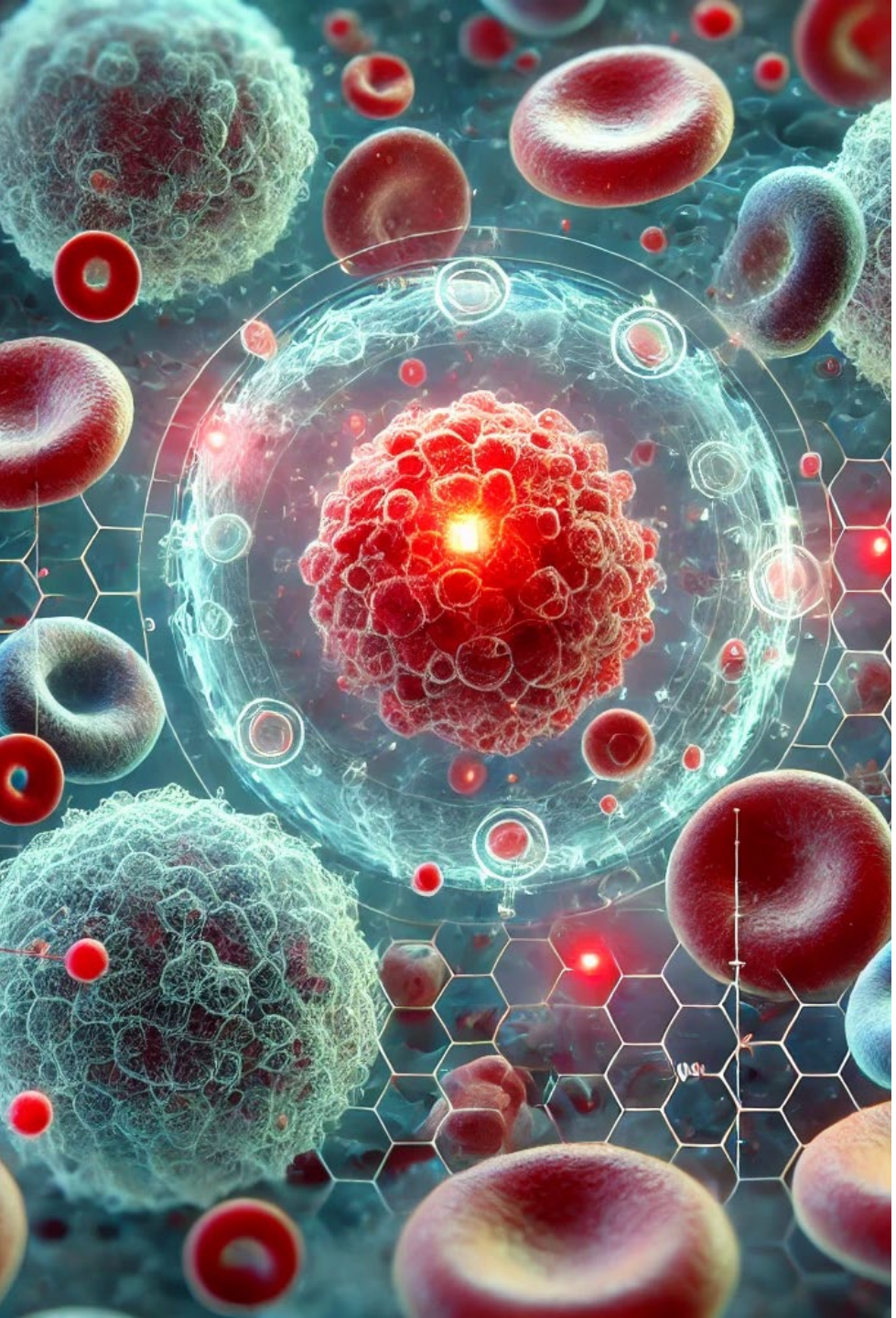

Unveiling the Hidden Enemy: The Laboratory's Role in Minimal Residual Disease (MRD) Detection

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Objectives

1

Trace the evolution of Minimal Residual Disease (MRD) testing from its early concepts to current methodologies.

2

Explain the latest diagnostic techniques for MRD detection including flow cytometry, PCR, and NGS.

3

Assess the impact of advancements in MRD detection technologies on treatment decisions and patient outcomes.

What is Minimal Residual Disease (MRD)?

Small amount of cancer cells that remain after treatment

Some cells are not responsive to the drug used or develop resistance to the drug therapy used

Most patients do not have any signs/ symptoms of malignancy

Traditional methods of detection remission may be negative (peripheral blood smears or serum protein analysis)

New term

Measurable Residual Disease

MRD Testing Interpretation

Positive MRD Test

- Residual cancer cells present
- Patient has high risk of relapse

Negative MRD Test

- No residual cancer cells found
- Below detectable limits of extremely sensitive tests
- Correlates with longer remissions and potentially longer survival rates for many hematological malignancies

Remission and Relapse

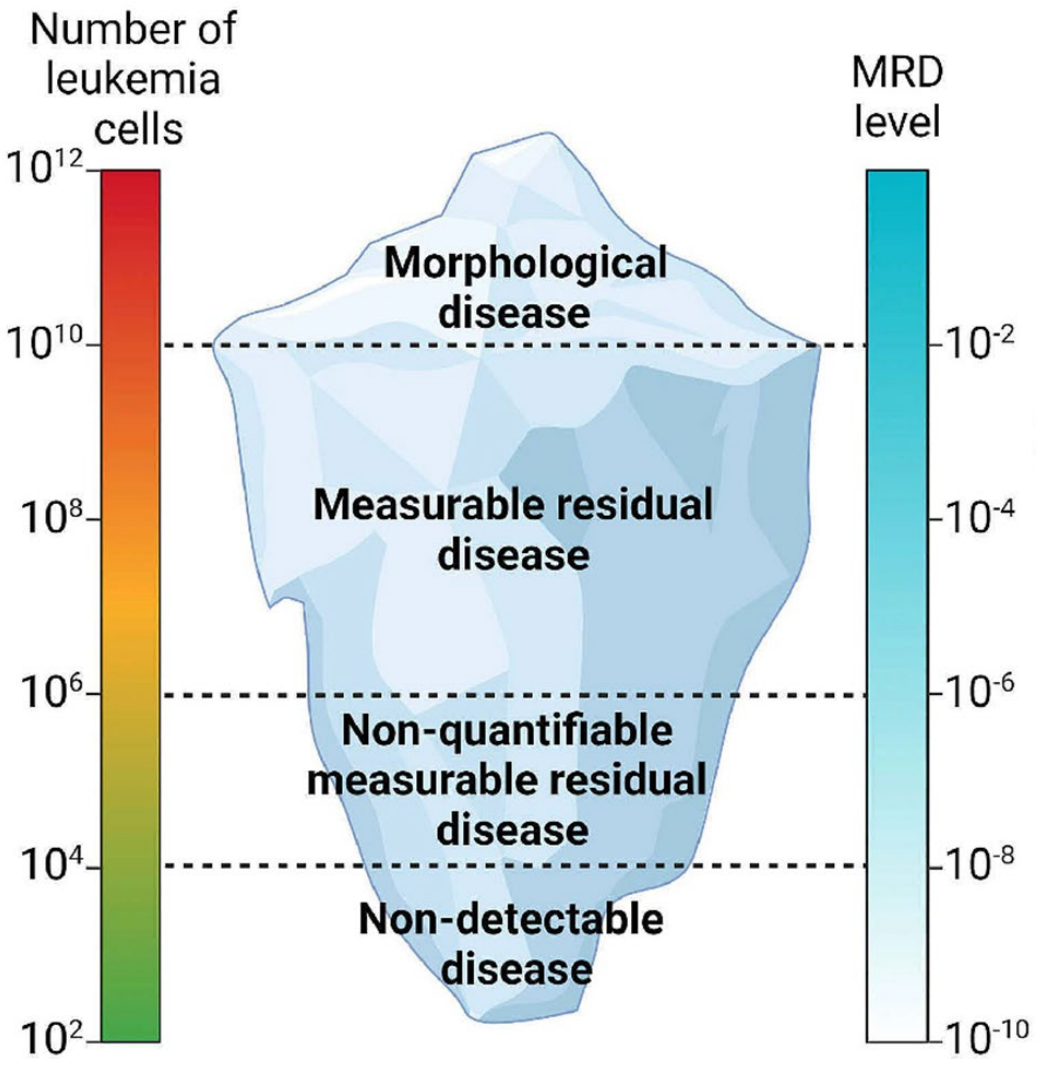
Complete Remission (CR) – absence of detectable disease following treatment

In the context of hematologic malignancy:

- No evidence of cancerous cells in the BM, blood, or other affected tissues based on standard clinical, radiological, and laboratory tests
- Patient's is free of signs/symptoms

Key milestone in cancer treatment

MRD may still be present



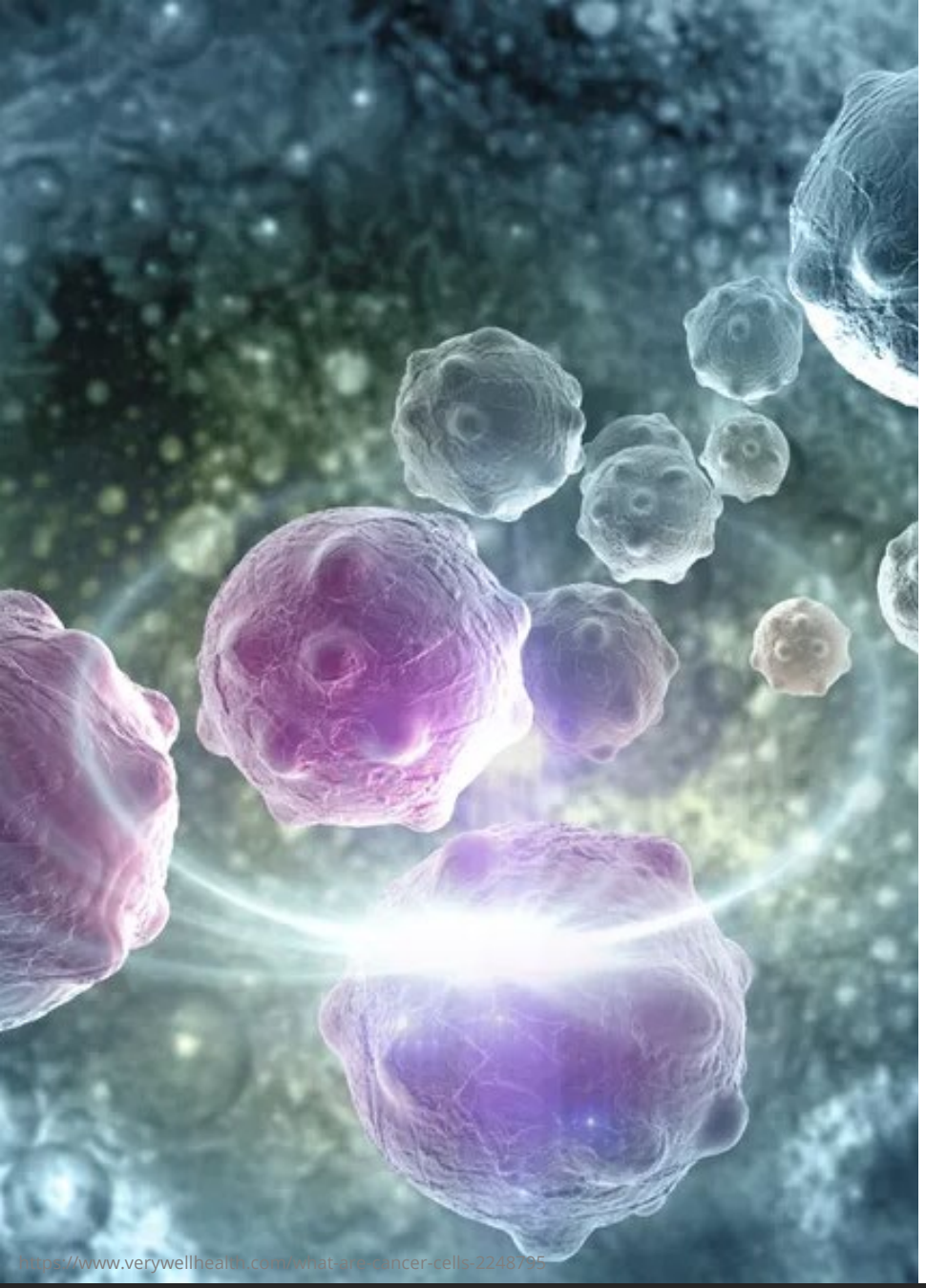
Remission and Relapse

Molecular Relapse – residual cancer cells are detected through molecular testing but cannot be detected through routine tests

