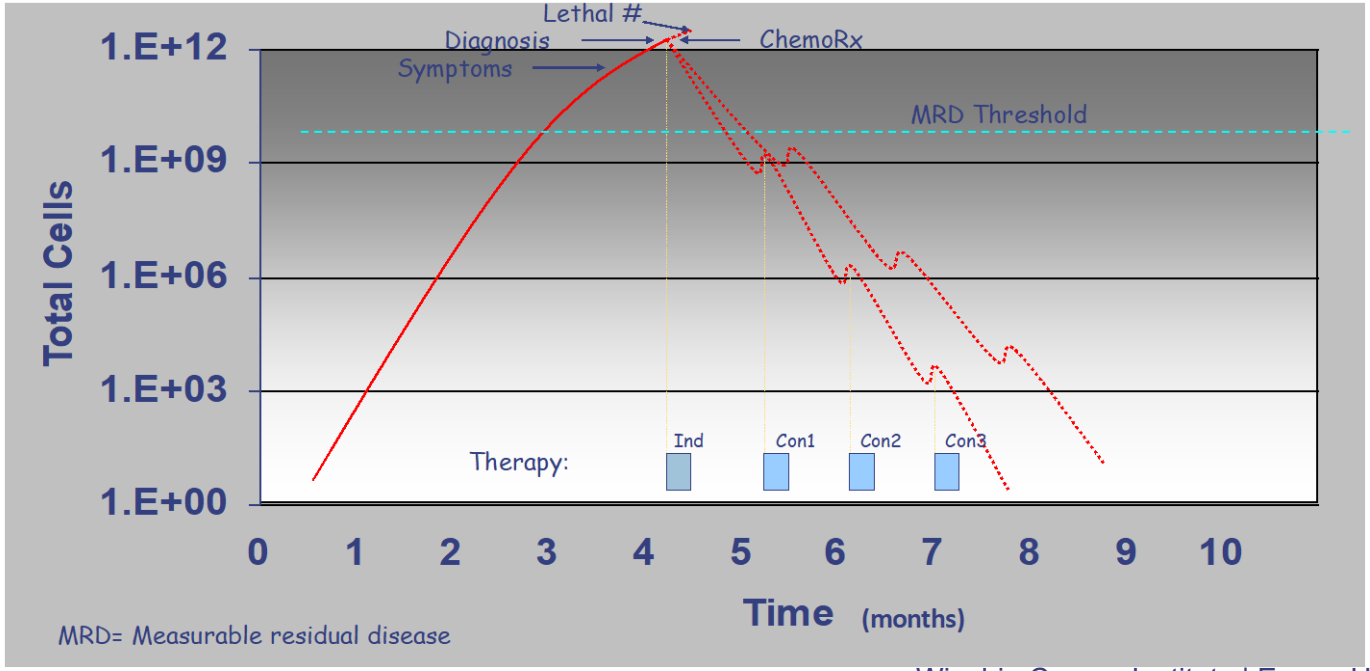
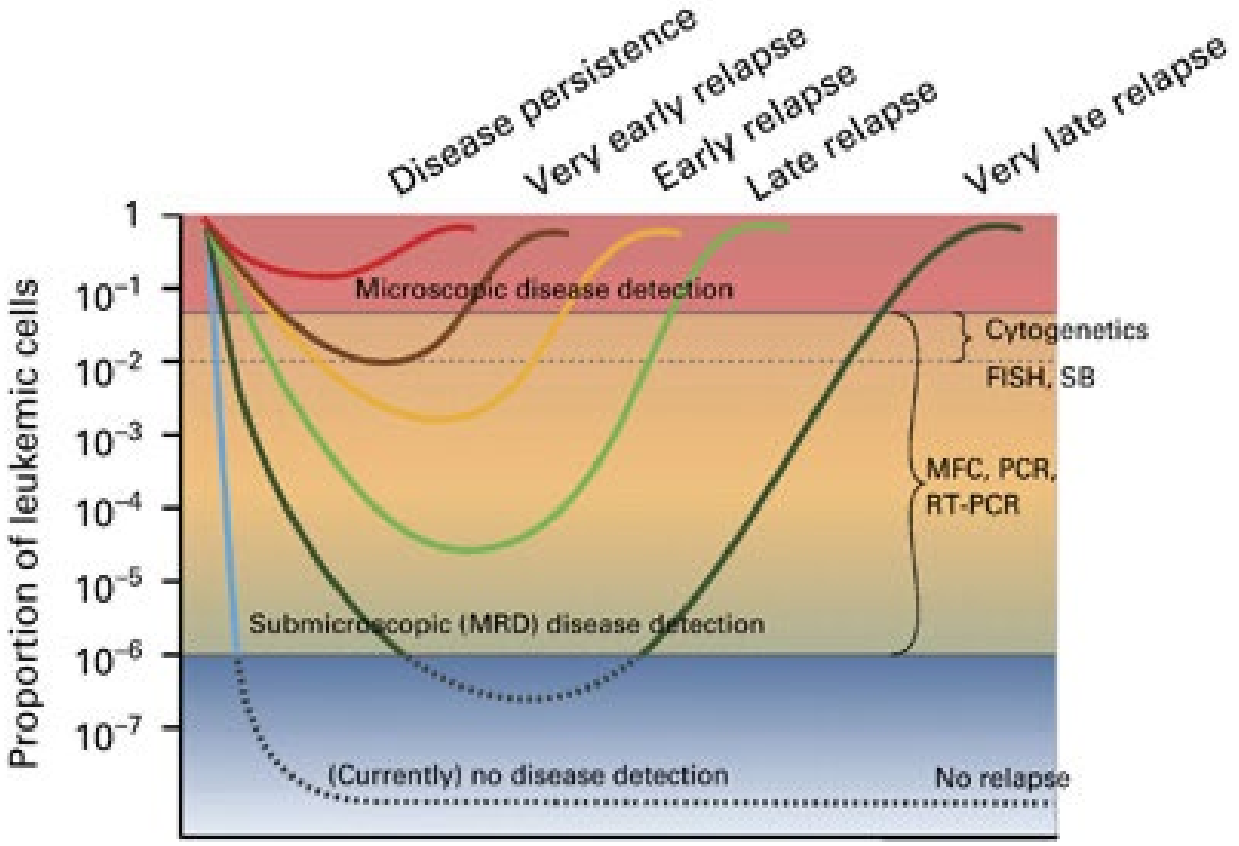


