CatALLyst™: Considerations for Measurable Residual Disease (MRD) and Testing Methodologies in Acute Lymphoblastic Leukemia (ALL)

CatALLyst™ | Igniting Collaboration in Acute Lymphoblastic Leukemia

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About CatALLyst™

- Recognizing the need for a comprehensive resource on measurable residual disease (MRD) education, Amgen Oncology engaged with several opinion leaders in acute lymphoblastic leukemia (ALL) and MRD. CatALLyst™ is an initiative that gives treaters of ALL a reference for management considerations and other helpful content gathered and inspired by this engagement

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Disclosures

[Speaker Name, Degree]

This speaker is one of the opinion leaders that Amgen brought together to help give treaters of acute lymphoblastic leukemia (ALL) a reference for management considerations and other helpful content.

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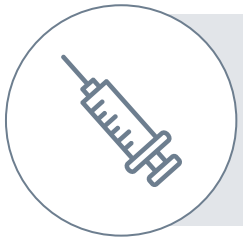
Educational Objectives

Learn the latest on MRD as an integral component of ALL management



Learn about different methodologies for MRD testing, including the benefits and limitations of each method and sample requirements

Explore key aspects of interpreting test results and potential implications for MRD-based treatment decisions

ALL, acute lymphoblastic leukemia; MRD, measurable residual disease.

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ALL, acute lymphoblastic leukemia.

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What Is Measurable Residual Disease (MRD): Understanding the Importance of MRD

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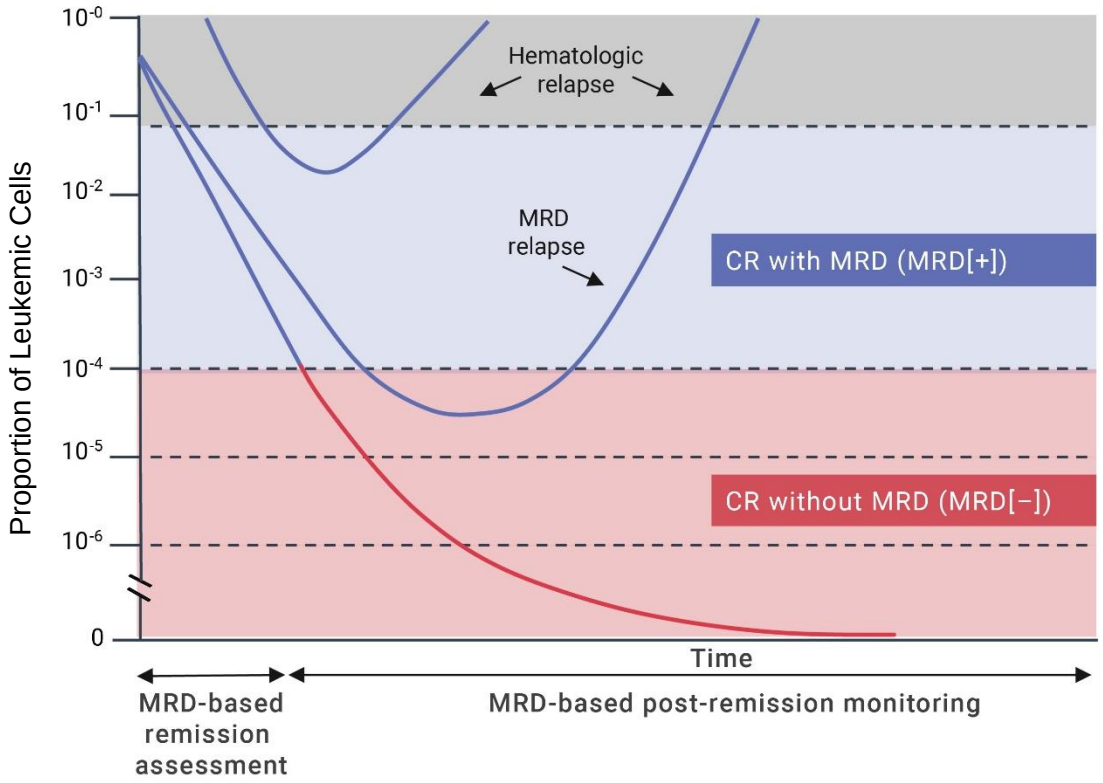
MRD Is a Strong Prognostic Indicator for Relapse in ALL

Patterns of Response and Relapse in ALL [1]



- A substantial proportion of adult patients with ALL relapse following achievement of CR, with a reported relapse rate of **40%–50%** across multiple treatment regimens [2]
- **~ 30%–40%** of adult patients who achieve CR following frontline chemotherapy may still test positive for MRD [3,4,*]
- MRD is defined as the presence of detectable leukemic cells within the bone marrow or peripheral blood during morphologic CR [5,6]
- While there is no consensus on a precise definition of MRD positivity, a sensitivity threshold of 10^{-4} has been shown to predict patient outcomes [6]

Patients who achieve CR may still have MRD following induction and consolidation therapy, which is a strong negative prognostic indicator for survival outcomes that can only be detected via MRD testing [7,8]

*Range based on two clinical studies in which MRD was measured at different time points. [3,4]
ALL, acute lymphoblastic leukemia; CR, complete remission; MRD, measurable residual disease.
1. Short NJ, et al. *Am J Hematol*. 2019;94:257-265. **2.** Hoelzer D. *Am Soc Clin Oncol Educ Book*. 2013;33:290-293. **3.** Gökbuget N, et al. *Blood*. 2012;120:1868-1876. **4.** Brüggemann M, et al. *Blood*. 2006;107:1116-1123. **5.** Bassan R, et al. *Haematologica*. 2019;104:2028-2039. **6.** Akabane H, et al. *Clin Adv Hematol Oncol*. 2020;18:413-422. **7.** Della Starza I, et al. *Front Oncol*. 2019;9:726. **8.** Berry DA, et al. *JAMA Oncol*. 2017;3:e170580.