Methods employed
- Multiparameter flow cytometry (MFC)
- Polymerase chain reaction (PCR)
- Next-generation sequencing (NGS)

Usually occurs before clinical or radiologic evidence of relapse

Predicts higher risk of future relapse and allows for timely intervention



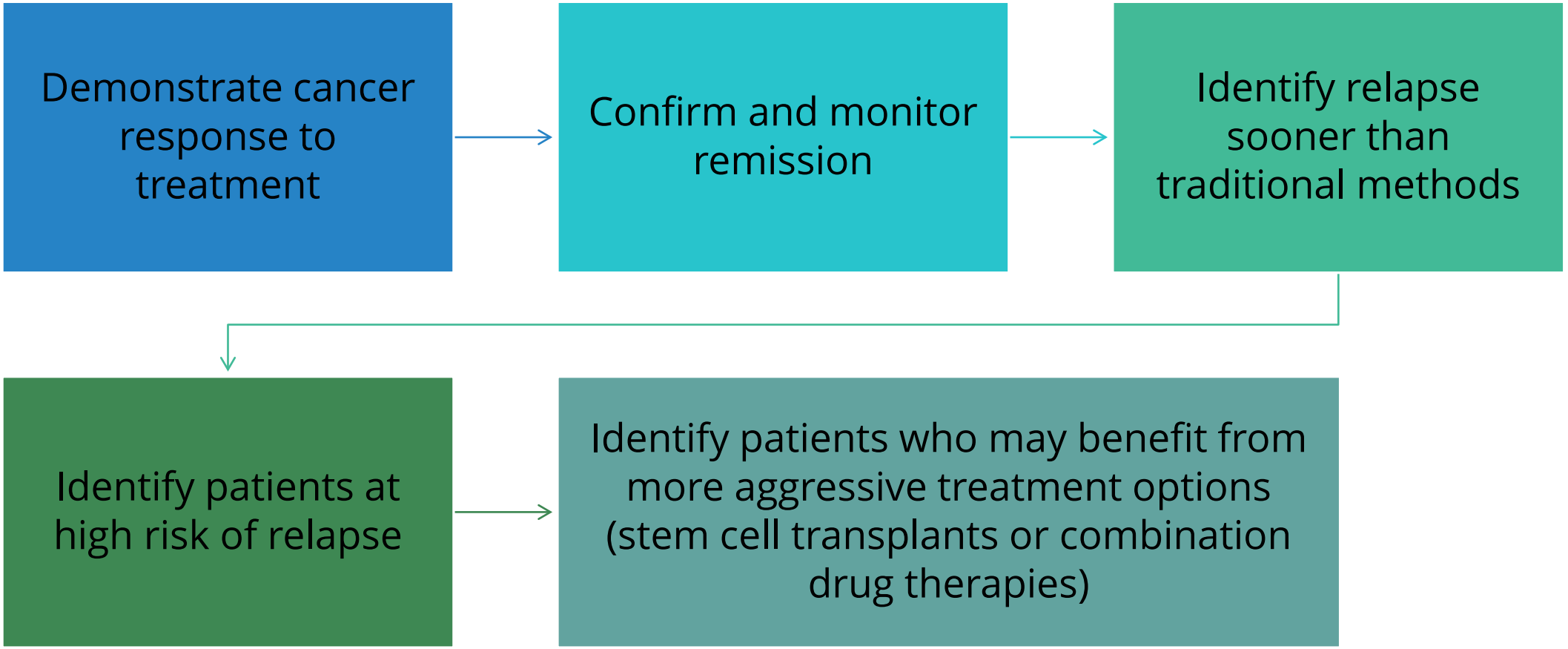
Remission and Relapse

Clinical Relapse – re-emergence of disease detected by clinical signs and symptoms

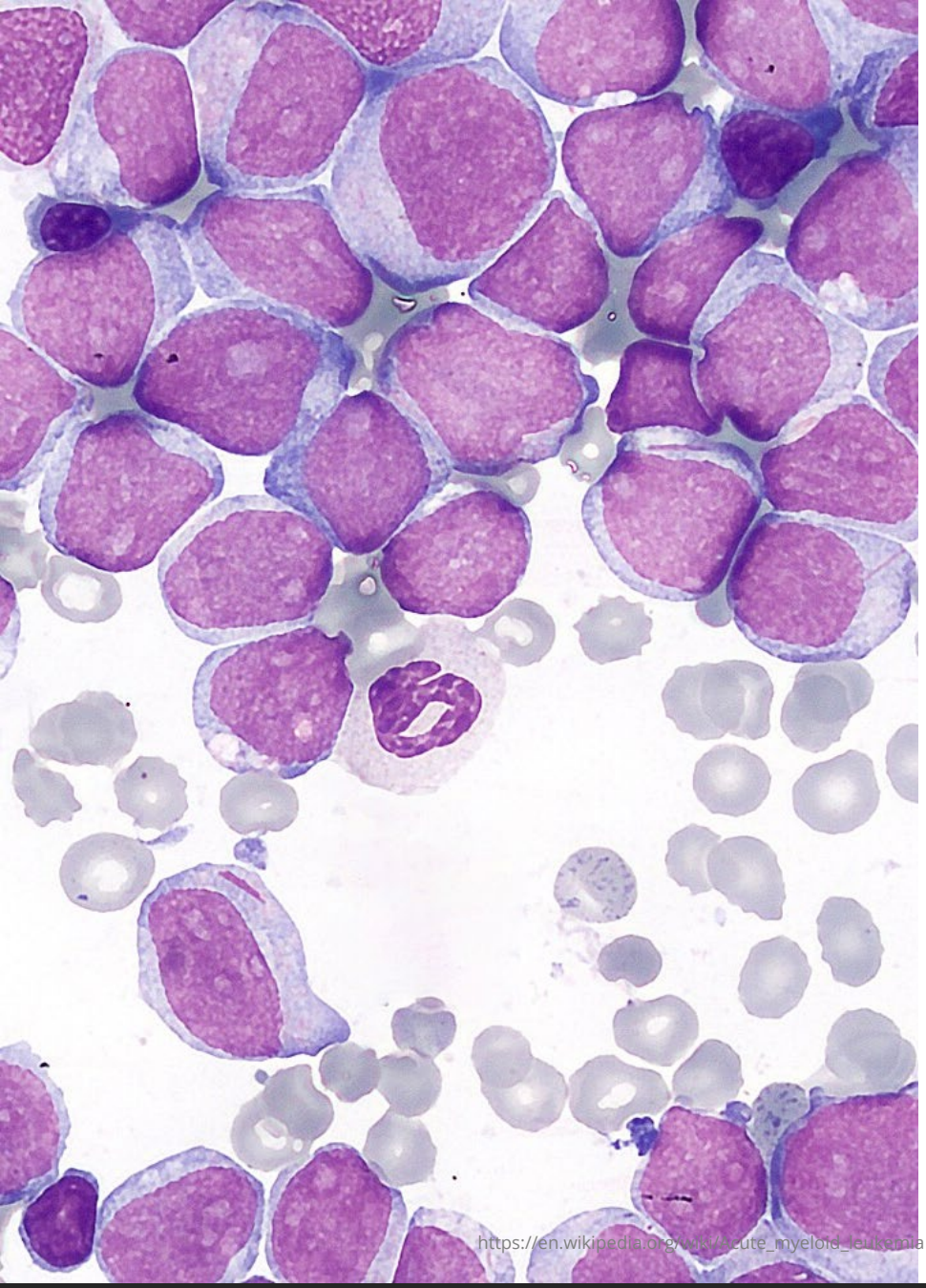
- Abnormal blood counts
- Organ enlargement (liver and spleen)
- Imaging findings
- Symptoms: fever, fatigue, pain

The goal of MRD testing is to identify and treat MRD before it becomes clinically apparent