Why do we measure MRD?

- New (deeper) response criterion: CR without MRD (**CR_{MRD-}**)
- Refine outcome prediction and inform post-remission treatment
- Identify impending relapse, and initiate early intervention
- Allow more robust post-transplant surveillance
- Use as a surrogate endpoint to accelerate drug testing and approval.

Schuurhuis, Heuser, Freeman, et al. Blood. 2018;131(12):1275-1291

Why do we measure MRD?



Bone Marrow Transplantation (2013) 48, 630–641

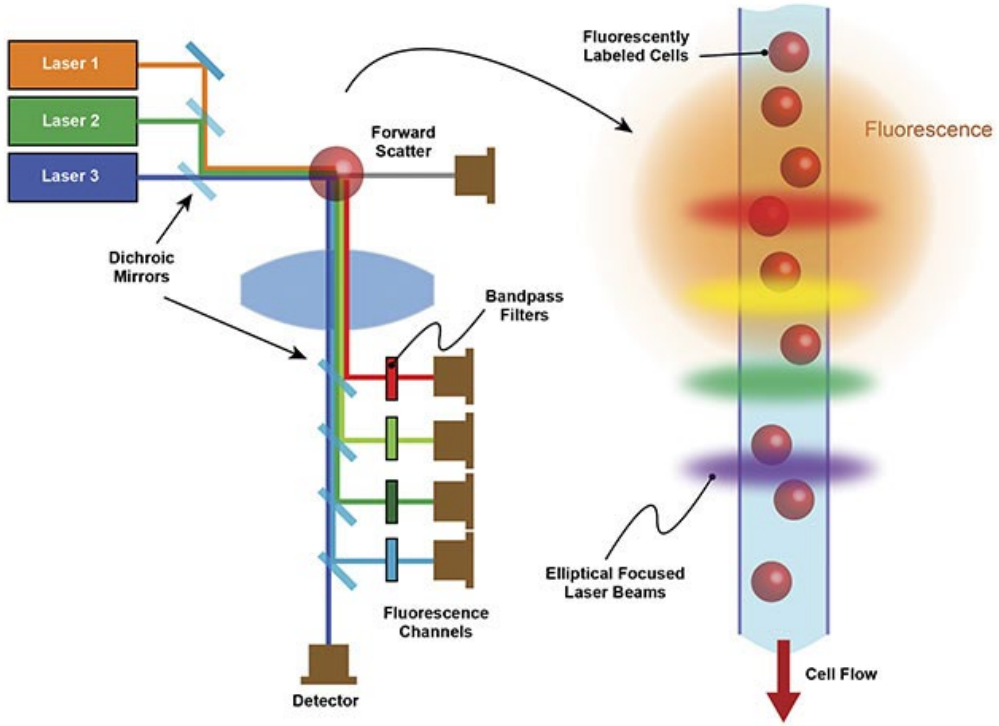
Methods to detect MRD: What sample to test