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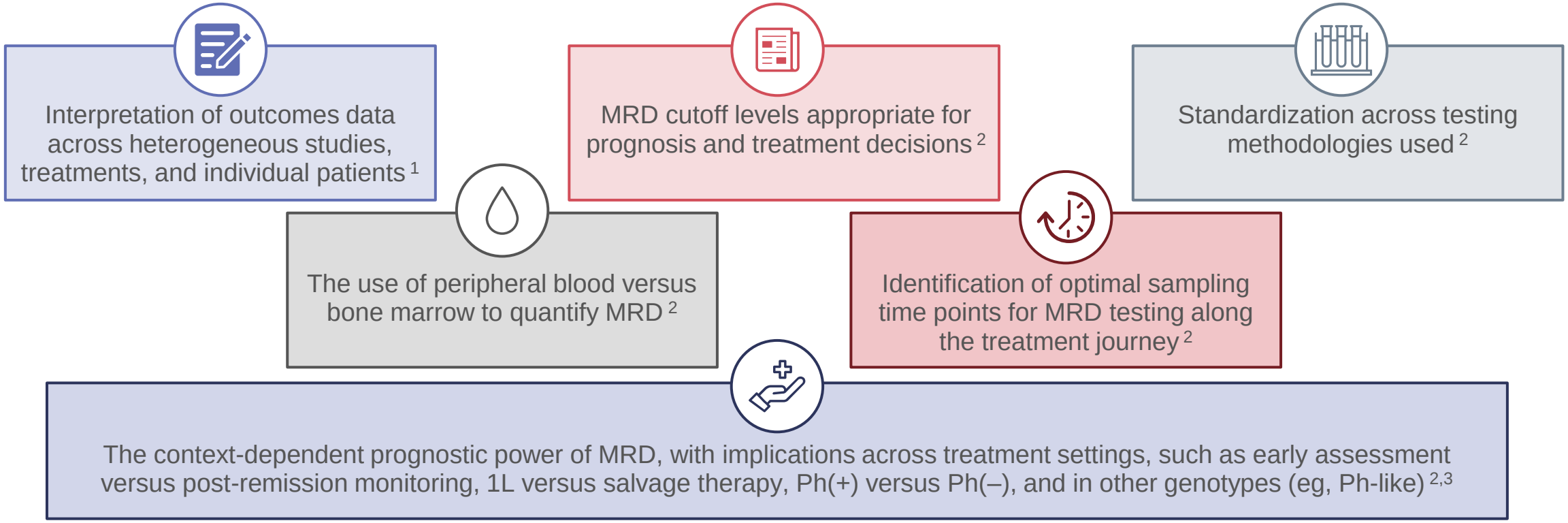
Research Is Ongoing to Advance the Understanding of the Impact of MRD in ALL [1,2]

Emerging Concepts of MRD



Further research is ongoing in emerging concepts of MRD to ensure that patients with ALL receive the best possible care throughout the course of treatment

1L, first-line; ALL, acute lymphoblastic leukemia; MRD, measurable residual disease; Ph(–), Philadelphia chromosome–negative; Ph(+), Philadelphia chromosome–positive.

1. Berry DA, et al. *JAMA Oncol*. 2017;3:e170580. **2.** Brüggemann M, et al. *Blood Adv*. 2017;1:2456-2466. **3.** Jain N, et al. *Blood*. 2017;129:572-581.

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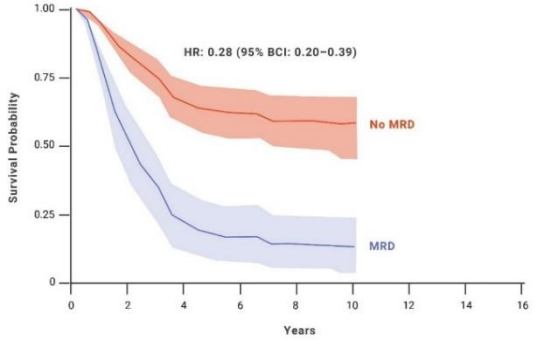
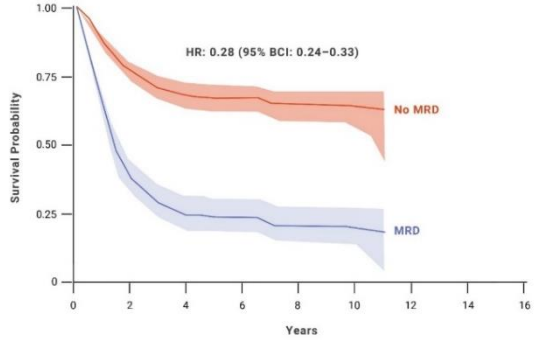
MRD Is a Predictor for Survival Outcomes in Adult and Pediatric Patients With ALL, Regardless of Treatment *

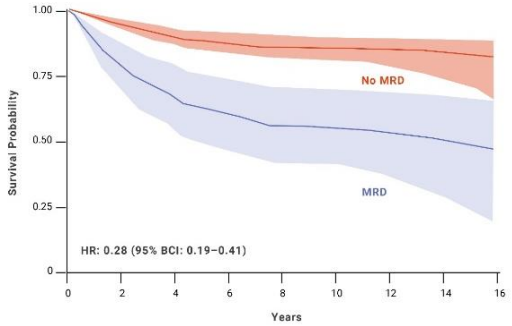
OS for Adult ALL: 5 Studies With 806 Patients



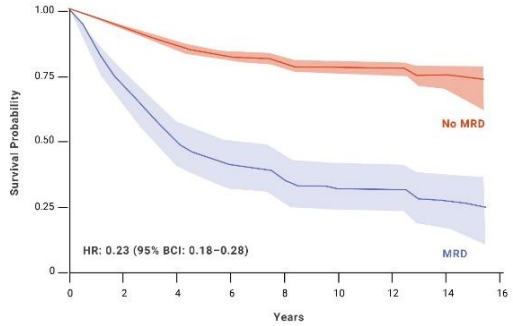
EFS for Adult ALL: 16 Studies With 2,065 Patients †



OS for Pediatric ALL: 5 Studies With 2,876 Patients



EFS for Pediatric ALL: 20 Studies With 11,249 Patients †



- These data include various treatments and are not intended to make any sort of survival claim, nor is the benefit specific to any treatment

Adult and pediatric patients who achieved MRD negativity had a greater chance of survival versus patients who remained MRD(+), regardless of age or cytogenetics

*A meta-analysis of 39 publications of distinct studies with 13,637 patients. Trials with fewer than 30 people or insufficient MRD description were excluded.
†The definition of EFS varied across trials, and included disease-free, recurrence-free, relapse-free, and event-free survival.
ALL, acute lymphoblastic leukemia; BCI, Bayesian credible interval; EFS, event-free survival; HR, hazard ratio; MRD, measurable residual disease; OS, overall survival.
Berry DA, et al. *JAMA Oncol*. 2017;3:e170580.

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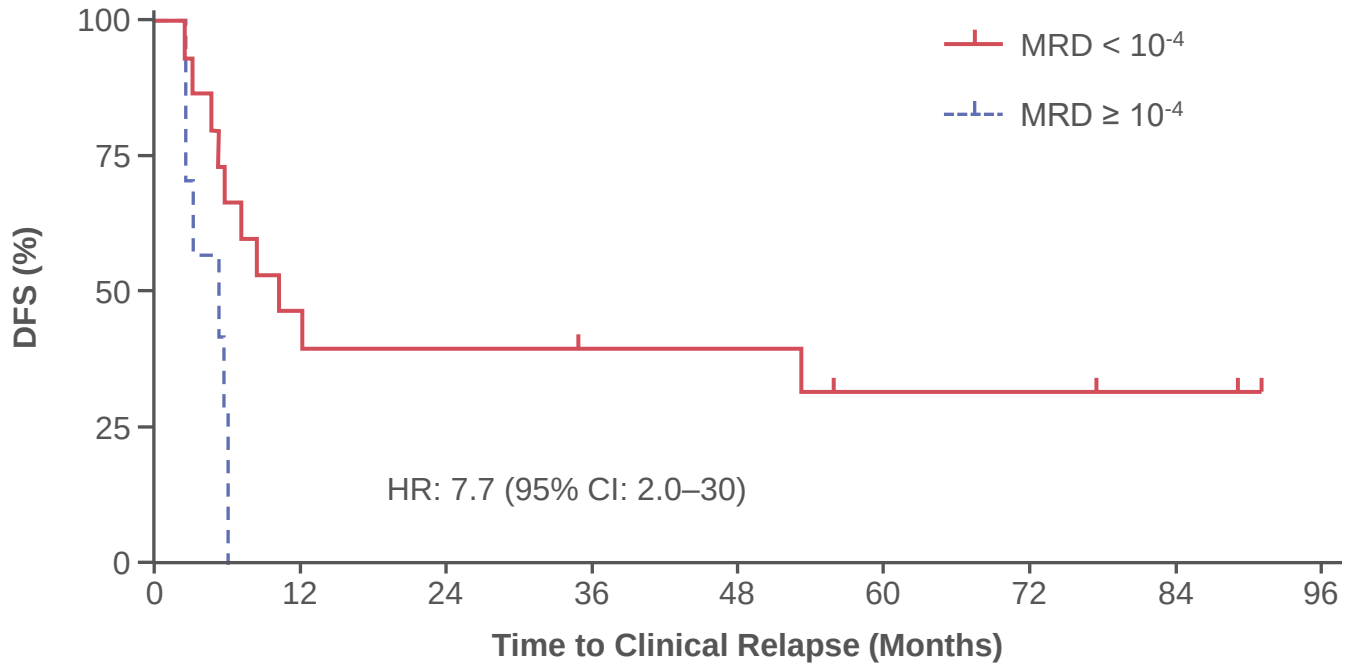
MRD Status May Be a Prognostic Factor for Post-HSCT Outcomes