Purpose of MRD Testing



Historical Context of MRD Testing



MRD Detection Before 1970

Relapse detection occurred through clinical observation of patient symptoms

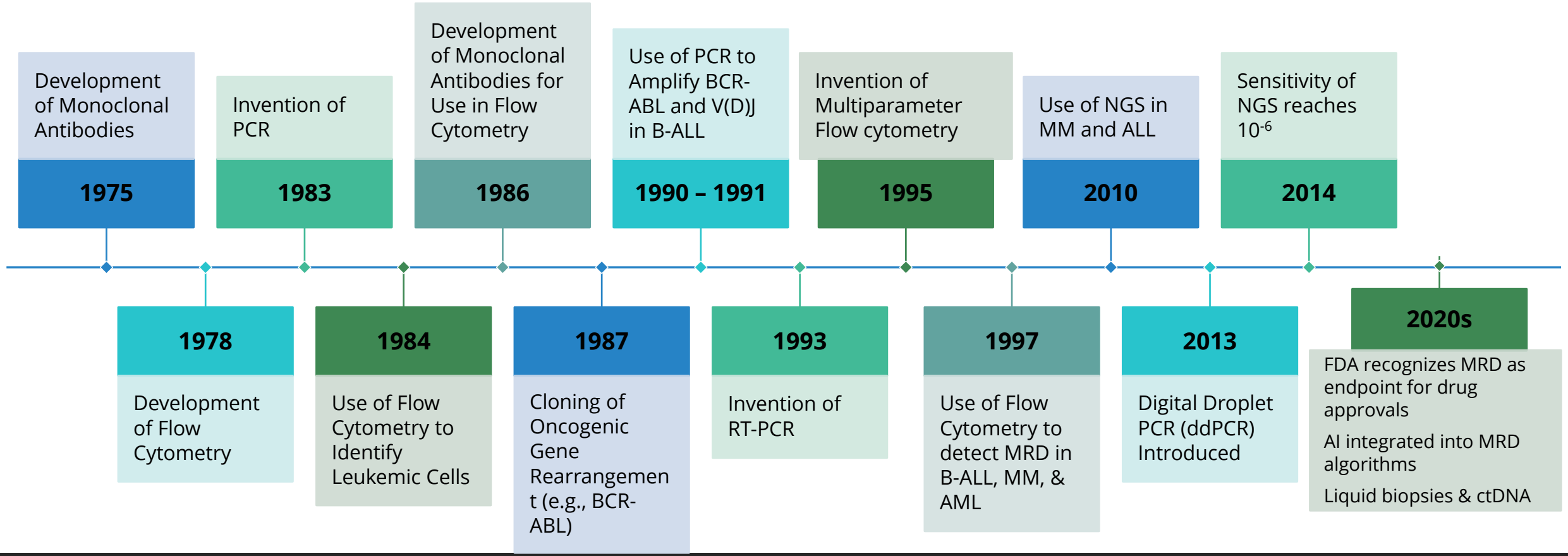
Peripheral Blood Smear

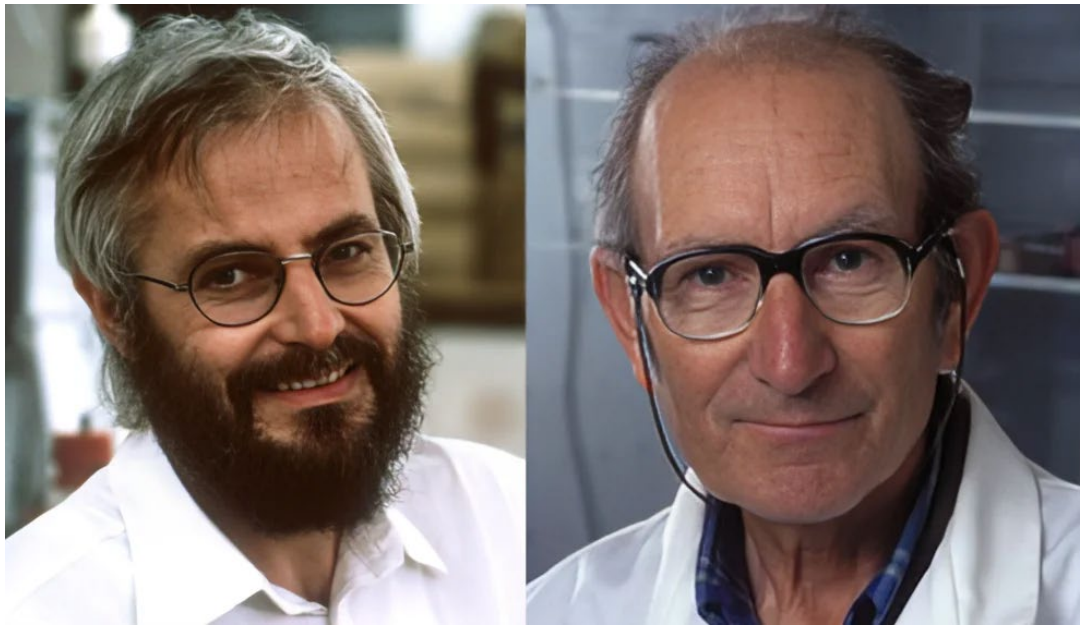
Bone Marrow Biopsy

Radiologic Imaging

Cytogenetics for specific cancers such as Philadelphia chromosome in CML

Timeline of MRD Detection





Georges Köhler and César Milstein won Nobel prize in physiology in 1984

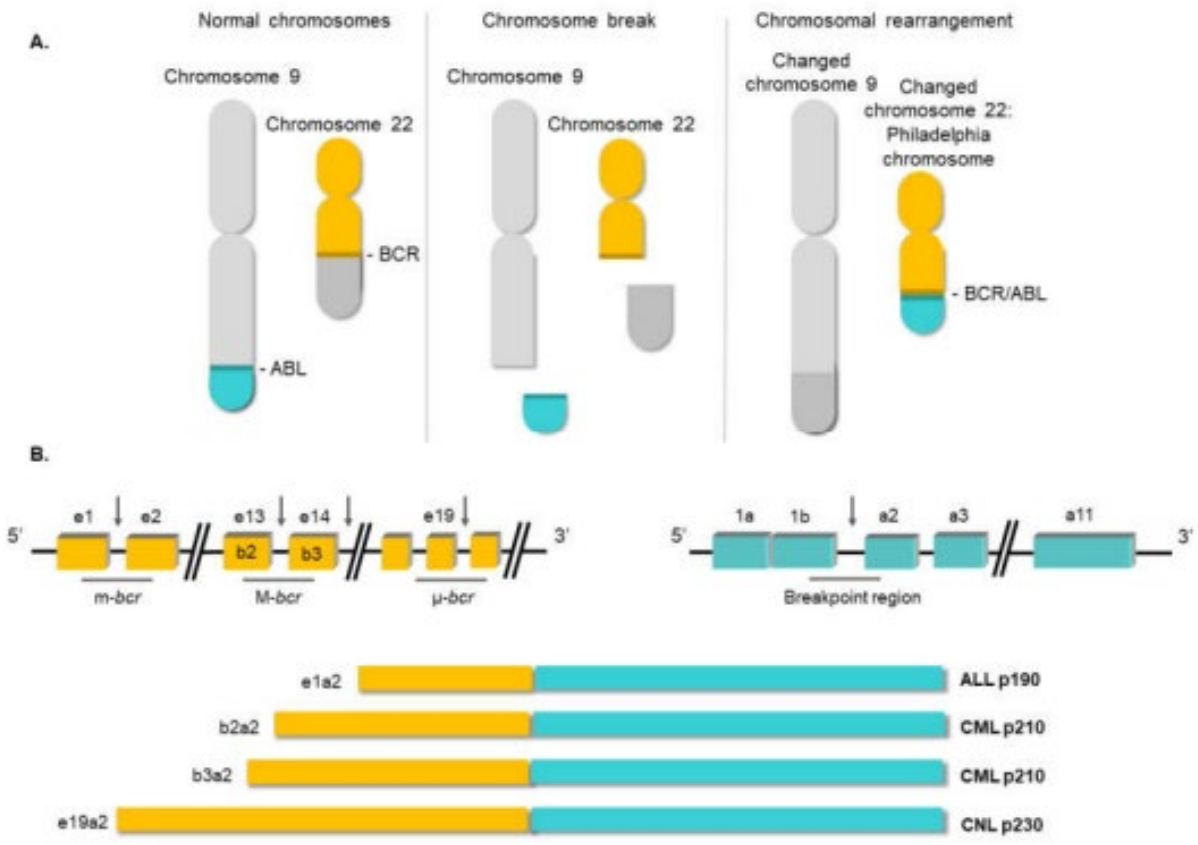
1970s – 1980s

1975: Development of Monoclonal Antibodies

- César Milstein and Georges Köhler developed monoclonal antibodies through hybridoma method
- Bind to specific antigens on leukemic cells
- Used in several laboratory methods
- Often visualized through fluorescence

1978: Development of Flow Cytometry

- Identifies individual cells in a suspension using cell markers



1980s

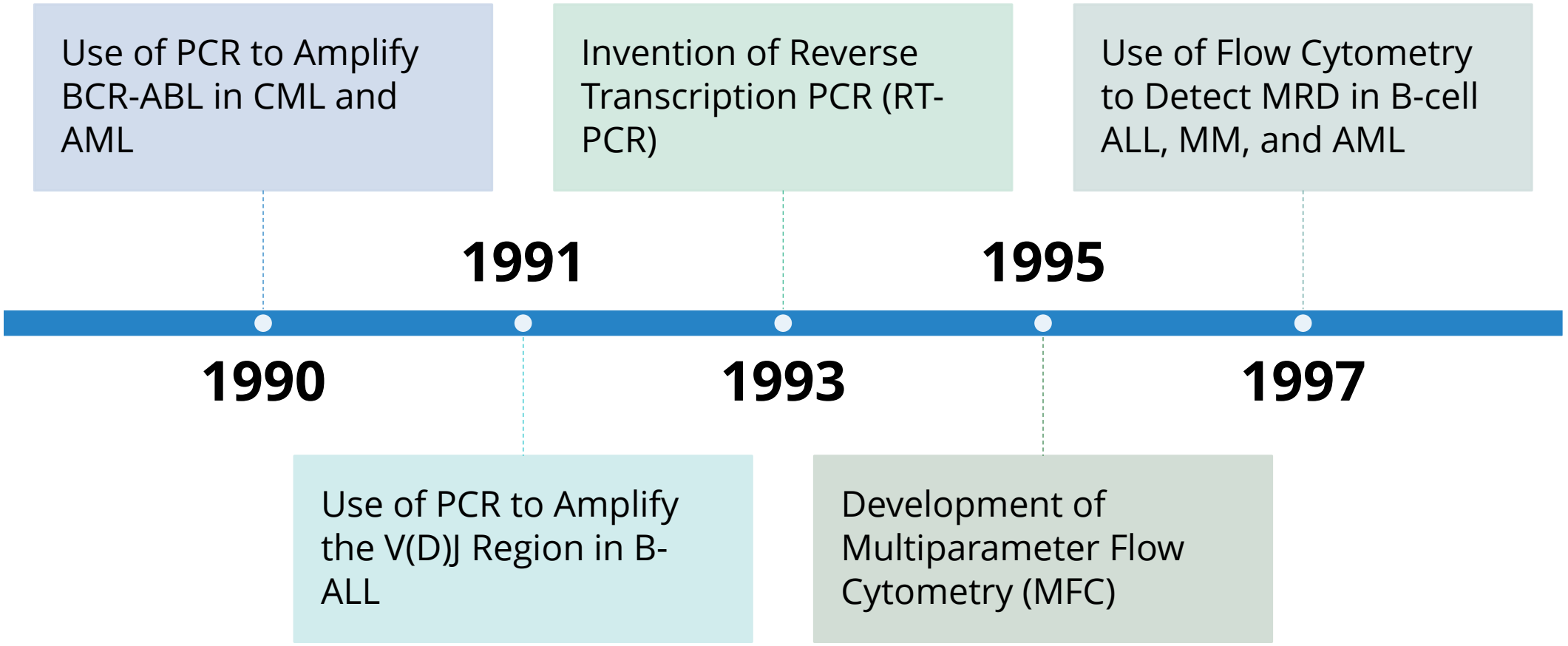
1983: Invention of PCR

1984: Use of Fluorescent Microscopy to Identify Leukemic Cells

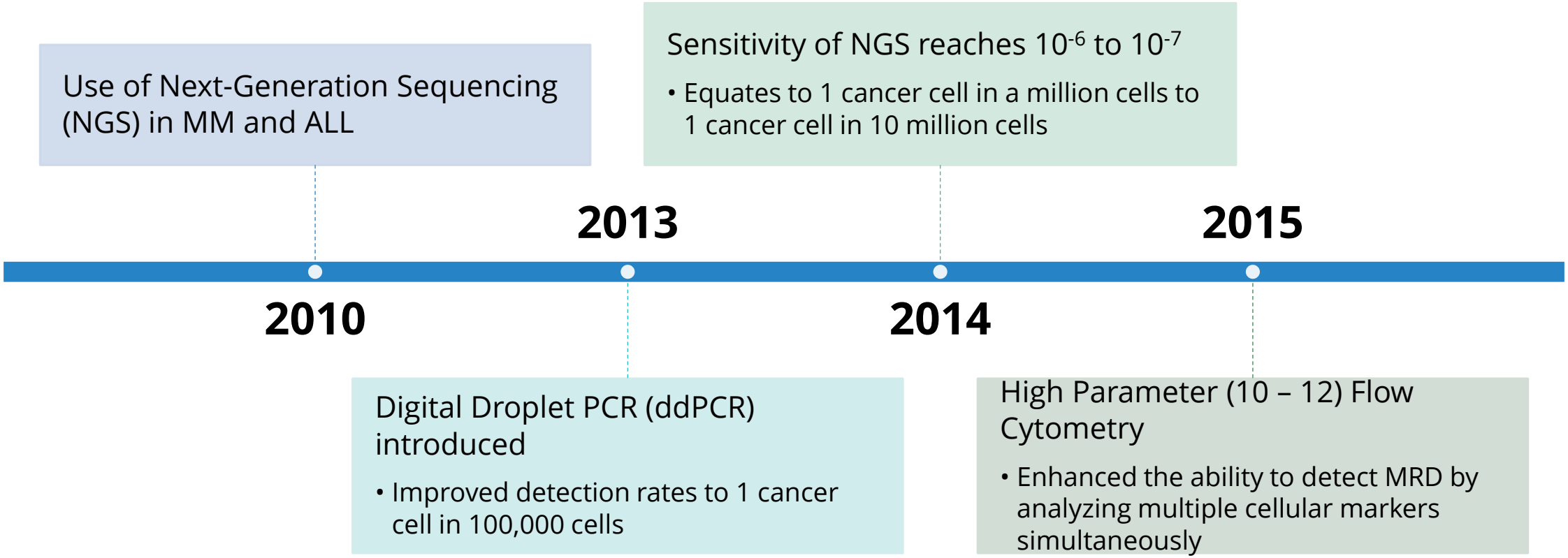
1986: Development of Monoclonal Antibodies for Use in Flow Cytometry

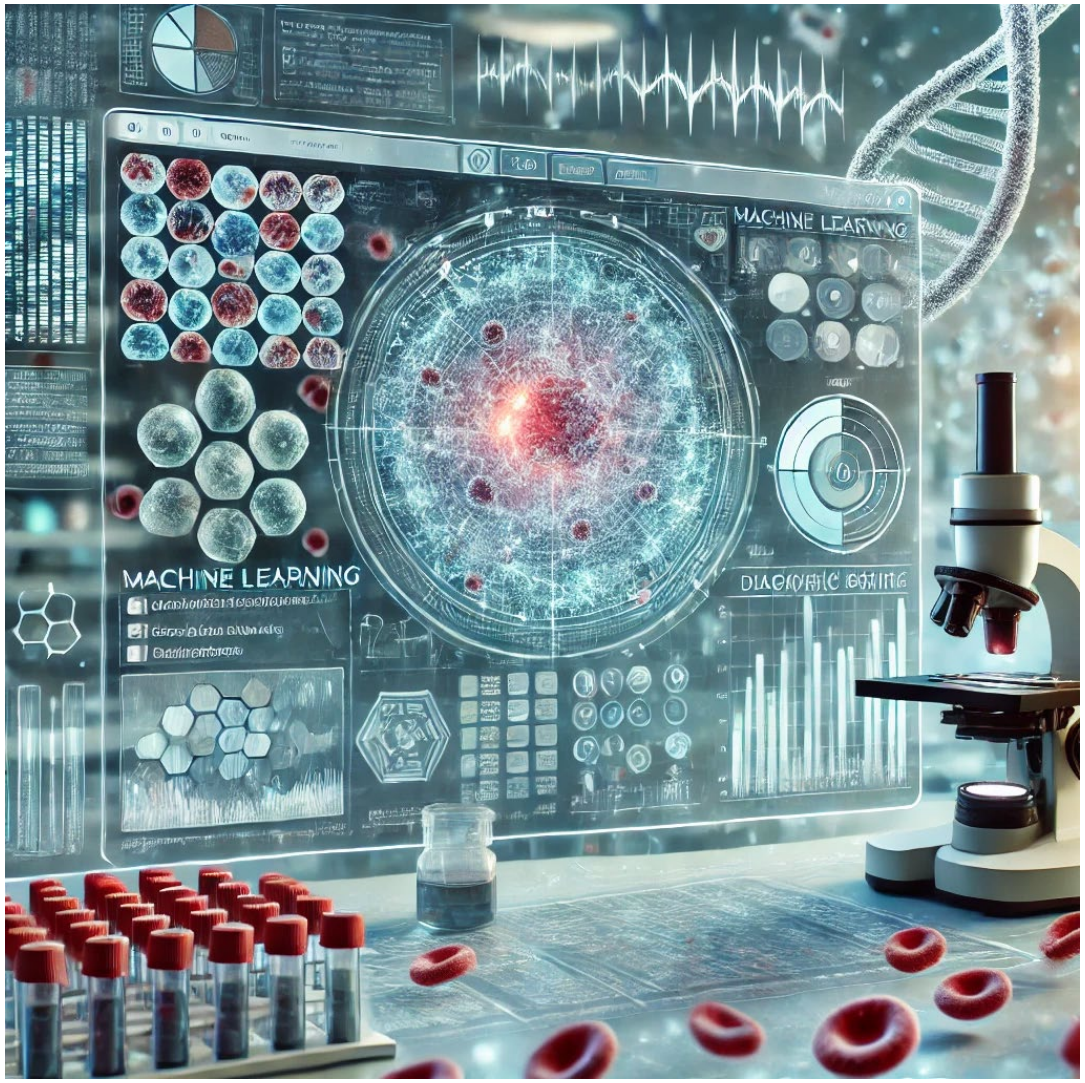
1987: Cloning of Oncogenic Gene Rearrangements (e.g., BCR-ABL)