- Bone marrow is 10-1000 times more sensitive than peripheral blood

Methods to detect MRD

Cell surface protein expression-based

- **Multiparameter flow cytometry**
  - Detects leukemia associated immunophenotypes (LAIP)
  - Often 7-8 “colors” simultaneously
  - Sensitivity ~0.1%
  - Generally, some combination of expression of:
    - CD7
    - CD34
    - CD33
    - CD13
    - CD117



From Photonics.com

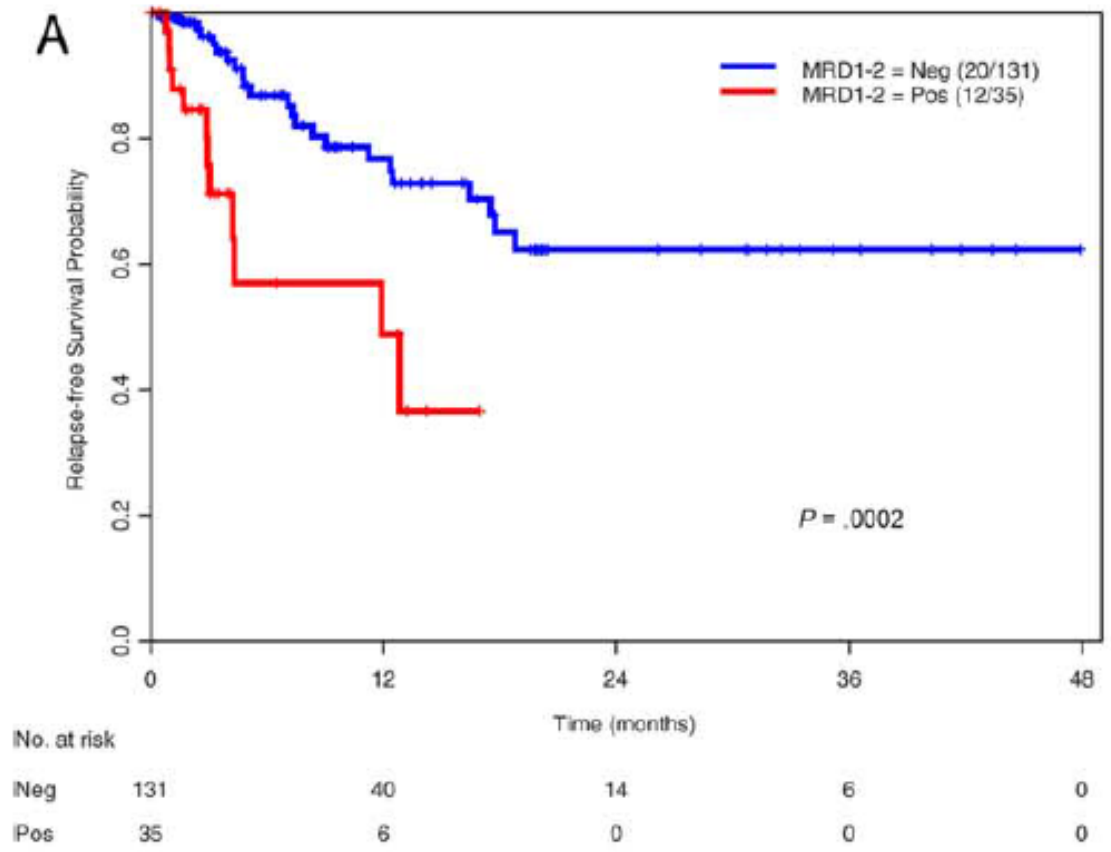
Methods to detect MRD

Nucleic acid-based

- **Real-time quantitative polymerase chain reaction (RQ-PCR)**
  - Detects fusions and point mutations at the DNA level
- **Reverse transcriptase-polymerase chain reaction (RT-PCR)**
  - Detects fusions and point mutations at the RNA level
- **Next-generation sequencing (NGS)**
  - Detects specific point mutations
- **Droplet digital PCR (ddPCR)**
- **Immunoglobulin/T-cell receptor (TCR) rearrangements (for ALL)**