- This study retrospectively analyzed the contribution of MRD in the survival of 29 patients ages 16 to 67 years with B-cell ALL who proceeded to HSCT between 2004 and 2010

Post-HSCT DFS Probability for Adult/AYA Patients With B-Cell ALL *



Achieving MRD(–) status prior to HSCT may be associated with improved post-HSCT outcomes in adult/AYA patients with ALL

*Of 27 patients available for MRD assessment, 22 patients had a blood sample available within 30 days before initiation of transplantation conditioning.
ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, measurable or minimal residual disease.
Logan AC, et al. *Biol Blood Marrow Transplant*. 2014;20:1307-1313.

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Considerations for How and When to Test for MRD: A Look Into Detection Methodologies

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MRD Can Be Quantified Using Methodologies With Differences in Targets, Sensitivities, and Turnaround Times

There are 3 common techniques to quantify MRD, with sensitivity thresholds ranging from < 0.01% to < 0.0001% [1]

	Flow Cytometry	Quantitative Polymerase Chain Reaction (Q-PCR)	Next-Generation Sequencing (NGS)
Description	• Rapid and quantitative method of identifying cancer cells [2]	• A method in which a section of DNA from cancer cells is replicated and amplified [2]	• Extremely sensitive and specific DNA sequencing method [3]
Target	• Leukemia-associated immunophenotypes [4]	• Ig and TCR gene rearrangements or abnormal gene fusions (eg, *BCR-ABL1*) [5]	• Ig and TCR gene rearrangements [3]
Typical Sensitivity *	• 1 cancer cell in 10,000 normal cells (0.01%) [3]	• 1 cancer cell in 100,000 normal cells (0.001%) [3]	• 1 cancer cell in 1,000,000 normal cells (0.0001%) [3]
Turnaround Time	• ~ 1 day [4,5]	• ~ 1–2 weeks (eg, *BCR-ABL1*) or 3–4 weeks (ASO-PCR) [6,7,†,‡]	• ~ 1 week [4]

MRD testing can be performed in house at some institutions, or the sample can be sent to an external CLIA-certified laboratory if necessary [8,9]

***Assays with < 0.01% sensitivity cannot be used to quantify MRD accurately.** [5] †For PCR-ASO, turnaround time is 3 to 4 weeks for diagnostic samples and ~ 1 week for follow-up analyses. [6]
‡Not widely available in the US. [10]
ASO, allele-specific oligonucleotide; BCR-ABL1, breakpoint cluster region protein-abelson murine leukemia viral oncogene homolog 1; CLIA, Clinical Laboratory Improvement Amendments; Ig, immunoglobulin; MRD, measurable residual disease; TCR, T-cell receptor.

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MRD Quantification Methodologies May Vary in Their Sample Requirements, Benefits, and Limitations

	Flow Cytometry	PCR	NGS
Sample Requirements	• Fresh bone marrow sample [1] • Baseline sample preferred but not required [1,*]	• Baseline sample, or prior sample obtained at diagnosis with detectable disease, is required [1]	• Baseline sample, or prior sample obtained at diagnosis with detectable disease, is required [1]
Considerations	• ≥ 6-color assays are the most commonly used vs other color assays to detect abnormal MRD immunophenotypes [2] • Adequate sensitivity for MRD quantification requires special calibration and assessment of a large number of cells that may not be available from some labs [3] • Requires significant expertise for analysis [1] • Limited standardization across testing facilities [1]	• *BCR-ABL1* PCR is applicable in only Ph(+) patients [4,5] • ASO-PCR utilizes patient-specific ASO primers (limited availability in the US) [4] • Limited standardization across testing facilities, depending on assay [1]	• An FDA-cleared NGS assay is available [1] • Limited standardization across testing facilities using other NGS approaches [1]

Consider consulting with a pathologist prior to MRD testing to discuss considerations that may yield the best results

*For DfN method only. [1]

ASO, allele-specific oligonucleotide; BCR-ABL1, breakpoint cluster region protein-abelson murine leukemia viral oncogene homolog 1; DfN, different-from-normal; MRD, measurable residual disease; NGS, next-generation sequencing; PCR, polymerase chain reaction; Ph(+), Philadelphia chromosome–positive.

1. Dalle IA, et al. *Ther Adv Hematol.* 2020;11:2040620720910023. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 1, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **3.** van Dongen JJM, et al. *Blood.* 2015;125:3996-4009. **4.** Akabane H, et al. *Clin Adv Hematol Oncol.* 2020;18:413-422. **5.** Brüggemann M, et al. *Semin Oncol.* 2012;39:47-57.

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for ALL Provide Guidance for MRD Testing Throughout the Treatment Journey

MRD is considered an essential component of patient evaluation over the course of sequential therapy in adult and pediatric patients with ALL [1,2,*]

Diagnosis

Baseline sample may be required or helpful to characterize leukemic clones to perform subsequent MRD analysis †

End of Induction ‡

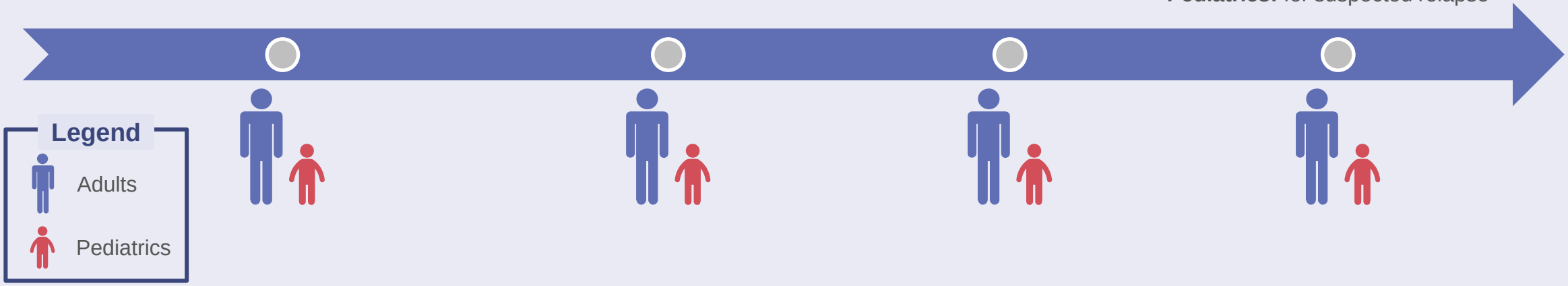
CR does not exclude the possible presence of residual leukemic cells in the bone marrow