1990s


Use of PCR to Amplify BCR-ABL in CML and AML
Invention of Reverse Transcription PCR (RT-PCR)
Use of Flow Cytometry to Detect MRD in B-cell ALL, MM, and AML
1990
1991
1993
1995
1997
Use of PCR to Amplify the V(D)J Region in B-ALL
Development of Multiparameter Flow Cytometry (MFC)

2000s – 2010s


Use of Next-Generation Sequencing (NGS) in MM and ALL
Sensitivity of NGS reaches 10^{-6} to 10^{-7}
• Equates to 1 cancer cell in a million cells to 1 cancer cell in 10 million cells
2010
2013
2014
2015
Digital Droplet PCR (ddPCR) introduced
• Improved detection rates to 1 cancer cell in 100,000 cells
High Parameter (10 – 12) Flow Cytometry
• Enhanced the ability to detect MRD by analyzing multiple cellular markers simultaneously



2020s

2020: FDA officially recognized MRD negativity as a surrogate endpoint

- Especially for drug approvals in MM

AI Integration

- Integrated into flow cytometry and NGS analysis
- Algorithms improve consistency and accuracy of MRD identification

Liquid Biopsies

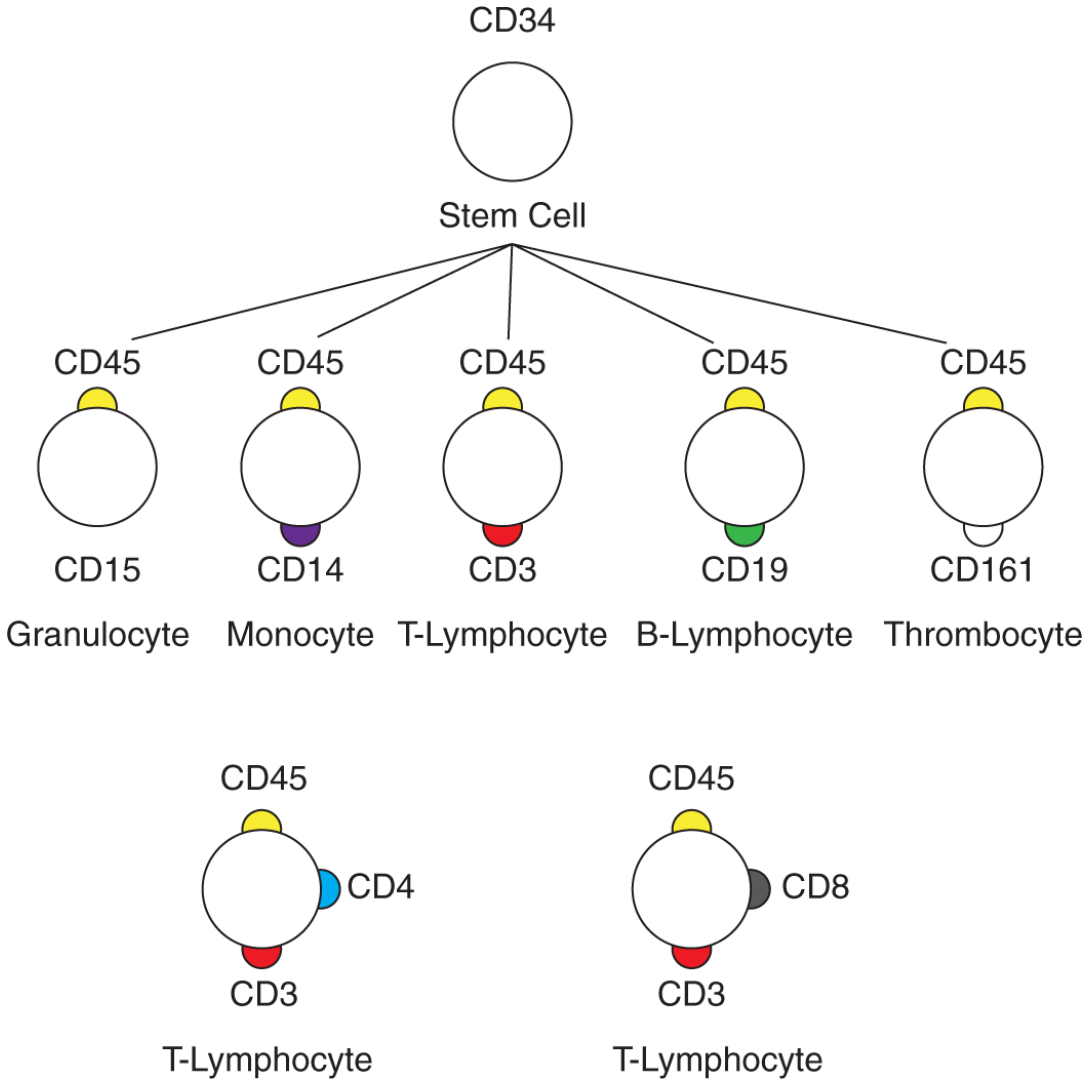
- Analyze circulating tumor DNA (ctDNA)
- Allows for real-time monitoring of disease without need for invasive procedures (BM biopsy)

Understanding MRD Testing Technologies

FLOW CYTOMETRY

POLYMERASE CHAIN REACTION (PCR)

NEXT-GENERATION SEQUENCING (NGS)



Flow Cytometry Overview

Technique that detects individual cells in a heterogenous sample by identifying the presence or absence of protein markers on the cell's surface, in the cytoplasm, or on the cell's nucleus

Applications in Clinical Hematology

- Automated leukocyte differentials
- Counting reticulocytes and platelets
- Immunophenotyping

Multiparameter Flow Cytometry (MFC) for MRD

Flow cytometry that can simultaneously recognize several different phenotypic markers

Advantages

- High Sensitivity: Detects MRD down to 0.01% (1 in 10,000 cells)
- Efficient: Results in hours
- Detailed phenotyping available for a large group of malignancies

Disadvantages

- Requires high level of technical expertise in MRD markers and result interpretation
- Lower sensitivity than NGS
- Limited by abnormal markers on malignant cells

Approaches to Using FC for MRD Detection

Antigens are expressed differently in cancer cells compared to normal cells

Leukemia-associated immunophenotype (LAIP) approach

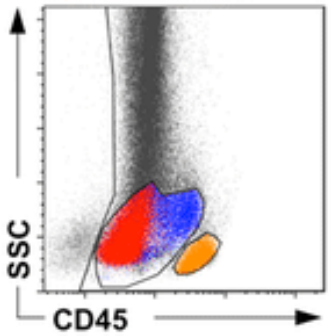
- The unique immunophenotype expressed by a patient's cancer cells is identified to create the leukemia's "fingerprint"
- After the patient undergoes treatment, MRD testing will look for cells with that specific immunophenotype

Different-from-Normal (DfN) approach

- A patient's post-treatment cells are compared to a library of normal cells
- Allows detection of residual malignant cells that do not match the initial LAIP due to antigen shifts or clonal evolution
- Interpretation required expertise and well-established normal cell profiles

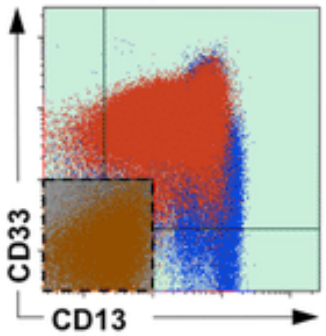
1 **CD45 / SSC**

individual gates: **blasts/monocytes, lymphocytes**



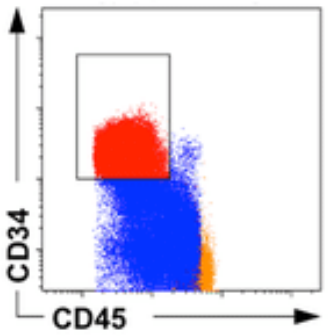
2 **CD33 / CD13**

fixed gates: **CD13⁺ and/or CD33⁺ blasts/ monocytes**



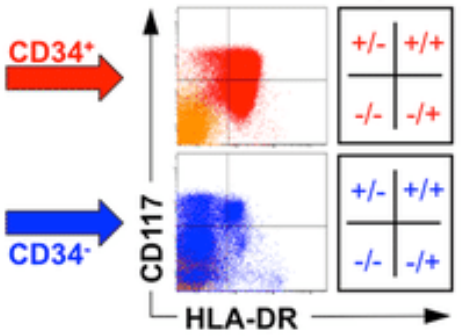
3 **CD45 / CD34**

fixed gates: **CD34⁺** or **CD34⁻ myeloid blasts/ monocytes**



4 **HLA-DR / CD117**

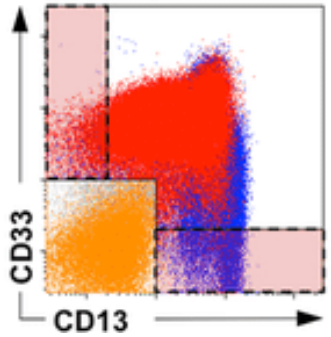
fixed gates: **HLA-DR$^{+/-}$** and **CD117$^{+/-}$ myeloid blasts/monocytes**



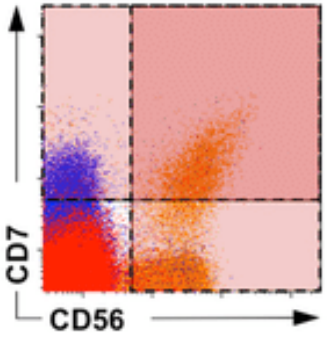
8 different myeloid blast populations by CD34, CD117 and HLA-DR

5 **CD33 / CD13** and **CD7 / CD56**

fixed gates: **CD33⁻** or **CD13⁻ myeloid blasts/ monocytes**



fixed gates: **CD7⁺** or **CD56⁺ myeloid blasts/monocytes**



32 different subpopulations by CD13, CD33, CD7 and CD56

6 **Applying reference values**

upper limit of the one-sided 97.5% reference range

Bone marrow donor	30
ALL in molecular CR	19
PCNSL	9
Hip surgery	32

7 **Results**

4 categories of MRD
- CD13 deficiency
- CD33 deficiency
- cross-lineage CD7
- cross-lineage CD56

Clinical Relevance of LAIP-DfN in MRD Detection

Sensitivity and Specificity

Personalized Medicine

Broad Applications

Flow Cytometry Process

1. **Sample Preparation**
   - Acceptable specimens: Whole blood, bone marrow, CSF, and lymph node and tissue biopsies
   - Cell count performed to optimize cellular ratio for analysis
   - Varies by type of specimen
     - BM aspirates passed through cell strainer to remove clumps and debris
     - CSF may have to be centrifuged more than once to concentrate cells
     - RBC lysing agents may be added to reduce interference from non-leukocyte cells

Flow Cytometry Process

2. Staining with Fluorescent Antibodies

- Cells are incubated with a panel of fluorescently labeled antibodies
- Antibodies can target antigens on the cell's surface, cytoplasm, or nucleus
- The sample is incubated for approximately 20 to 30 minutes in the dark at 4°C to avoid photobleaching
- After staining, cells are washed to remove unbound antibody and resuspended in buffer for analysis