MRD in adult AML

Detection of MRD early in therapy is associated with higher risk of relapse

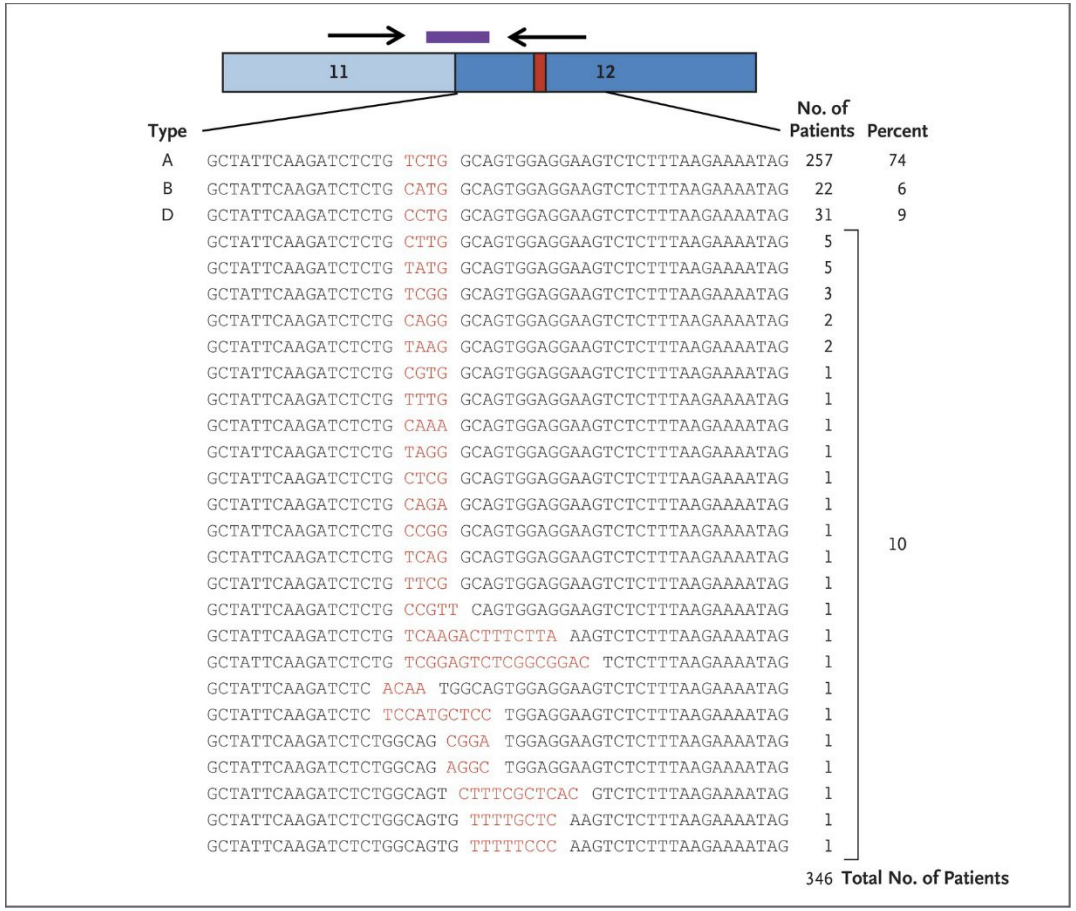


MRD detection by multi-parameter flow cytometry

Time point: 1-2 months into therapy

Ravandi, Jorgensen, Borthakur, et al. Cancer 2017. 123:426-35