End of Consolidation §

Surveillance

Adults: every 3–6 months, as clinically indicated for at least 5 years

Pediatrics: for suspected relapse **



MRD status plays an important role in a patient's treatment journey, and an MRD(+) test result may prompt additional intervention or a change in treatment [1,2]

*AYA patients may be included in either pediatric or adult patient populations. [1,2] †Dependent on MRD testing technique used. [1,2] ‡Additional time points should be guided by the regimen used. Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden. [1,2] §Additional time points should be guided by the regimen used. [2] **MRD testing may be included with a bone marrow aspirate. [2]

ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; CR, complete remission; MRD, measurable residual disease; NCCN, National Comprehensive Cancer Network.

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Considerations Prior to MRD Testing

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MRD Assessment Requires a Standardized Process for Sample Acquisition, Processing, and Handling to Ensure Accurate Results [1]

Sample Considerations Prior to MRD Testing

Source

- The use of bone marrow is preferred for MRD assessment [2]
  - When a bone marrow sample cannot be acquired, peripheral blood may be used as an alternative sample when high sensitivity methods for quantification are used [3,4]
- A baseline sample acquired at diagnosis or relapse identifies disease characteristics used for subsequent MRD analysis [5]

Consider collaborating with the multidisciplinary team prior to submitting an MRD test to avoid sample rejection and to ensure optimal results

ALL, acute lymphoblastic leukemia; EDTA, ethylenediaminetetraacetic acid; MRD, measurable residual disease; NCCN, National Comprehensive Cancer Network.
1. Correia RP, et al. *Int J Lab Hematol.* 2021;43:354-363. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 1, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **3.** Brüggemann M, et al. *Blood Adv*. 2017;1:2456-2466. **4.** Akabane H, et al. *Clin Adv Hematol Oncol.* 2020;18:413-422. **5.** Dalle IA, et al. *Ther Adv Hematol.* 2020;11:2040620720910023. **6.** Helgestad J, et al. *Pediatr Blood Cancer*. 2011;57:224-226. **7.** clonoSEQ®. https://adaptivebiotech.showpad.com/share/orMGe2KgT49rCt5j6RSBA. Accessed December 2, 2021. **8.** Cellnetix. https://cellnetix.com. Accessed December 1, 2021. **9.** Arup Laboratories. https://ltd.aruplab.com. Accessed December 1, 2021.

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Quality / Volume

- NCCN Guidelines® for ALL state that the optimal sample for MRD assessment is the first or an early pull of the bone marrow aspirate [2]
  - The highest-quality sample comes from the first pull to avoid hemodilution, with a nearly 50% average reduction in leukemic cells in the second pull [6]
  - A small (eg, 2–3 mL) sample volume is preferred [2,6]

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  - A small (eg, 2–3 mL) sample volume is preferred [2,6]

Processing and Handling

- Stabilize sample with EDTA or heparin based on assay and sample type [1,7]
- Label sample appropriately to avoid sample rejection [7,8]
- Store sample at ambient temperature, refrigerated, or frozen, based on assay requirements [7-9]
- Prepare sample and ship within defined window based on assay requirements for optimal results and to avoid rejection [1,7-9]

Consider collaborating with the multidisciplinary team prior to submitting an MRD test to avoid sample rejection and to ensure optimal results

ALL, acute lymphoblastic leukemia; EDTA, ethylenediaminetetraacetic acid; MRD, measurable residual disease; NCCN, National Comprehensive Cancer Network.

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MRD Testing Includes Several Steps That Involve Multidisciplinary Team Collaboration Throughout the Testing Journey

MRD Sample Journey

1 Order MRD Test and Conduct Biopsy

- Hematologist/oncologist orders **MRD test** at diagnosis, after therapy, and at subsequent time points as clinically indicated [1,2]
- Hematologist/oncologist **performs a bone marrow aspirate/biopsy,** then **sends the sample** to the in-house laboratory [1,2]
  - Identification of the first small-volume pull for MRD evaluation to improve sample quality [3]

Key Stakeholders

Hematologist/Oncologist | Pathologist | In-House or External Laboratory

*If in-house MRD testing is unavailable, the sample can be sent to an external CLIA-certified laboratory. [7,8]

CLIA, Clinical Laboratory Improvement Amendments; MRD, measurable residual disease.

1. Arber DA, et al. *Arch Pathol Lab Med.* 2017;141:1342-1393. **2.** Short NJ, et al. *Am J Hematol.* 2019;94:257-265. **3.** Helgestad J, et al. *Pediatr Blood Cancer*. 2011;57:224-226. **4.** Akabane H, et al. *Clin Adv Hematol Oncol.* 2020;18:413-422. **5.** Della Starza I, et al. *Front Oncol.* 2019;9:726. **6.** Dalle IA, et al. *Ther Adv Hematol.* 2020;11:2040620720910023. **7.** Ayala R, et al. *J Lab Precis Med.* 2018;11:105. **8.** Centers for Disease Control and Prevention. www.cdc.gov. Accessed December 1, 2021.

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- Hematologist/oncologist **performs a bone marrow aspirate/biopsy,** then **sends the sample** to the in-house laboratory [1,2]
  - Identification of the first small-volume pull for MRD evaluation to improve sample quality [3]

2 Sample Processing & Handling

- In-house pathologist prepares bone marrow sample for MRD testing [2]
  OR
- In-house laboratory ensures high quality bone marrow sample and sends sample to an external laboratory for MRD assessment [2,*]

Key Stakeholders

Hematologist/Oncologist | Pathologist | In-House or External Laboratory

*If in-house MRD testing is unavailable, the sample can be sent to an external CLIA-certified laboratory. [7,8]

CLIA, Clinical Laboratory Improvement Amendments; MRD, measurable residual disease.

1. Arber DA, et al. *Arch Pathol Lab Med.* 2017;141:1342-1393. **2.** Short NJ, et al. *Am J Hematol.* 2019;94:257-265. **3.** Helgestad J, et al. *Pediatr Blood Cancer*. 2011;57:224-226. **4.** Akabane H, et al. *Clin Adv Hematol Oncol.* 2020;18:413-422. **5.** Della Starza I, et al. *Front Oncol.* 2019;9:726. **6.** Dalle IA, et al. *Ther Adv Hematol.* 2020;11:2040620720910023. **7.** Ayala R, et al. *J Lab Precis Med.* 2018;11:105. **8.** Centers for Disease Control and Prevention. www.cdc.gov. Accessed December 1, 2021.