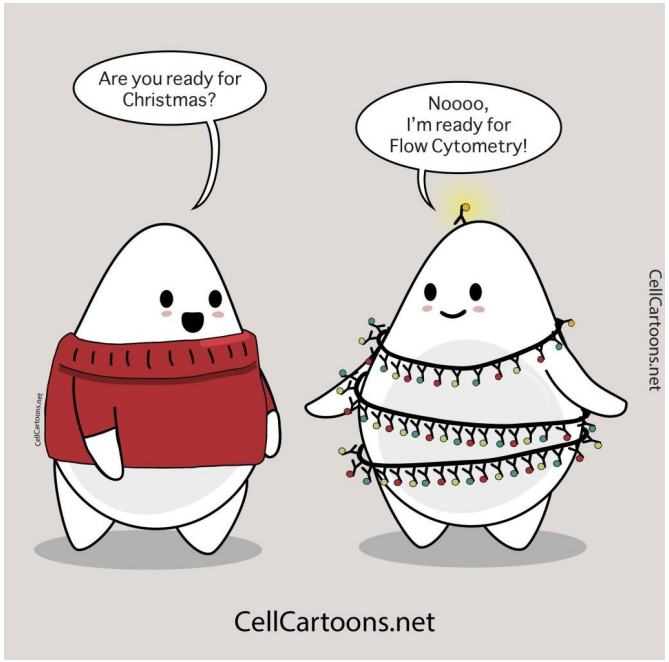


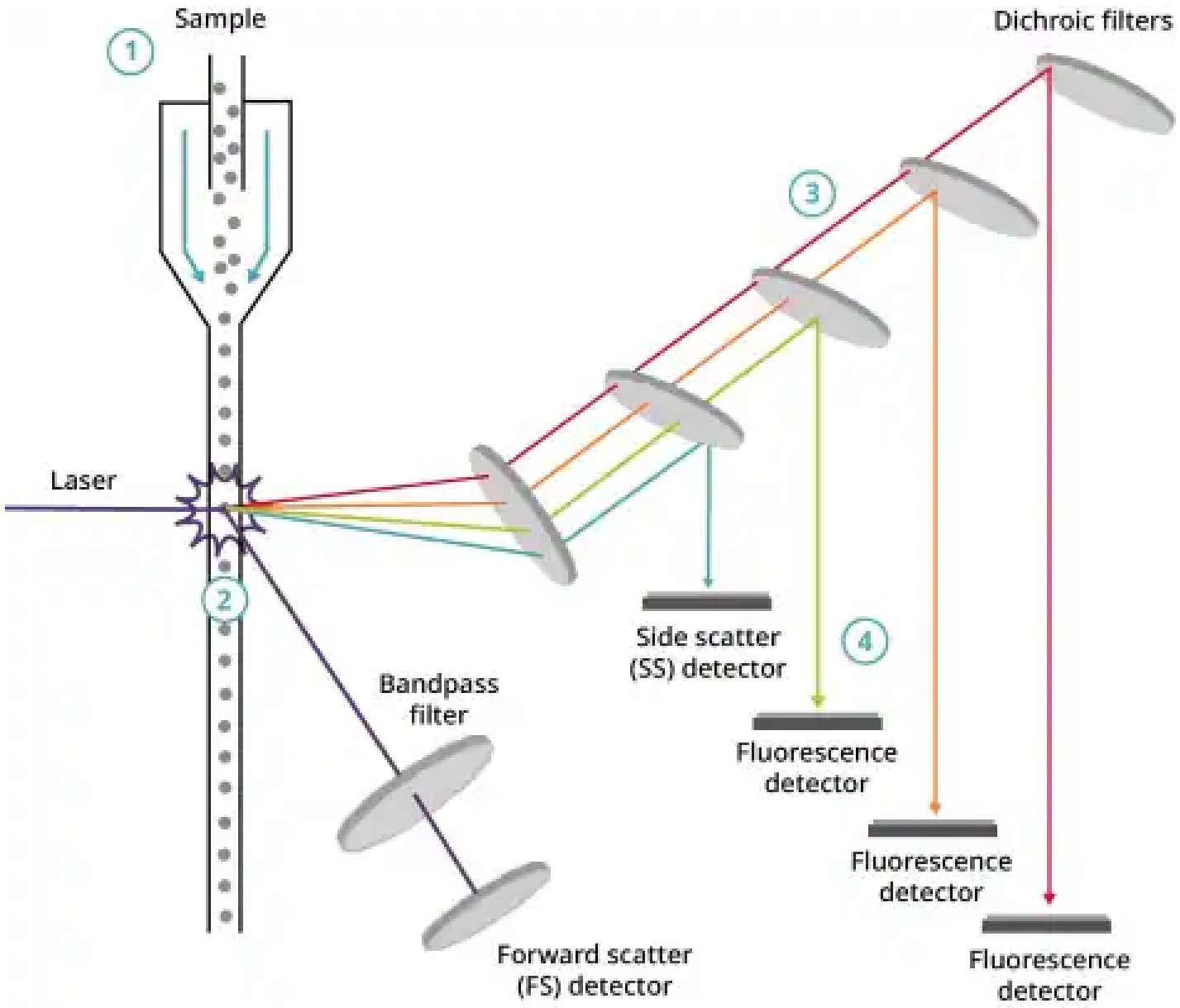
Table 1 Surface or intracellular antigens commonly assessed by flow cytometry for lineage classification and immunophenotyping of hematolymphoid malignant neoplasms

Lineage	Antigens
Stem cells	CD34, CD38, CD45
B cells	CD5, CD10, **CD19, CD20, CD22**, CD23, CD25, CD34, CD38, CD43, CD45, **CD79a**, CD103, CD200, FMC2, **cIgM, Kappa, Lambda**, LEF1, TdT
Plasma cells	CD19, CD20, CD38, CD45, CD56, CD117, CD138, **cKappa, cLambda**
T cells/NK cells	CD1a, **CD2, CD3**, CD4, **CD5**, CD7, **CD8**, CD10, CD16, CD25, CD26, CD30, CD34, CD45, CD56, **αβ-TCR, γδ-TCR**, TdT, **TRBC1**
Myelomonocytic cells	CD4, CD7, CD10, CD11b, CD11c, **CD13, CD14**, CD15, CD16, **CD33**, CD34, CD36, CD38, CD45, CD56, **CD64, CD65**, CD71, CD117, CD123, **cMPO, cLyso**, HLA-DR
Erythroblasts	CD34, CD36, CD38, CD45, CD71, CD117, **CD235a**
Megakaryoblasts	CD33, CD34, CD38, **CD41, CD42**, CD45, **CD61**, CD117, HLA-DR

The antigens in bold are lineage-specific markers. cIgM, cytoplasmic IgM; cKappa, cytoplasmic kappa; cLambda, cytoplasmic lambda; cLyso, cytoplasmic lysozyme; cMPO, cytoplasmic peroxidase; TCR, T-cell receptor; TdT, terminal deoxynucleotidyl transferase; TRBC1, TCR β chain constant 1.

Flow Cytometry Process

4. RUNNING THE FLOW CYTOMETER

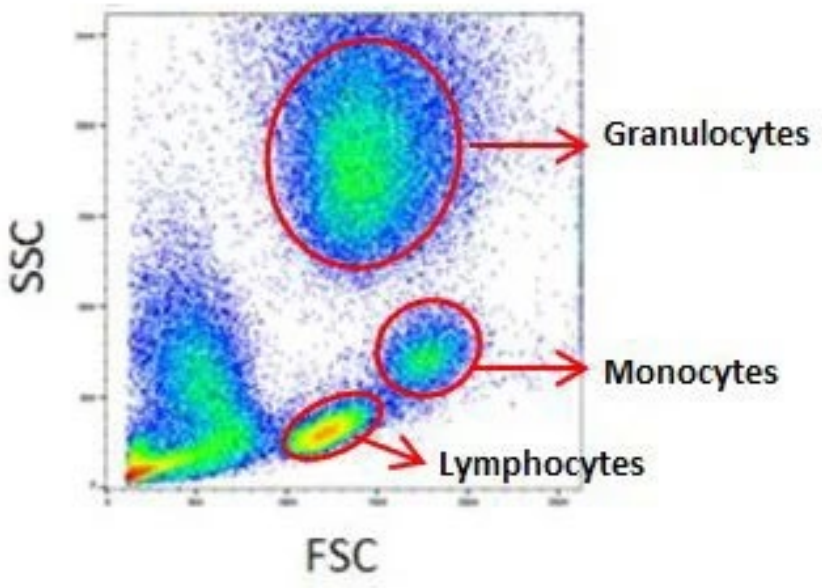


Flow Cytometry Process

5. **Data Analysis**

Cell Gating

- Sequential Gating
  - Unwanted cells are eliminated based on scatter properties to isolate the cell population of interest
  - This is adjusted to exclude dead cells, debris, and doublets
- Population-Specific Gating
  - Based on antigen expression patterns (LAIP and DfN approaches)
- Boolean Gating
  - AND, OR, NOT logic



Flow Cytometry Process

5. **Data Analysis**

   Techniques

   - Algorithms are used to cluster cells based on their marker expression profiles to help find small clusters of abnormal cells that may not be evident through manual gating alone
   - Histograms and dot plots are used to graphically visualize normal from abnormal cell populations
   - Specialized software and machine learning applications are emerging to assist with complex or rare hematological malignancies

Score	B-Lymphoid	T-Lymphoid	Myeloid
2	CD79a	CD3	MPO
	cCD22	TC Ralpha/beta	
	cIgM		
1	CD19	CD2	CD117
	CD20	CD5	CD13
	CD10	CD8	CD33
		CD10	CD65
0.5	TdT	TdT	CD14
	CD34	CD7	CD15

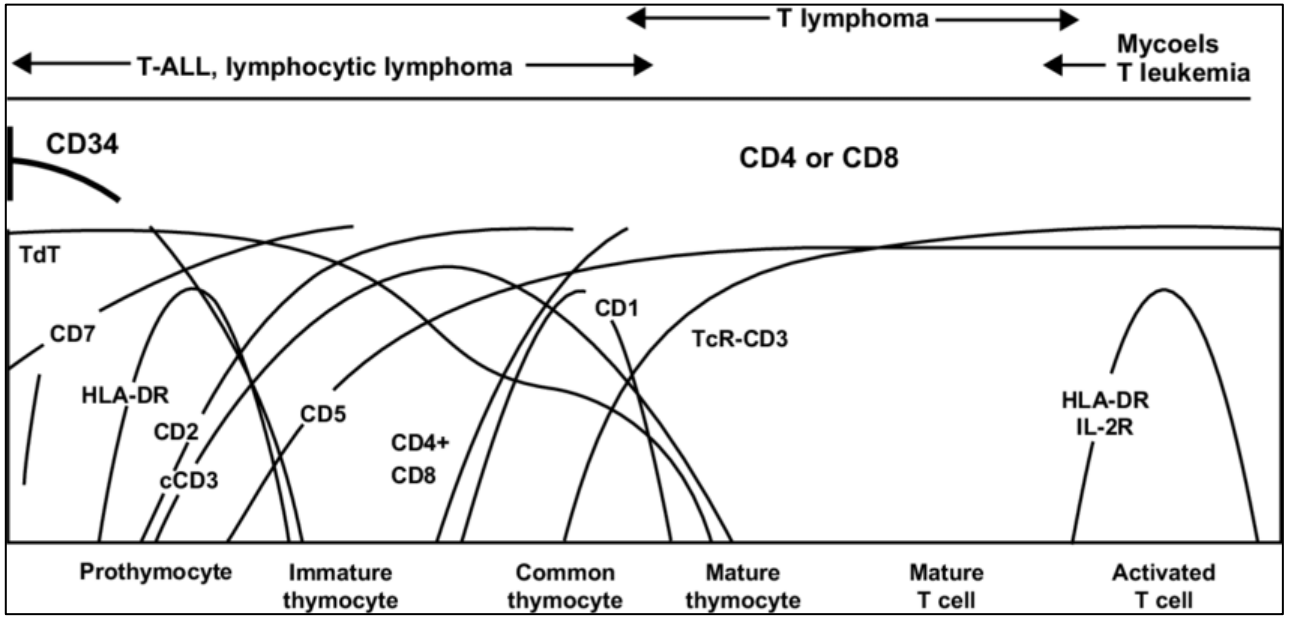
Abbreviation: TCR, T-cell receptor.