MRD in adult AML: RT-PCR-based assay for mutated NPM1



A diversity of mutations occur in NPM1 and can be detected by RT-PCR

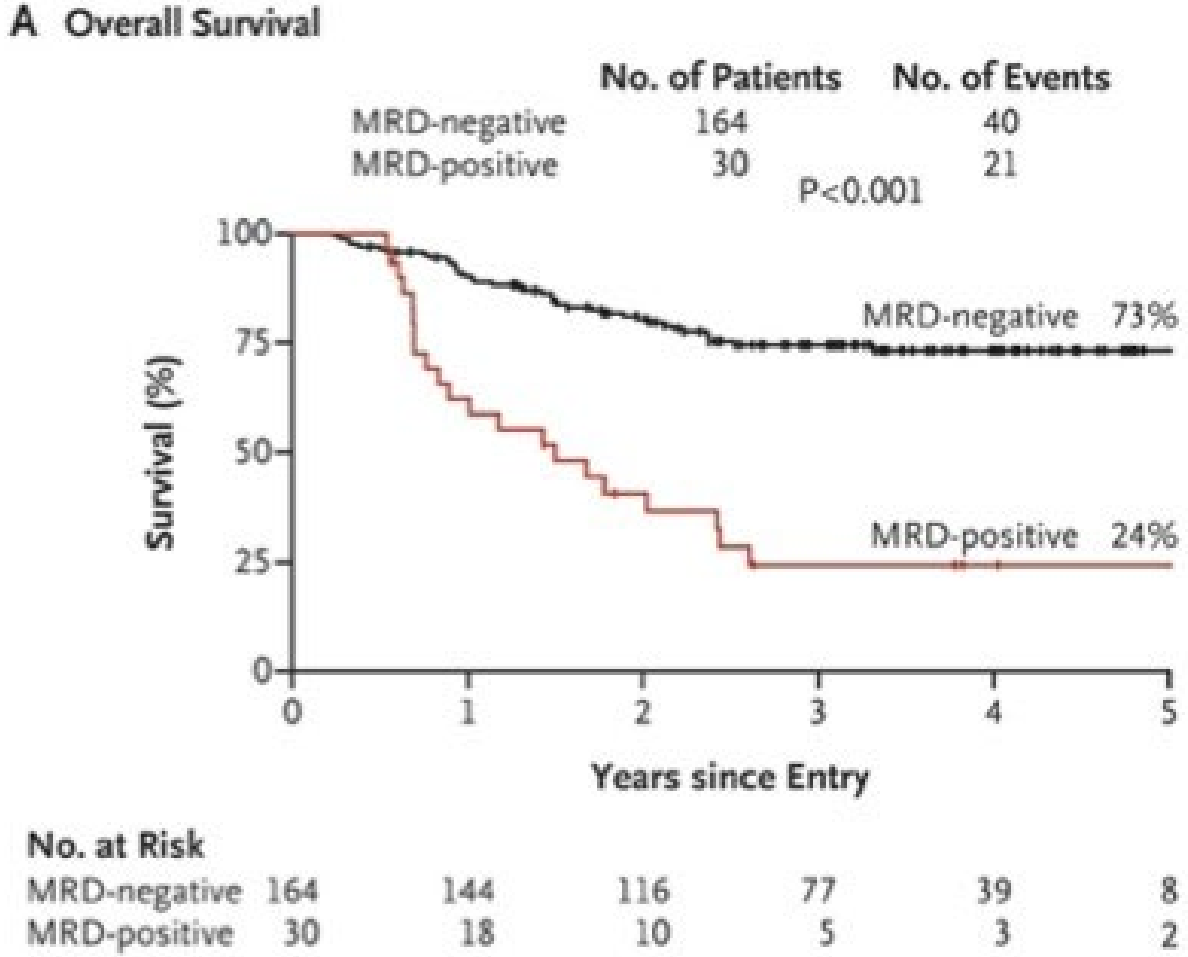
N Engl J Med 2016; 374:422-433

MRD in adult AML: RT-PCR-based assay for mutated NPM1

MRD status predicts for relapse