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MRD Testing Includes Several Steps That Involve Multidisciplinary Team Collaboration Throughout the Testing Journey

MRD Sample Journey

1 Order MRD Test and Conduct Biopsy

- Hematologist/oncologist orders **MRD test** at diagnosis, after therapy, and at subsequent time points as clinically indicated [1,2]
- Hematologist/oncologist **performs a bone marrow aspirate/biopsy,** then **sends the sample** to the in-house laboratory [1,2]
  - Identification of the first small-volume pull for MRD evaluation to improve sample quality [3]

2 Sample Processing & Handling

- In-house pathologist prepares bone marrow sample for MRD testing [2]

OR

- In-house laboratory ensures high quality bone marrow sample and sends sample to an external laboratory for MRD assessment [2,*]

3 Conduct MRD Test and Report Results

- In-house pathologist conducts MRD assessment then compiles report of bone marrow evaluations [1]

OR

- External laboratory performs MRD assessment, generates results, and sends results to in-house pathologist to compile report [1]

Key Stakeholders

Hematologist/Oncologist | Pathologist | In-House or External Laboratory

*If in-house MRD testing is unavailable, the sample can be sent to an external CLIA-certified laboratory. [7,8]

CLIA, Clinical Laboratory Improvement Amendments; MRD, measurable residual disease.

1. Arber DA, et al. *Arch Pathol Lab Med.* 2017;141:1342-1393. **2.** Short NJ, et al. *Am J Hematol.* 2019;94:257-265. **3.** Helgestad J, et al. *Pediatr Blood Cancer*. 2011;57:224-226. **4.** Akabane H, et al. *Clin Adv Hematol Oncol.* 2020;18:413-422. **5.** Della Starza I, et al. *Front Oncol.* 2019;9:726. **6.** Dalle IA, et al. *Ther Adv Hematol.* 2020;11:2040620720910023. **7.** Ayala R, et al. *J Lab Precis Med.* 2018;11:105. **8.** Centers for Disease Control and Prevention. www.cdc.gov. Accessed December 1, 2021.

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OR

- External laboratory performs MRD assessment, generates results, and sends results to in-house pathologist to compile report [1]

4 Interpret Results and Make Treatment Decision

- Pathologist reviews report, interprets results, and sends report to hematologist/oncologist [1,4]
  - Consider the possibility of false-negative and false-positive results [5]
- Hematologist/oncologist makes MRD-based treatment decision [4]
  - MRD(+) result may prompt additional intervention or a change in treatment mechanism of action [6]
  - MRD(–) result may prompt continued patient monitoring for MRD [4]

Key Stakeholders

Hematologist/Oncologist | Pathologist | In-House or External Laboratory

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Considerations for How to Interpret MRD Results: Interpretation and Next Steps

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The Opinion Leaders Brought Together by Amgen Oncology Suggest a Standardized Approach to Reporting MRD Test Results in ALL

Consider focusing your review on the following information within an MRD pathology report to help support consistent interpretation of results and to inform MRD-based treatment decisions

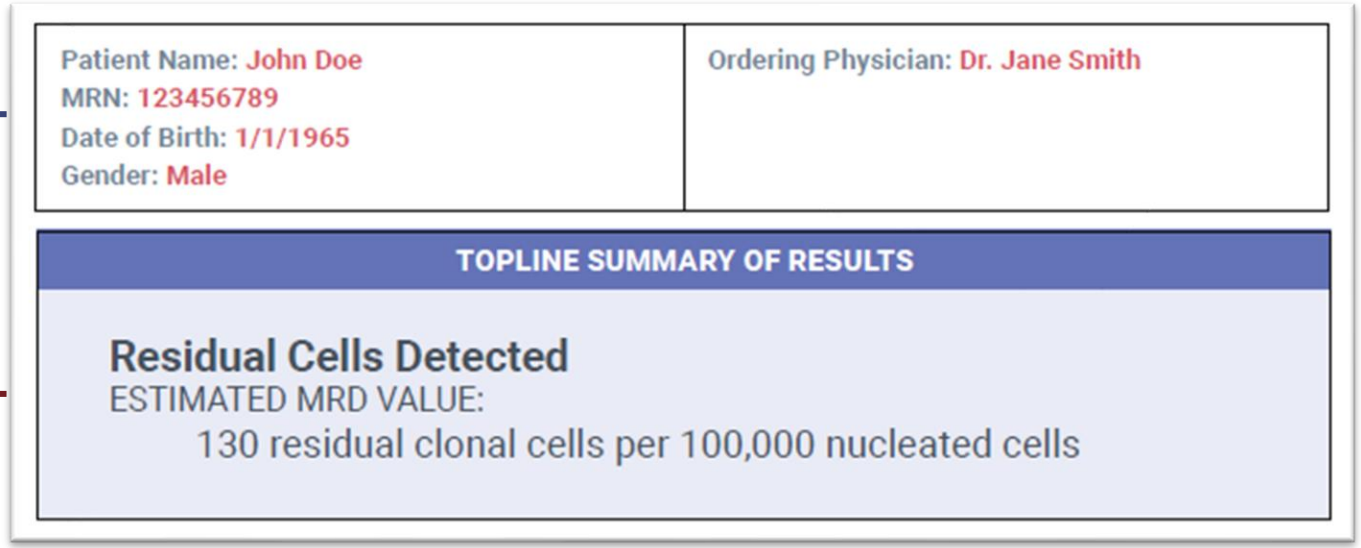
Patient Information

Provides the multidisciplinary team with relevant information on the patient

Topline Summary of Results

It can be helpful to include a topline summary of results (eg, number of residual leukemic cells detected) on the front page of the pathology report, so that the patient's MRD status is immediately available in order to help assist the hematologist/ oncologist in determining a treatment plan

Sample MRD Pathology Report*



*The above MRD pathology report is a sample report that only highlights information that the opinion leaders brought together by Amgen Oncology view as important to document in reports. This sample report is for educational and informational purposes only.

ALL, acute lymphoblastic leukemia; MRD, measurable residual disease.

Arber DA, et al. *Arch Pathol Lab Med*. 2017;141:1342-1393.

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The Opinion Leaders Brought Together by Amgen Oncology Suggest a Standardized Approach to Reporting MRD Test Results in ALL (cont'd)