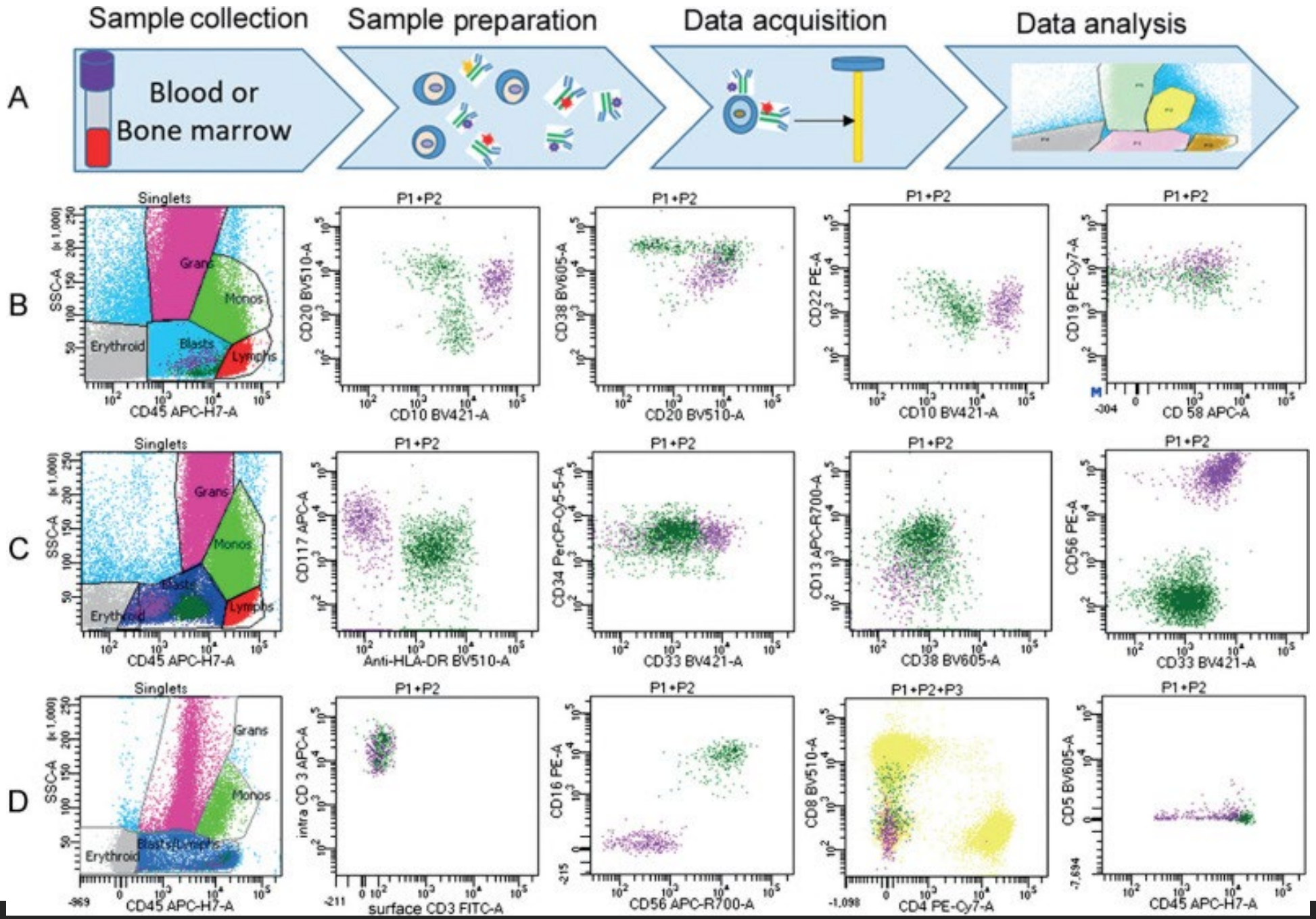
	Pro-T-ALL	Pre-T-ALL	Cortical-T-ALL	Mature-T-ALL
TdT	Positive			Negative
cCD3	Positive			
CD7	Positive			
CD2	Negative	Positive		
CD5	Negative	Positive		
CD4	Negative		Positive for CD4 and CD8	Positive for CD4 or CD8
CD8	Negative			
CD1a	Negative		Positive	Negative
sCD3	Negative			Positive

Note: Reproduced from NewBU.[65]
Abbreviation: T-ALL, T-acute lymphoblastic leukemia.

	Precursor B-ALL	Common ALL	Pre-B-ALL	Mature-B-ALL
HLA-DR cCD22 CD79a CD19	Positive			
TdT	Positive			Negative
CD10	Negative	Positive		Negative
cIgM	Negative		Positive	Negative
sIg	Negative			Positive

Note: Reproduced from NewBU.[65]
Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-acute lymphoblastic leukemia.




A
Sample collection
Sample preparation
Data acquisition
Data analysis
Blood or
Bone marrow
B
Singlets
Grans
Monos
Erythroid
Blasts
Lymphs
SSC-A
CD45 APC-H7-A
P1+P2
CD20 BV510-A
CD10 BV421-A
CD38 BV605-A
CD20 BV510-A
CD22 PE-A
CD10 BV421-A
CD19 PE-Cy7-A
CD 58 APC-A
C
CD117 APC-A
Anti-HLA-DR BV510-A
CD34 PerCP-Cy5-5-A
CD33 BV421-A
CD13 APC-R700-A
CD38 BV605-A
CD56 PE-A
CD33 BV421-A
D
Blasts/Lymphs
intra CD 3 APC-A
surface CD3 FITC-A
CD16 PE-A
CD56 APC-R700-A
P1+P2+P3
CD8 BV510-A
CD4 PE-Cy7-A
CD5 BV605-A

Pacific Blue™	OC515™	FITC	PE	PerCP-Cyanine5.5	PE-Cyanine7	APC	APC-C750
CD20+CD4	CD45	CD8 + SmIgLambda	CD56 + SmIgKappa	CD5	CD19 + TCRγδ	SmCD3	CD38

LST

Reagent composition:

Lyophilized tubes:

- 12 antibodies against **surface antigens** (5 vials, 5 tests per vial)

Compensation vials (4 tubes in lyophilized format):

- PerCP-Cyanine 5.5-CD5
- PE-Cyanine7-CD19+TCRγδ
- APC-C750-CD38
- OC515-CD45

"The LST kit is an 8-color antibody combination designed by the EuroFlow™ consortium aiming to detect populations of mature B-, T- and NK-cells lineage for research purposes."

Standardized Protocols

EuroFlow External Quality Assessment Program

- Developed by Children's Oncology Group (COG)
- Different protocols created for specific malignancies
  - EuroFlow Lymphoid Screening Tube
  - Multiple Myeloma MRD tube
  - B Cell Precursor-ALL MRD tube
  - Primary Immunodeficiency Orientation tube

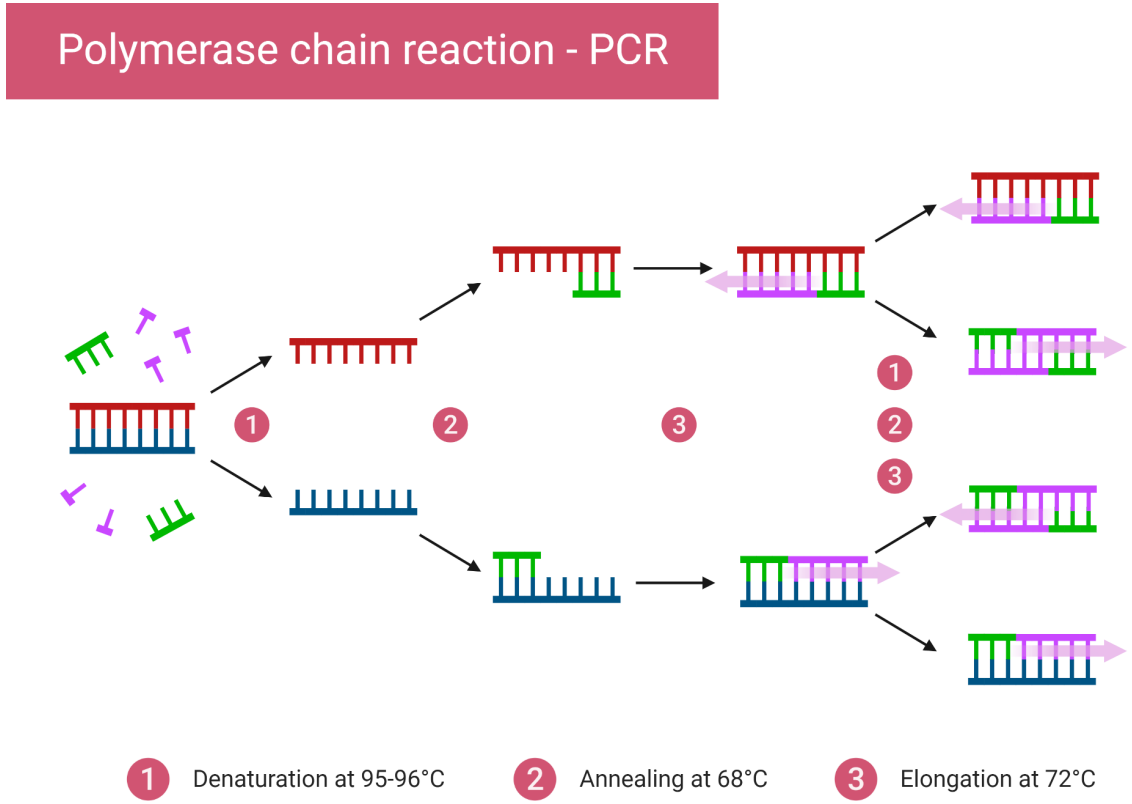
PCR Overview

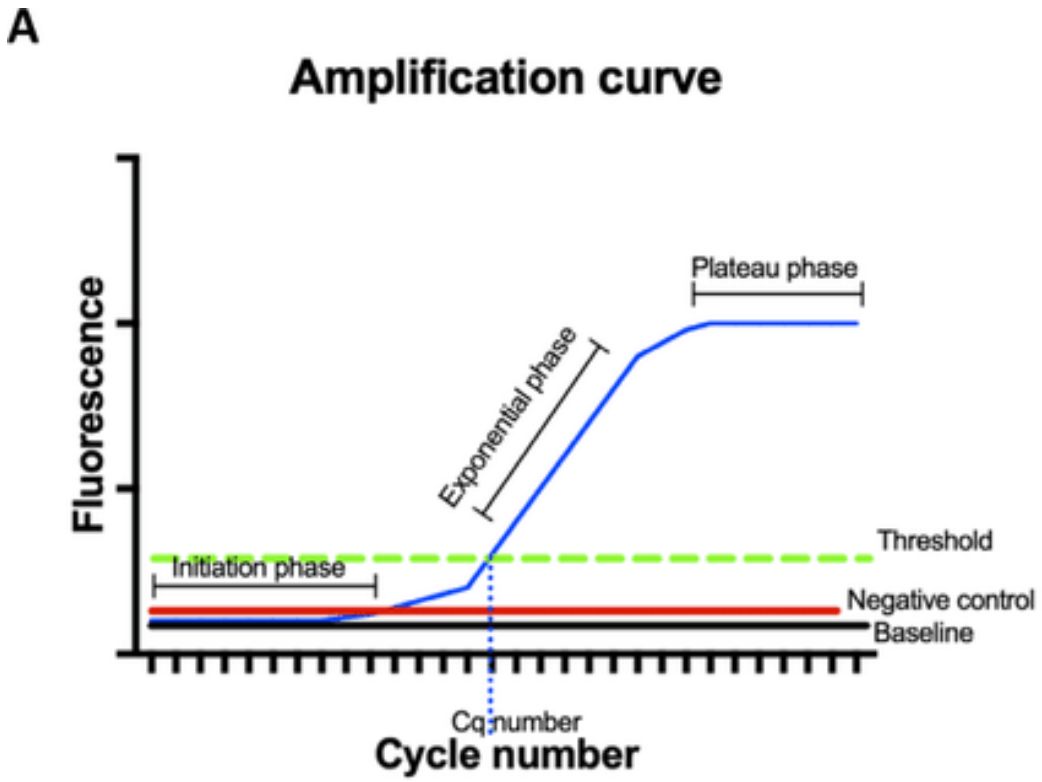
Technique used to make copies of a piece of DNA

Able to target gene rearrangements, fusion genes, and mutated genes

Two PCR Techniques Used in MRD Testing

- Real-time quantitative PCR (RT-qPCR)
- Droplet Digital PCR (ddPCR)





Real-time quantitative PCR (RT-qPCR)

Variation of PCR where fluorescent probes quantify amplified product at the end of each cycle