N Engl J Med 2016; 374:422-433

MRD in adult AML: RT-PCR-based assay for mutated NPM1



MRD status predicts overall survival

N Engl J Med 2016; 374:422-433

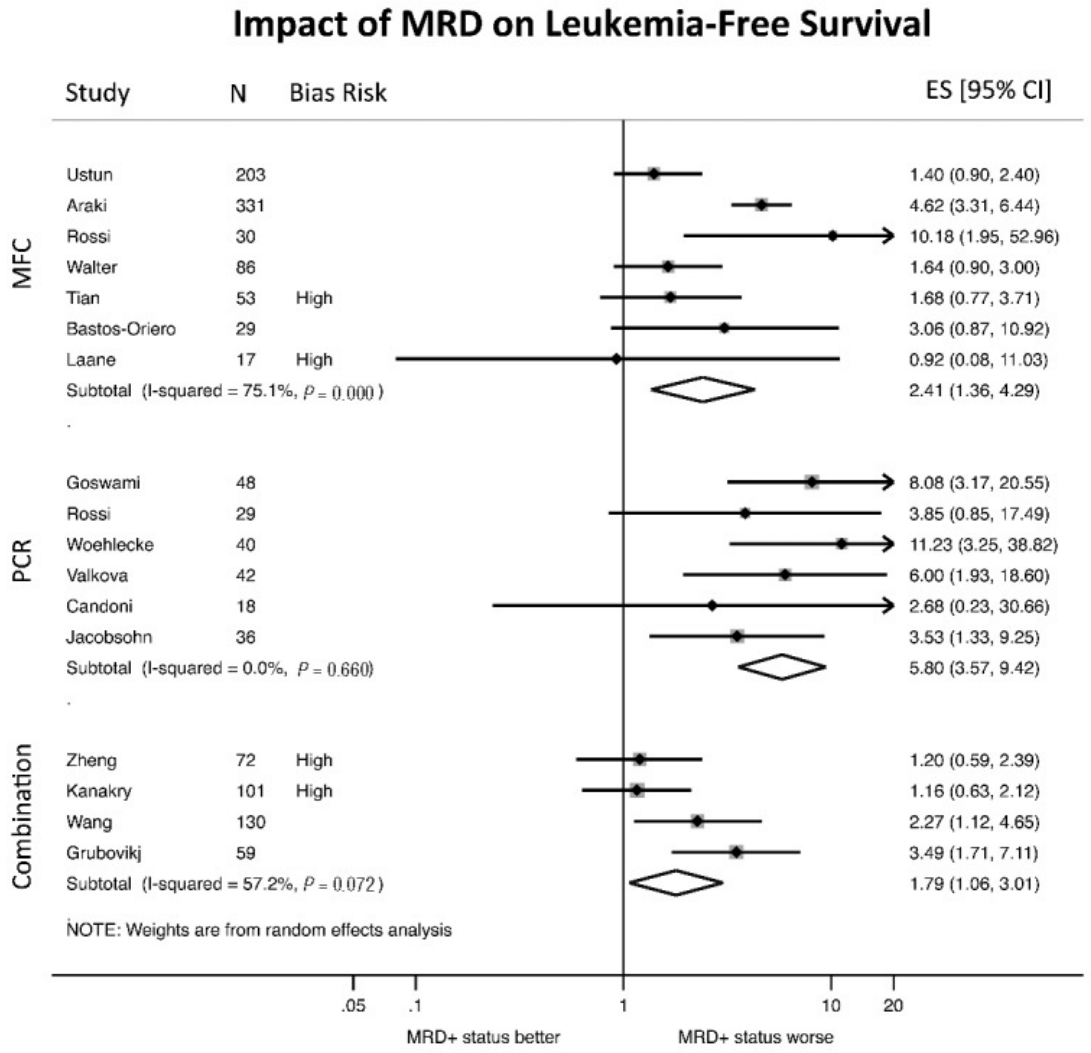
MRD in adult AML:
NGS and Flow cytometry provide complementary information