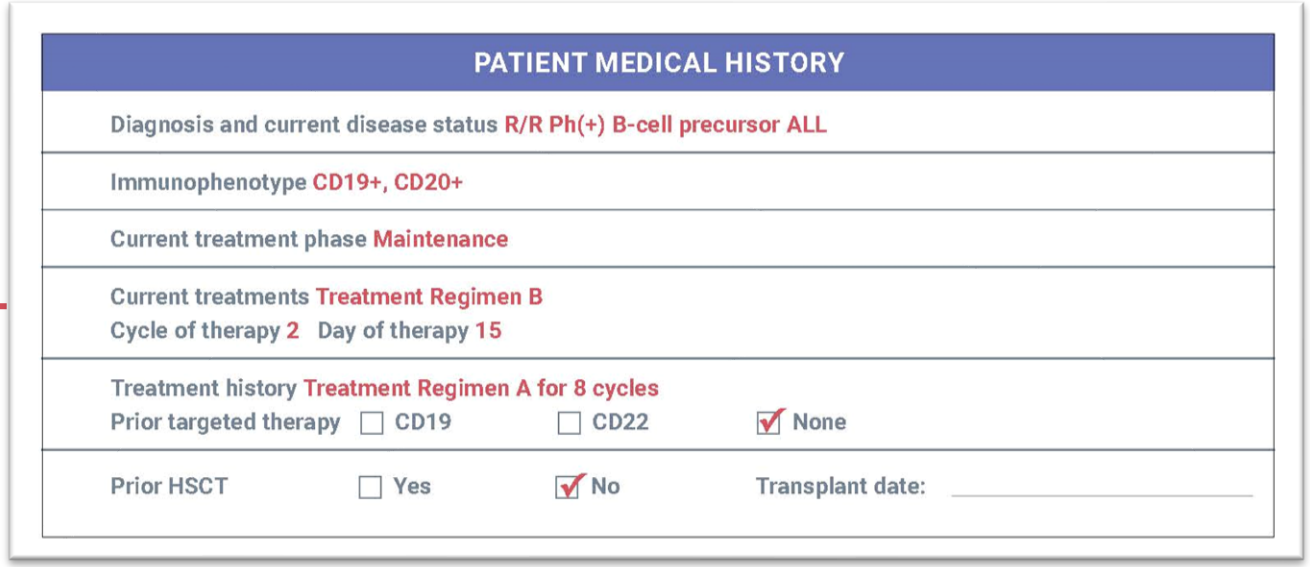
Consider focusing your review on the following information within an MRD pathology report to help support consistent interpretation of results and to inform MRD-based treatment decisions

Patient Medical History

Provides the multidisciplinary team with the patient's detailed medical history, which may guide the team in determining the need for additional testing, interpreting MRD test results, and making treatment decisions [1]

- Inclusion of treatment history (eg, prior anti-CD19- or anti-CD22-targeted therapy) provides relevant information that may confound MRD test results [2]

Sample MRD Pathology Report*



PATIENT MEDICAL HISTORY			
Diagnosis and current disease status R/R Ph(+) B-cell precursor ALL			
Immunophenotype CD19+, CD20+			
Current treatment phase Maintenance			
Current treatments Treatment Regimen B Cycle of therapy 2 Day of therapy 15			
Treatment history Treatment Regimen A for 8 cycles Prior targeted therapy ☐ CD19	☐ CD22	☑ None	
Prior HSCT	☐ Yes	☑ No	Transplant date: _____

*The above MRD pathology report is a sample report that only highlights information that the opinion leaders brought together by Amgen Oncology view as important to document in reports. This sample report is for educational and informational purposes only.

ALL, acute lymphoblastic leukemia; CD, cluster of differentiation; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, measurable residual disease; Ph(+), Philadelphia chromosome–positive; R/R, relapsed or refractory.

1. Arber DA, et al. *Arch Pathol Lab Med*. 2017;141:1342-1393. **2.** Brüggemann M, et al. *Blood.* 2012;120:4470-4481.

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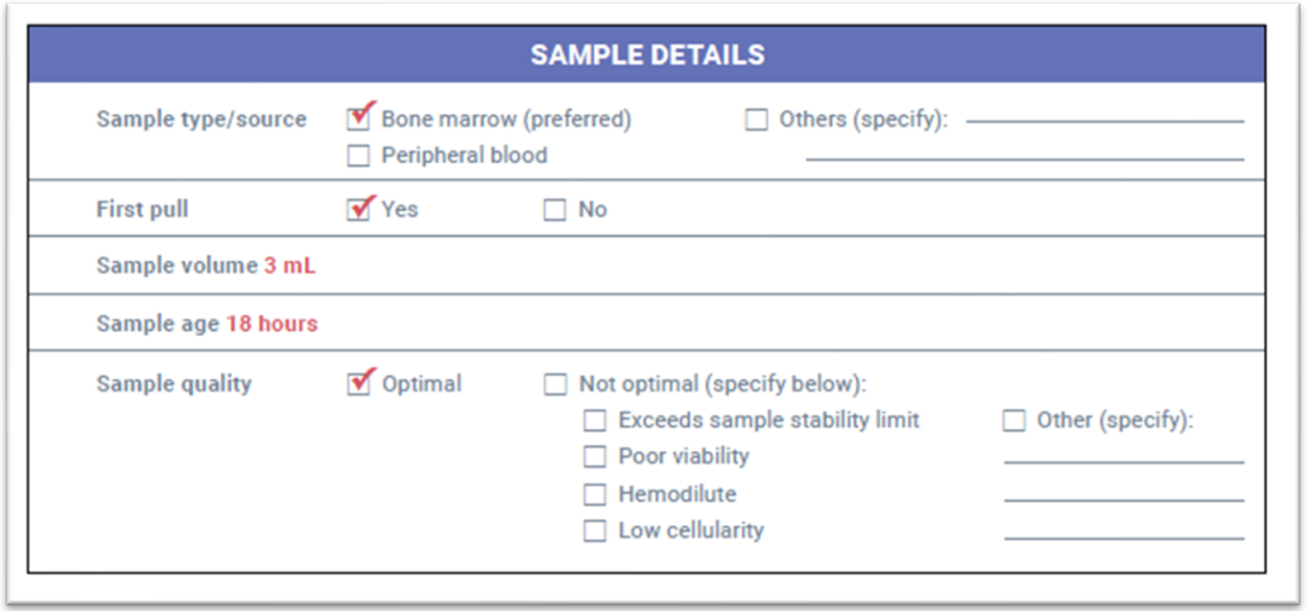
The Opinion Leaders Brought Together by Amgen Oncology Suggest a Standardized Approach to Reporting MRD Test Results in ALL (cont'd)

Consider focusing your review on the following information within an MRD pathology report to help support consistent interpretation of results and to inform MRD-based treatment decisions

Sample Details

Provides information involved in sample acquisition, processing, and handling procedures, which can help with interpretation of the accuracy and reliability of the results [1-4]

Sample MRD Pathology Report*



SAMPLE DETAILS		
Sample type/source	☑ Bone marrow (preferred) ☐ Peripheral blood	☐ Others (specify): _____
First pull	☑ Yes	☐ No
Sample volume 3 mL		
Sample age 18 hours		
Sample quality	☑ Optimal	☐ Not optimal (specify below): ☐ Exceeds sample stability limit ☐ Poor viability ☐ Hemodilute ☐ Low cellularity ☐ Other (specify): _____

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ALL, acute lymphoblastic leukemia; MRD, measurable residual disease.

1. Correia RP, et al. *Int J Lab Hematol.* 2021;43:354-363. **2.** Paietta E. In: Wiernik PH, et al, eds. *Neoplastic Diseases of the Blood*. 6th ed. Springer; 2018:237-279. **3.** clonoSEQ®. https://adaptivebiotech.showpad.com/share/vENsMo9HgtZXfBdE0nd5x. Accessed December 1, 2021. **4.** Della Starza I, et al. *Front Oncol.* 2019;9:726.