Used to detect antigen-receptor gene rearrangements in lymphoid malignancies

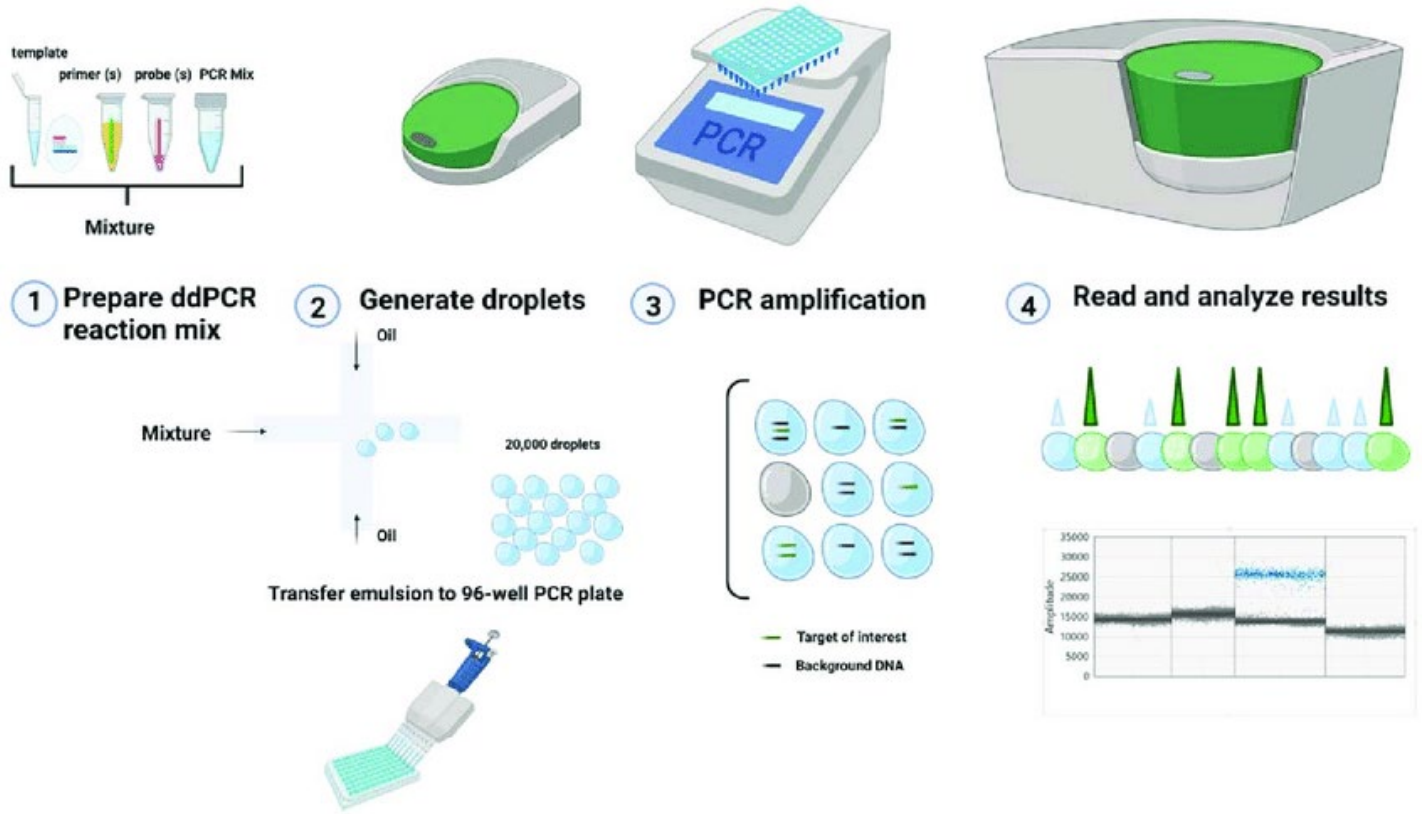
Used to detect fusion genes in AML and ALL such as BCR:ABL1 and ETV6:RUNX1

Droplet Digital PCR (ddPCR)

Each PCR sample is partitioned into thousands of microscopic droplets before amplification

Each droplet is an individual PCR reaction

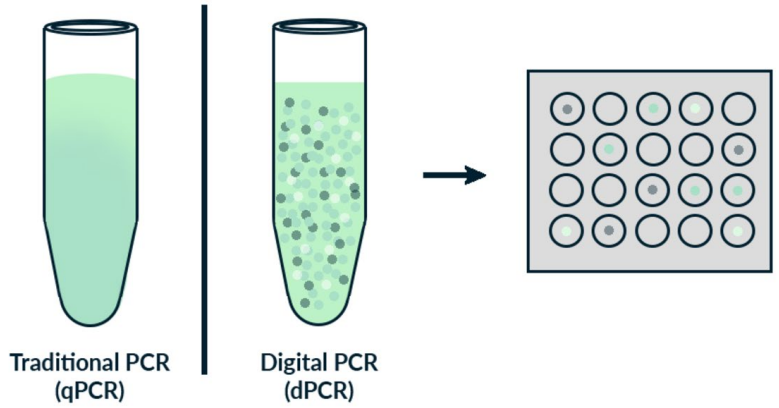
Fluorescence detects droplets containing the target sequence



Droplet Digital PCR (ddPCR)

Advantages

- More accurate than RT-qPCR
- Higher amplification efficiency
- Less affected by PCR inhibitors
- Multiplexing capable
- No calibration curve needed – absolute quantification
- Able to quantify low concentration targets



Disadvantages

- Expensive
- Not as efficient for large scale screening of numerous samples/targets
- Sample preparation and data analysis are complex
- Needs standardization

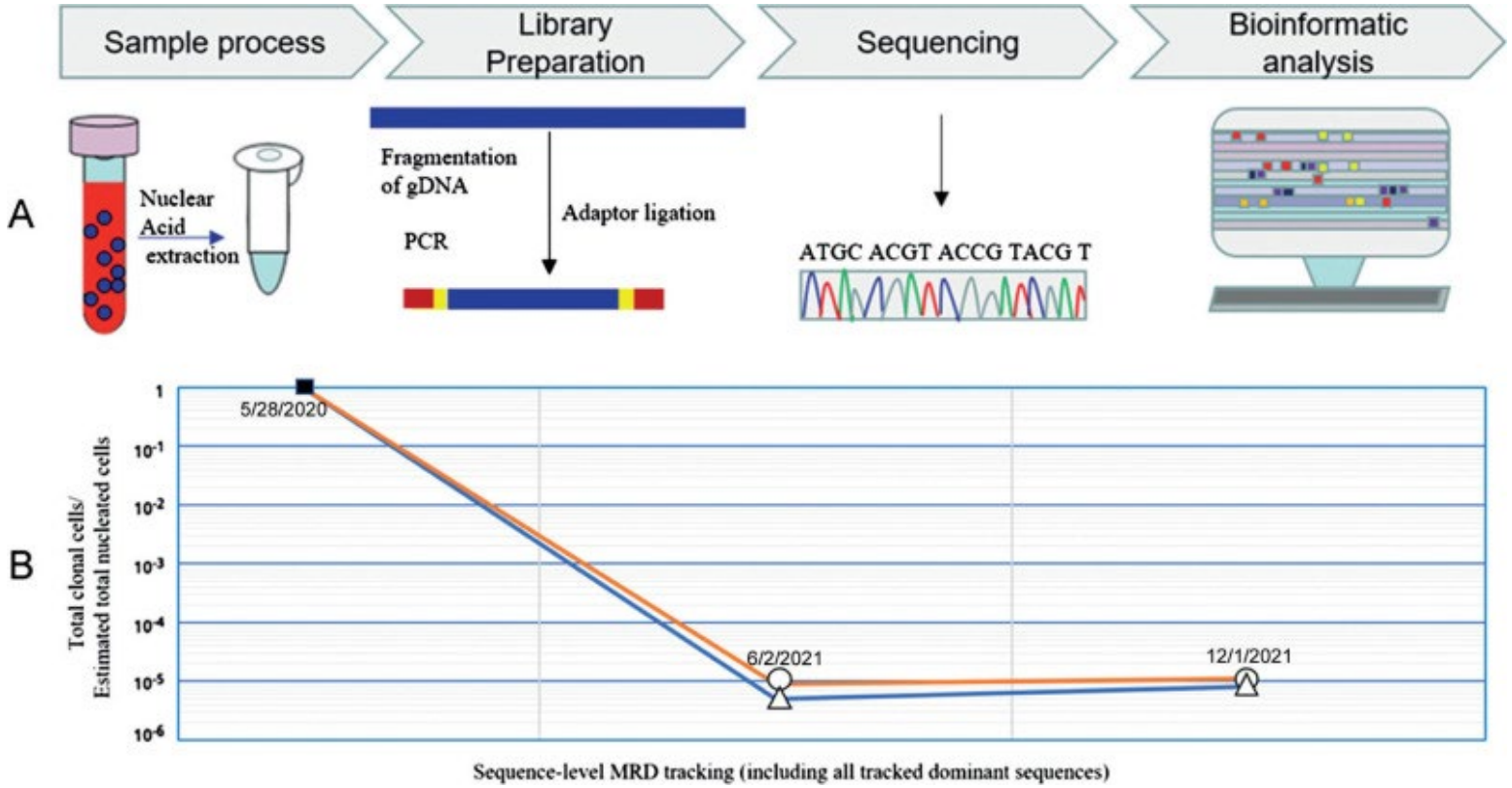
Next-Generation Sequencing (NGS) Overview

Technique that read and analyze millions of DNA pieces at once

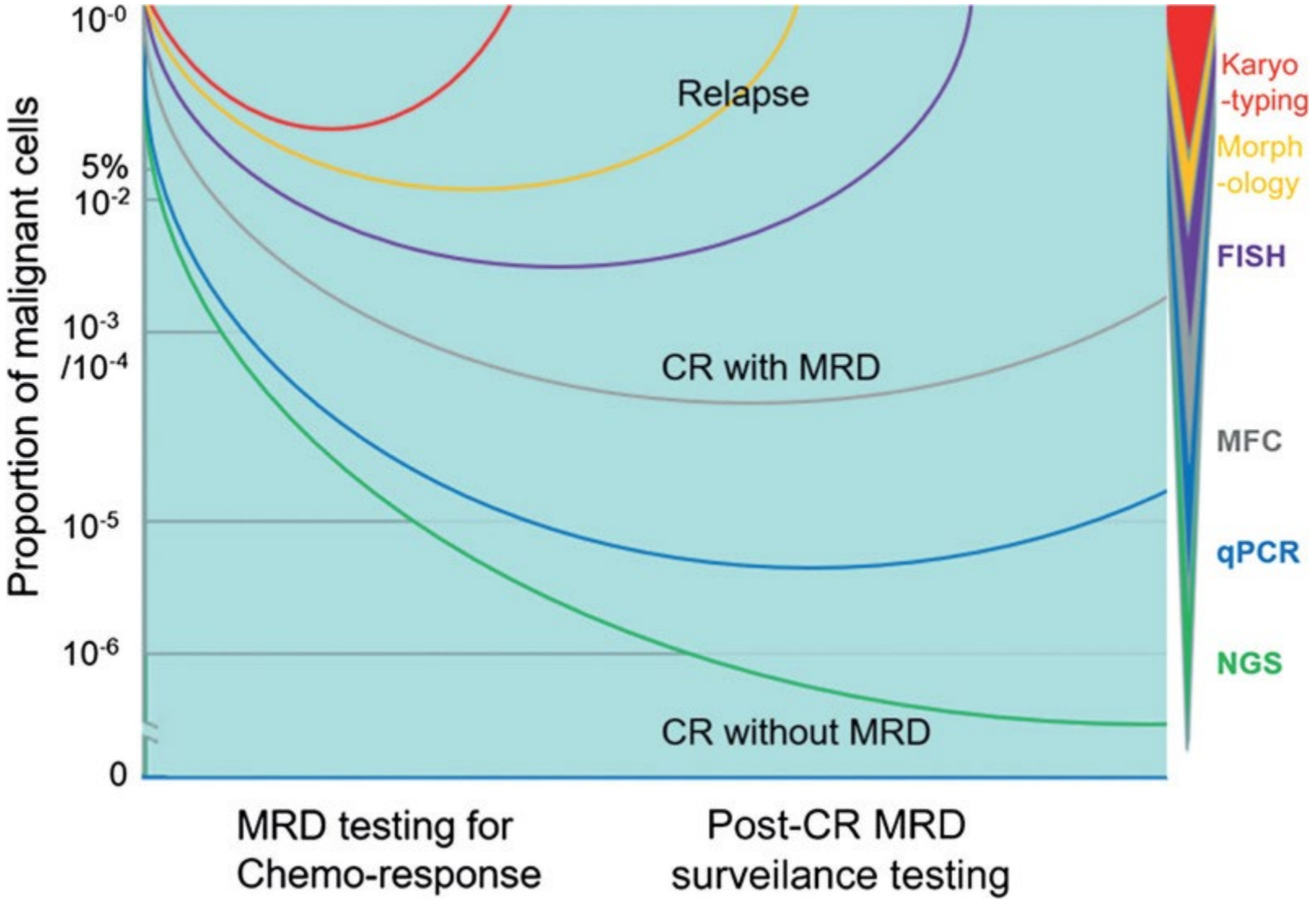
It works by breaking DNA into smaller fragments, reading each piece, and then putting them back together to understand the full sequence