Jongen-Lavrencic, T. Grob, D. Hanekamp, F. NEJM 2018; 378:1189-99

MRD in adult AML: NGS

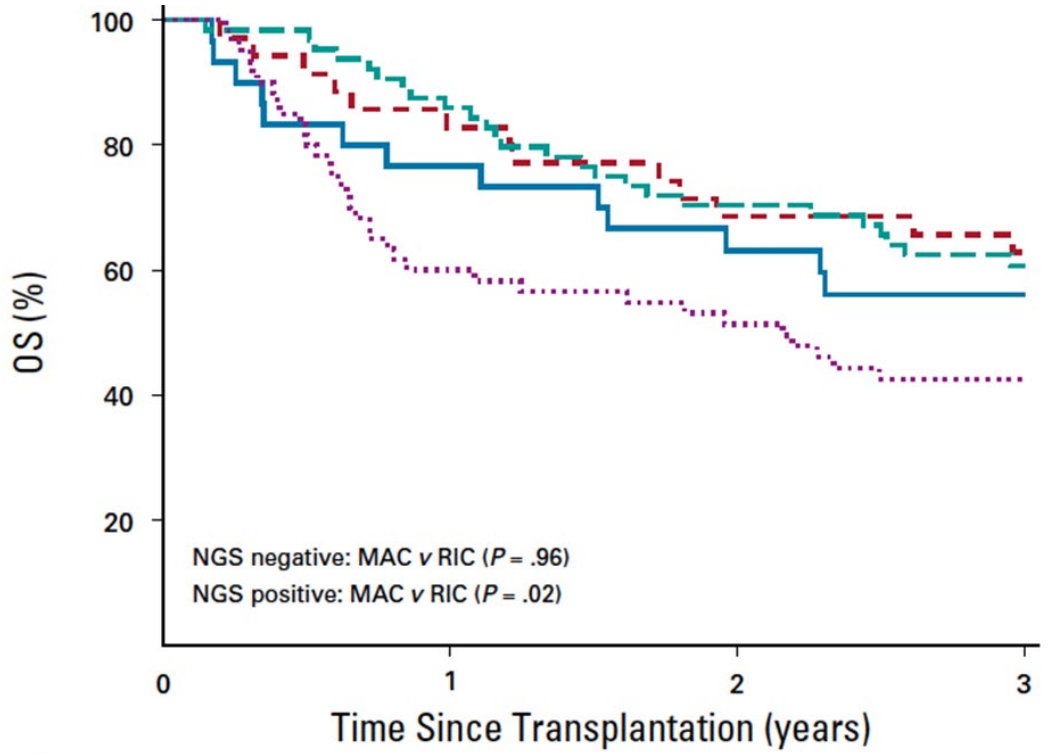
Jongen-Lavrencic, T. Grob, D. Hanekamp, F. NEJM 2018; 378:1189-99

MRD in adult AML:
MRD detection is a negative prognostic indicator prior to transplant



Buckley, Wood, Othus, et al. Haematologica 2017. Vol. 102(5):865-873

MRD in adult AML:
MRD detection may guide choice of conditioning regimen in transplant



No. at risk				
NGS negative				
MAC	30	23	18	16
RIC	35	29	24	22
NGS positive				
MAC	65	55	45	35
RIC	60	36	29	24

Buckley, Wood, Othus, et al. Haematologica 2017. Vol. 102(5):865-873

MRD in adult ALL

The majority of adults with ALL will have MRD detectable after induction therapy

- **Associated with higher risk of relapse**

MRD in adult ALL: Philadelphia-positive ALL

Use of RT-PCR for BCR-ABL

MRD (0.1%) at time of first CR was not prognostic

However, MRD-negativity at 3, 6, 9, and 12 months was associated with better survival