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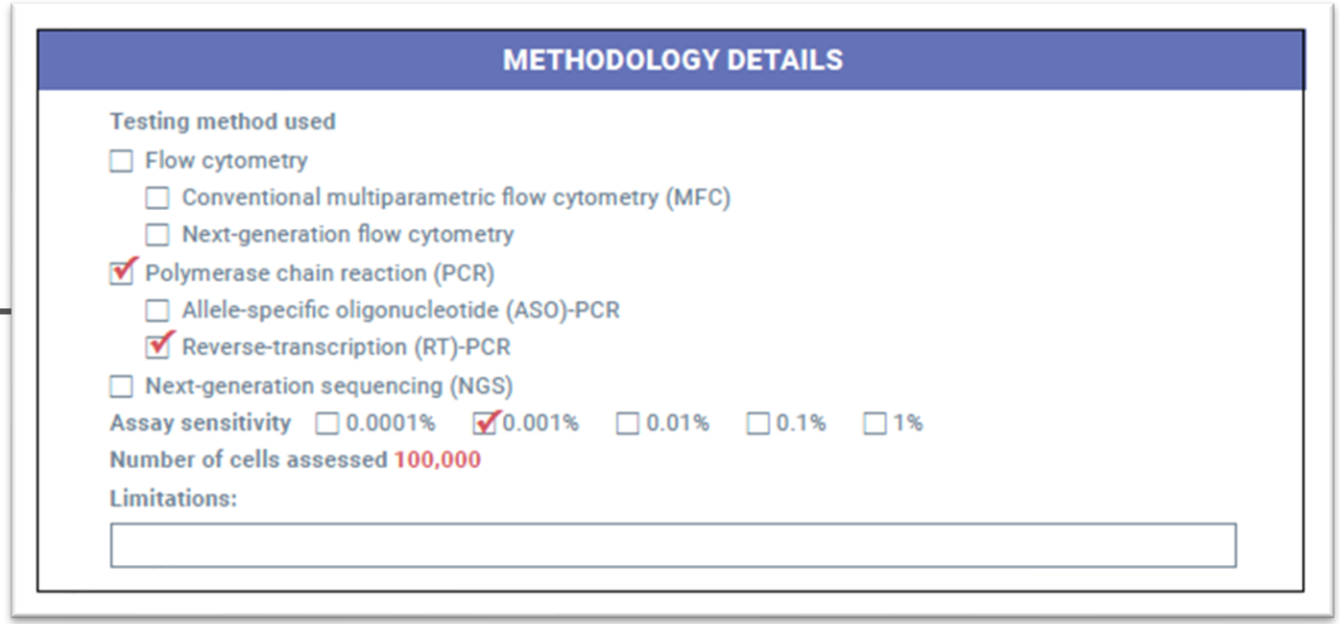
The Opinion Leaders Brought Together by Amgen Oncology Suggest a Standardized Approach to Reporting MRD Test Results in ALL (cont'd)

Consider focusing your review on the following information within an MRD pathology report to help support consistent interpretation of results and to inform MRD-based treatment decisions

Methodology Details

Assists the treating oncologist in determining quality of data analysis in order to interpret results and make informed MRD-based treatment decisions [1,2]

Sample MRD Pathology Report*



METHODOLOGY DETAILS

Testing method used

- ☐ Flow cytometry
  - ☐ Conventional multiparametric flow cytometry (MFC)
  - ☐ Next-generation flow cytometry
- ☑ Polymerase chain reaction (PCR)
  - ☐ Allele-specific oligonucleotide (ASO)-PCR
  - ☑ Reverse-transcription (RT)-PCR
- ☐ Next-generation sequencing (NGS)

Assay sensitivity ☐ 0.0001% ☑ 0.001% ☐ 0.01% ☐ 0.1% ☐ 1%

Number of cells assessed 100,000

Limitations:

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ALL, acute lymphoblastic leukemia; MRD, measurable residual disease.

1. clonoSEQ®. https://adaptivebiotech.showpad.com/share/vENsMo9HgtZXfBdE0nd5x. Accessed December 1, 2021. **2.** Della Starza I, et al. *Front Oncol.* 2019;9:726.

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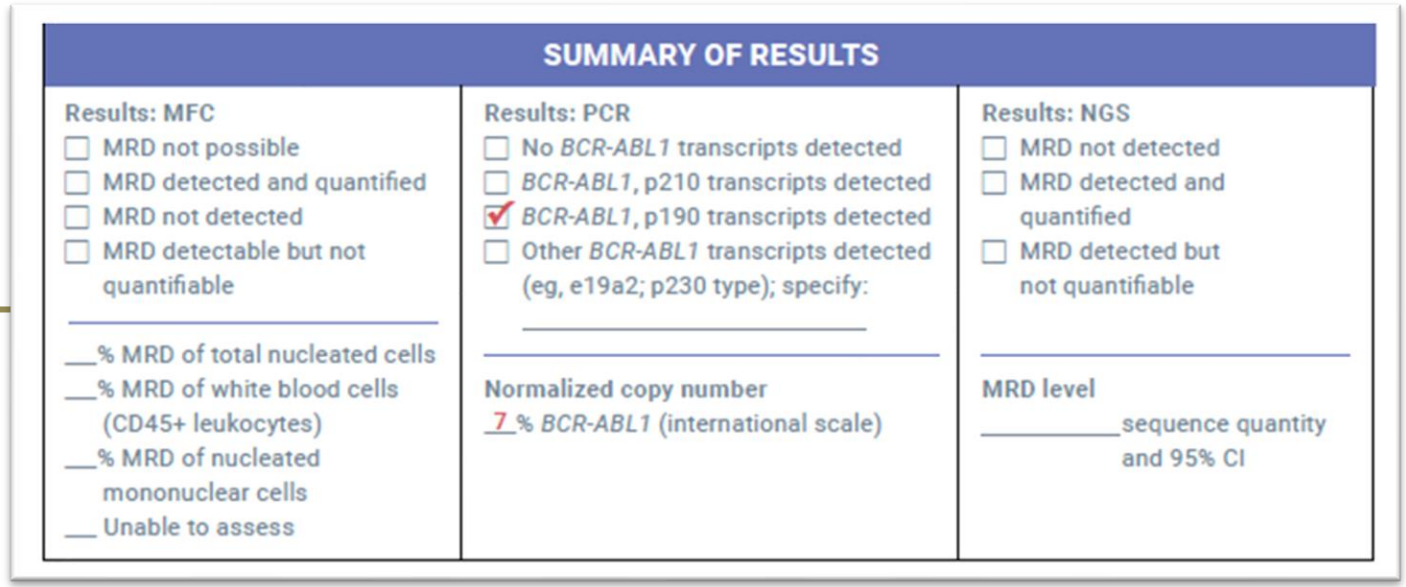
The Opinion Leaders Brought Together by Amgen Oncology Suggest a Standardized Approach to Reporting MRD Test Results in ALL (cont'd)

Consider focusing your review on the following information within an MRD pathology report to help support consistent interpretation of results and to inform MRD-based treatment decisions

Summary of Results

Provides the treating oncologist with an overview of MRD test results, including the number of residual leukemic cells detected, to guide appropriate treatment decisions

Sample MRD Pathology Report*



SUMMARY OF RESULTS

Results: MFC
- ☐ MRD not possible
- ☐ MRD detected and quantified
- ☐ MRD not detected
- ☐ MRD detectable but not quantifiable

___% MRD of total nucleated cells
___% MRD of white blood cells (CD45+ leukocytes)
___% MRD of nucleated mononuclear cells
___ Unable to assess

Results: PCR
- ☐ No *BCR-ABL1* transcripts detected
- ☐ *BCR-ABL1*, p210 transcripts detected
- ☑ *BCR-ABL1*, p190 transcripts detected
- ☐ Other *BCR-ABL1* transcripts detected (eg, e19a2; p230 type); specify: _____

Normalized copy number
7 % *BCR-ABL1* (international scale)

Results: NGS
- ☐ MRD not detected
- ☐ MRD detected and quantified
- ☐ MRD detected but not quantifiable

MRD level
_____ sequence quantity and 95% CI

Consider documenting test results in a clearly visible, concise, and easy-to-interpret summary within MRD testing reports

*The above MRD pathology report is a sample report that only highlights information that the opinion leaders brought together by Amgen Oncology view as important to document in reports. This sample report is for educational and informational purposes only.