Role in MRD Testing

- Detects very small amounts of cancer cells that remain after treatment
- Identifies genetic mutations and rare MRD markers often missed in other methods
- Monitor responses to treatment
- Treatment plans can be tailored to patient's specific genetic profile


A
Sample process
Library Preparation
Sequencing
Bioinformatic analysis
Nuclear Acid extraction
Fragmentation of gDNA
PCR
Adaptor ligation
ATGC ACGT ACCG TACG T
B
Total clonal cells/ Estimated total nucleated cells
1
10-1
10-2
10-3
10-4
10-5
10-6
5/28/2020
6/2/2021
12/1/2021
Sequence-level MRD tracking (including all tracked dominant sequences)

NGS

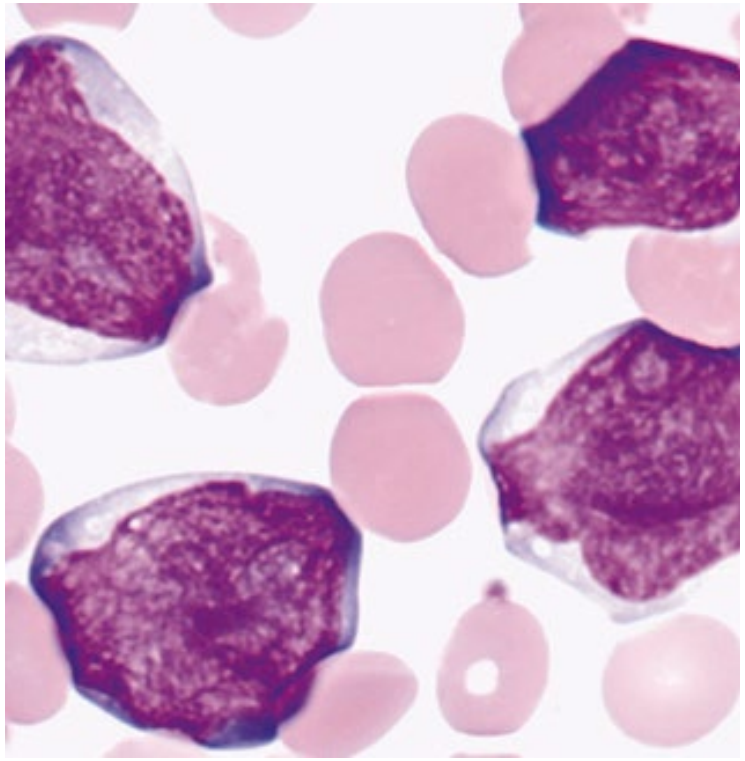

Proportion of malignant cells
10-0
5%
10-2
10-3
/10-4
10-5
10-6
0
Relapse
CR with MRD
CR without MRD
Karyo
-typing
Morph
-ology
FISH
MFC
qPCR
NGS
MRD testing for
Chemo-response
Post-CR MRD
surveilance testing

Comparative Analysis of MRD Detection Technologies

Method	Sensitivity	Advantages	Disadvantages
Multiparameter Flow Cytometry using LAIP & DfN	10^{-3} to 10^{-5}	Fast (within hours) High applicability Relatively inexpensive Personalized Detects phenotypic shifts	Requires fresh sample/viable cells High level of expertise needed Limited standardization
RT-qPCR for gene fusions	10^{-4} to 10^{-5}	Sensitive Relatively simple Standarized	Limited applicability Risk of cross contamination Can’t detect clonal evolution
Digital PCR	10^{-3} to 10^{-5}	Sensitive Absolute quantification No standard curve needed Not affected by PCR inhibitors	Lacks standardization Can’t detect clonal evolution May need patient specific primers
Next-Generation Sequencing	10^{-6}	Highly sensitive No need for patient specific primers Wide applicability Can sometimes track clonal evolution	Requires specimen pretreatment No standardization Requires high expertise Expensive

Clinical Applications of MRD Testing

Acute Lymphoblastic Leukemia (ALL)



Blood cancer with aggressive growth of immature lymphoblasts

Primarily affects children between ages 2 to 5

- Accounts for 25% of pediatric cancers and up to 75% of childhood leukemias

Rare in adults, but risk of ALL increases with age

Morphology

- Lymphoblasts appear in two forms: small with scant blue cytoplasm and indistinct nucleoli, or larger with prominent nucleoli and irregular nuclear membranes, which can resemble AML blasts

ALL WHO Classification

B-cell ALL

- Several subtypes with known gene translocations
- **ETV6:RUNX1 fusion**
  - Common in children
  - Excellent prognosis
  - Formed from t(12;21)(p13;q22)
- **BCR:ABL1 fusion (Philadelphia chromosome)**
  - More common in adults
  - Poor prognosis; improved with the development of tyrosine kinase inhibitors
  - t(9;22)(q34;q11)

T-cell ALL

- Classified into early T-precursor ALL and T-ALL not otherwise specified (NOS)

MRD Testing in Acute Lymphoblastic Leukemia (ALL)

Detected using MFC, PCR, and NGS

Regular MRD checks during induction and maintenance chemotherapy (1.5 to 2.5 years) is standard

- First evaluated 2 to 4 weeks after induction therapy
- MRD negativity after first test indicates good response and less invasive treatments needed
- Recommended to test every 3 months to catch relapses early
- MFC & NGS most frequently used in B-ALL
- RT-PCR added for Ph+ ALL

MRD Strong Predictor of ALL Relapse

Large scale studies of over 13,000 ALL patients found that reaching MRD negative status improved chances of event-free survival regardless of the method used for MRD testing

MRD-negative patients had a 75% lower risk of relapse or death compared to those with detectable levels of MRD

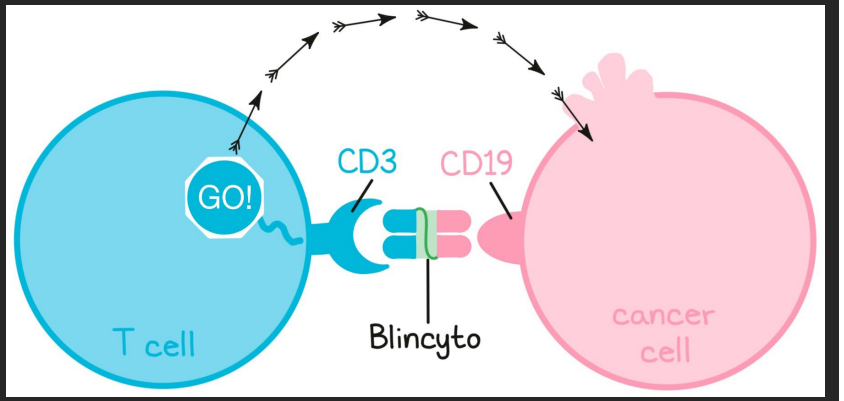
MRD Therapeutic Implications for ALL

Allogenic hematopoietic cell transplantation is indicated for adults with relapsed or refractory ALL or patients with MRD positivity after induction therapy

Studies have demonstrated that patients with pre-transplant MRD levels of $>10^{-4}$ have 7.7 times higher risk of relapse after transplantation

These patients need additional chemotherapy to reduce cancer loads before Allo HCT

MRD Role in Monitoring New Therapies



Blinatumomab: CD19/CD3 bispecific T-cell engager (BiTE) antibody

Given to patients with refractory or relapsed Precursor B-ALL with poor prognosis

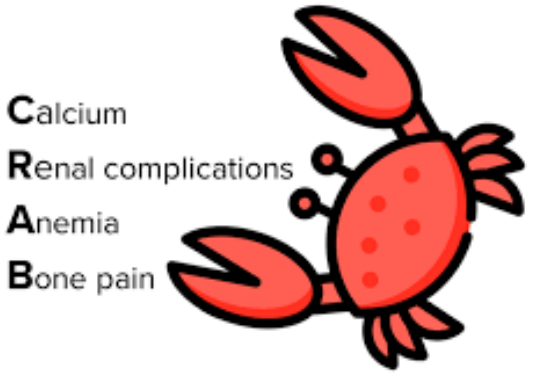
Targets CD-19 positive B-cells to be destroyed by T-cells

43% of patients with relapsed/refractory B-precursor ALL achieved complete remission after 2 cycles of treatment

This increased the median overall survival from 4.5 months with chemo alone to 13 months for patients who took BiTE

MRD negativity showed strong correlation to long-term survival and improved T-cell expansion

Multiple Myeloma (MM)



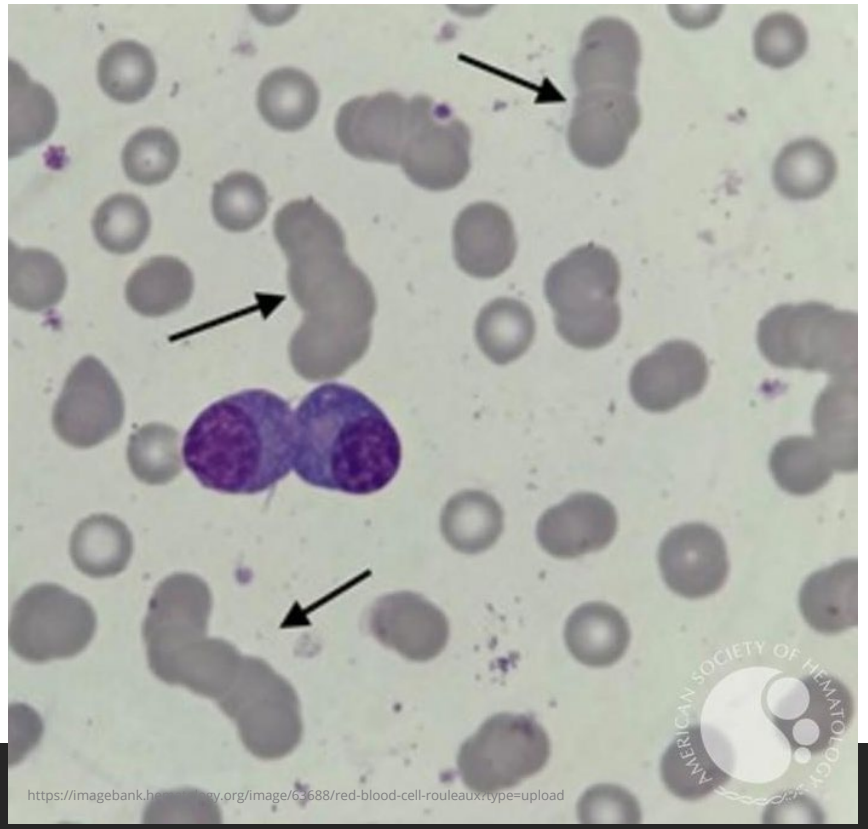
Accumulation of malignant plasma cells in the bone marrow that create lytic bone lesions

Primarily affects middle-aged to elderly

Symptoms: hypercalcemia, bone pain, anemia, kidney problems and frequent infections

Laboratory Tests

- CBC (anemia) & Chem panel (high calcium)
- SPE – monoclonal gammopathy (usually IgG)
- Bence Jones protein in urine
- Hyperviscosity to plasma



MRD Testing in Multiple Myeloma (MM)

FDA approved MRD testing as clinical endpoint for the accelerated approval of new drugs therapies in MM

Replaces overall response rates; which typically took 10 years of research to see real lasting benefit for patients

While the average survival has increased from 3.5 years to 10 years, 60% of MM patients will survive 5 years after diagnosis

MRD testing has the potential to speed up drug discovery and improve patient outcomes with efficient, sensitive, and personalized detection

Future Questions in MRD Detection

- Who should be evaluated?
- What is the optimal time for MRD evaluation?
- What are the precise thresholds for MRD testing that correlate with clinically significant outcomes?
- Does the clinical benefit outweigh testing costs?
- Which malignancies benefit the most from MRD testing?
- What role does MRD testing have in liquid biopsy testing for circulating tumor DNA and circulating tumor cells?
- Are MRD positive cells truly dormant or potentially capable of reactivating disease?

Summary

Minimal residual disease testing plays a crucial role in detecting small numbers of cancer cells that remain after treatment, which may not be visible through routine clinical tests

Techniques, such as multiparameter flow cytometry, PCR, and next-generation sequencing, allow for early relapse detection

MRD testing guides treatment decision, predicts relapse, and enables timely interventions

In certain hematological malignancies, such as ALL and MM, MRD testing is a marker for treatment response and survival outcomes

The FDA now recognizes MRD negativity as a key endpoint for drug approvals

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Questions?