At 3 and 12 months, MRD-negativity by MFC was associated with improved survival

Blood. 2013 Aug;122(7):1214-21

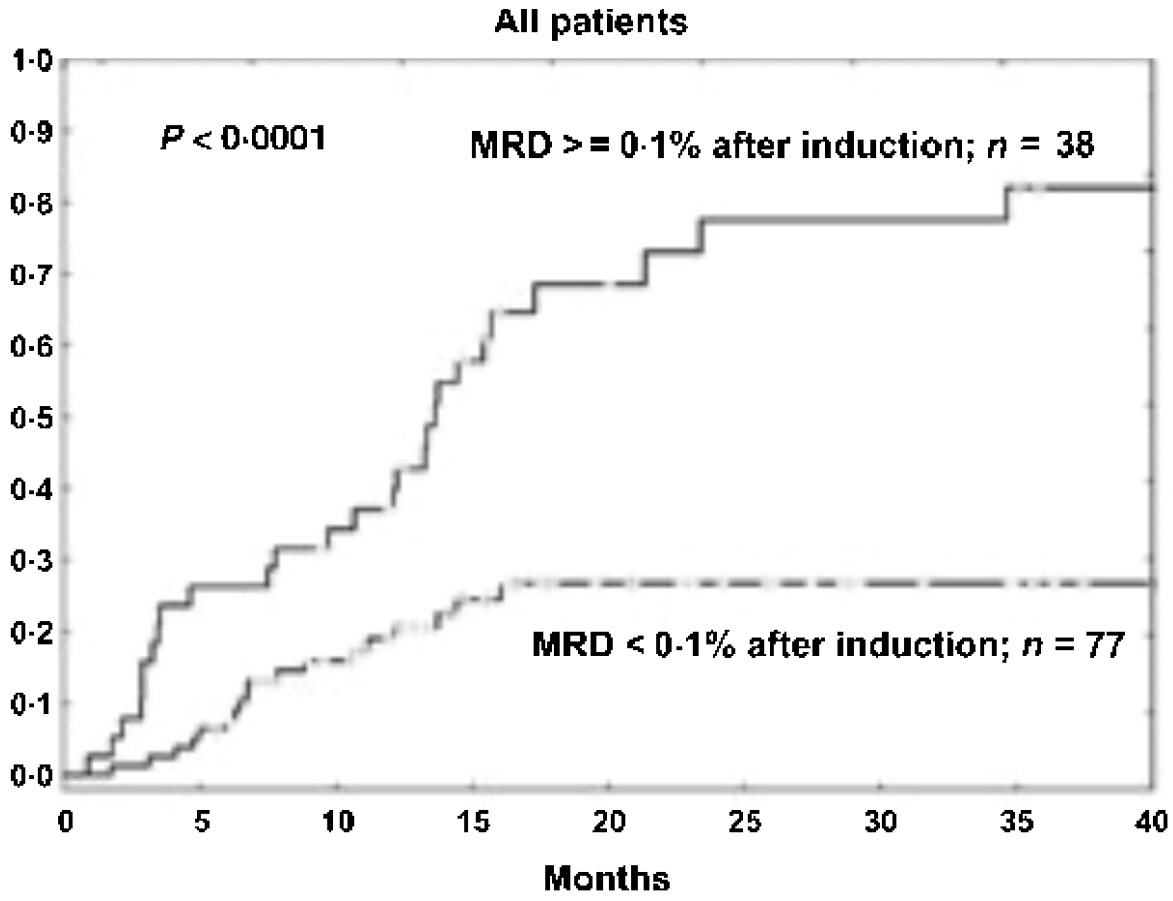
MRD in adult ALL: Philadelphia-positive ALL

MDR-positivity post transplant is associated with increased risk of relapse (Relative risk=5.7)

- **Risk higher for patients with p190 from of BCR-ABL versus p210 form**

Blood. 2013 Aug;122(7):1214-21

MRD in adult ALL: Philadelphia-negative ALL



MRD after induction by multi-parameter flow cytometry predicts relapse in all subtypes of ALL

British Journal of Haematology, 142, 227–237, 2008

MRD in adult ALL: Salvage

Novel approaches have the ability to achieve MRD negativity in patients with disease refractory to conventional therapy

- Blinatumomab
- Inotuzumab ozogamicin
- CD19-directed chimeric antigen receptor T (CAR-T) cells

Conclusions

MRD analysis is a powerful way to quantitate remaining leukemia after therapy

MRD provides prognostic information that can inform therapeutic decisions and allow for early intervention with salvage therapies

- However, it is not always deterministic of outcome

MRD may provide a valuable surrogate marker to accelerate the analysis of therapeutic clinical trials

Current Challenges

To harmonize the various methods to measure MRD to maximize both sensitivity and predictive power

To convert MRD data into quantitation of residual leukemia

To determine the threshold below which “cure” can be achieved