ALL, acute lymphoblastic leukemia; BCR-ABL1, breakpoint cluster region protein-abelson murine leukemia viral oncogene homolog; CI, confidence interval; MRD, measurable residual disease.

clonoSEQ®. https://adaptivebiotech.showpad.com/share/vENsMo9HgtZXfBdE0nd5x. Accessed December 1, 2021.

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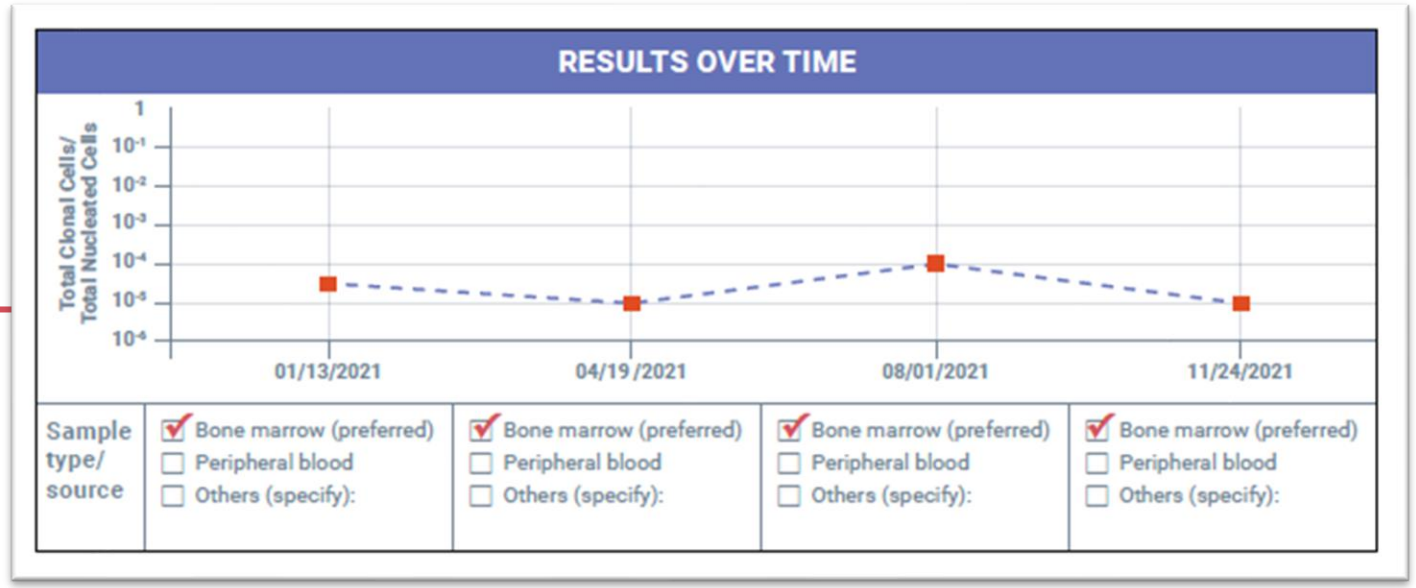
The Opinion Leaders Brought Together by Amgen Oncology Suggest a Standardized Approach to Reporting MRD Test Results in ALL (cont'd)

Consider focusing your review on the following information within an MRD pathology report to help support consistent interpretation of results and to inform MRD-based treatment decisions

Results Over Time

Provides the multidisciplinary team with a snapshot of the patient's MRD status over the course of treatment, giving the team additional context

Sample MRD Pathology Report*



Consider standardizing information contained in an MRD pathology report to ensure consistency across practices

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Considerations When Interpreting MRD Test Results for Proactive Treatment Planning

If the quality of the original sample is low, an additional sample may be necessary [1,2]

Interpretation of MRD results may be influenced by the maximum sensitivity of the test being used [3]

Consider the possibility of false-negative or false-positive results based on the test being used [3]

An MRD(+) test result may warrant additional intervention or a change in treatment [4,5]

Continue to monitor the patient's MRD status following an MRD(–) test result, as clinically applicable [6]

Based on clinical experience, the opinion leaders brought together by Amgen Oncology encourage multidisciplinary team collaboration to ensure optimal results in MRD assessment and to inform appropriate treatment decisions

MRD, measurable residual disease.

1. Brüggemann M, et al. *Blood.* 2012;120:4470-4481. **2.** Paietta E. In: Wiernik PH, et al, eds. *Neoplastic Diseases of the Blood*. 6th ed. Springer; 2018:237-279. **3.** Della Starza I, et al. *Front Oncol.* 2019;9:726. **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Acute Lymphoblastic Leukemia V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 1, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Pediatric Acute Lymphoblastic Leukemia V.1.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed December 1, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **6.** Akabane H, et al. *Clin Adv Hematol Oncol*. 2020;18:413-422.

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Summary

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Summary

MRD is a significant prognostic indicator of survival outcomes in pediatric and adult patients with ALL [1]

MRD status plays an important role in a patient's treatment journey and can be quantified with distinct methodologies that differ in targets, sensitivities, and limitations [2]

MRD assessment is a multistep process that involves multidisciplinary team collaboration to ensure appropriate sample acquisition, processing, and handling for accurate results [3,4]

Documentation of key information within an MRD pathology report, such as patient information, sample details, methodology details, and a summary of results, can inform MRD-based treatment decisions [3,5-8]

ALL, acute lymphoblastic leukemia; MRD, measurable residual disease.

1. Berry DA, et al. *JAMA Oncol*. 2017;3:e170580. **2.** Dalle IA, et al. *Ther Adv Hematol.* 2020;11:2040620720910023. **3.** Arber DA, et al. *Arch Pathol Lab Med.* 2017;141:1342-1393. **4.** Short NJ, et al. *Am J Hematol*. 2019;94:257-265. **5.** Brüggemann M, et al. *Blood Adv*. 2017;1:2456-2466. **6.** Paietta E. In: Wiernik PH, et al, eds. *Neoplastic Diseases of the Blood*. 6th ed. Springer; 2018:237-279. **7.** clonoSEQ®. https://adaptivebiotech.showpad.com/share/vENsMo9HgtZXfBdE0nd5x. Accessed December 1, 2021. **8.** Della Starza I, et al. *Front Oncol*. 2019;9:726.

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