Annals of Hematology (2019) 98:2347–2355
https://doi.org/10.1007/s00277-019-03782-z

ORIGINAL ARTICLE

Clinician-friendly reports of molecular measurable residual disease monitoring in acute promyelocytic leukemia

Qisheng Wu [1,2,3,4] · Rui Zhang [1,3] · Rongxue Peng [1,3] · Yu Fu [1,2,3] · Jiawei Zhang [1,2,3] · Kun Chen [1,2,3] · Jinming Li [1,2,3]

Received: 6 August 2018 / Accepted: 11 August 2019 / Published online: 24 August 2019
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Abstract

Molecular measurable residual disease (MRD) monitoring based on real-time quantitative reverse transcription PCR (RT-qPCR) plays an important role in acute promyelocytic leukemia (APL) management, but the performance status of clinical reports is unknown. This study focuses on the specific elements in molecular MRD monitoring report and their impact on clinical decision-making. The participating laboratories were asked to submit real and formal clinical reports for mock samples panel with APL clinical case. The MRD-specific elements were analyzed and summarized. The significance of longitudinal MRD monitoring curve and the missing MRD-specific elements for clinical decision-making were assessed. MRD-specific elements were significantly missing in clinical reports. The element "testing results" existed great inconsistencies in the written form of testing items and data. The longitudinal MRD monitoring curve of false-negative or false-positive MRD result was obviously different from all-correct. It not only identified MRD time point of tissue sampling relative to treatment and ensured the reliability of the negative MRD results, but also gave MRD diagnosis, clinical interpretation, and further recommendation. Clinician-friendly reports with MRD-specific elements can better serve clinical practice. The correctly intuitive results and clinically important MRD-specific elements can provide a good description of the reliability and clinical significance of MRD results.

Keywords Clinician-friendly reports · Measurable residual disease · Molecular MRD monitoring · *PML/RARA* · Acute promyelocytic leukemia

Introduction

Acute promyelocytic leukemia (APL) is a life-threatening coagulopathy [1] with an annual incidence rate of 0.23/100,000 persons that accounts for approximately 10% of de novo acute myeloid leukemia (AML) cases in younger adults [2]. *PML/RARA* fusion gene (FG) produced by the characteristic chromosomal translocation t(15;17) is present in almost all APL cases [3]. Molecular detection of *PML/RARA* FG plays an important role in the proper management of APL, including APL etiological diagnosis, molecular targeted therapy, measurable residual disease (MRD, formerly known as minimal residual disease) monitoring, and molecular remission [4–9]. The rigorous longitudinal MRD monitoring by real-time quantitative reverse transcription PCR (RT-qPCR), performed at the post-consolidation phase, was undertaken as a tool to identify impending relapse and enable early intervention for better prognosis [4, 9, 10].

In clinical management of APL, clinical reports are an important and indispensable medium between medical laboratories and competent hematologists. Whether in admission diagnosis or MRD monitoring, clinician-friendly reports should have the presentation requirements to adapt to the APL management. The reports not only have clear and accurate test results, but also carry the corresponding comprehensive clinical interpretations and further recommendations. In addition to positive or negative results for *PML/RARA*, quantitative

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-019-03782-z) contains supplementary material, which is available to authorized users.

✉ Jinming Li
jmli@nccl.org.cn

1 National Center for Clinical Laboratories, Beijing Hospital, National Center of Gerontology, Beijing, People's Republic of China

2 Graduate School, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, People's Republic of China

3 Beijing Engineering Research Center of Laboratory Medicine, Beijing Hospital, Beijing, People's Republic of China

4 Division of Pathology and Laboratory Medicine, Hebei Yanda Lu Daopei Hospital, Beijing, People's Republic of China

results for fusion gene transcript levels should be reported, including fusion gene copy number (FG_{CN}), control gene copy number (CG_{CN}), FG_{CN}/CG_{CN}, MRD value, and longitudinal MRD monitoring graph [11–14]. The qualified clinical reports for MRD monitoring can easily help clinicians to fully understand therapeutic effects of specific APL patient, giving clinicians a reasonable indicator of treatment resistance and disease relapse [4].

Although there exist many genetic laboratory reporting recommendations [15–20], little attention has been paid to the elements and format of clinical reports on molecular MRD monitoring of fusion gene–related AML. In particular, APL diagnosis and relapse monitoring rely on the molecular detection of *PML/RARA* fusion gene; clinician-friendly clinical reports issued by medical laboratories are very helpful for clinical decision-making. Therefore, in order to investigate the impact of the correctness of molecular MRD monitoring and the clinical report integrity on APL decision-making, we designed APL clinical cases and prepared corresponding mock leukocyte samples. Afterwards, based on a series of recommendations or consensus from European LeukemiaNet (ELN) [5, 12, 13, 21], we analyzed the various MRD-specific elements of clinical reports, summarized the significance of test results in clinical reports, and gave some suggestions for improving measures.

Material and methods

Design of APL clinical case

According to the NCCN Clinical Practice Guidelines in Oncology Acute Myeloid Leukemia (Version 3.2017) [4] and Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet [5], we designed the APL case based on real case repots. For longitudinal MRD monitoring documenting by *PML/RARA* transcript level, clinical information at MRD monitoring was provided, including induction, consolidation, maintenance, and follow-up (see Supplementary material 1).

Preparation and distribution of mock leukocyte samples

In accordance with the well-established protocol of our laboratory [22], we used MS2-armored RNA technology to prepare mock leukocyte samples for *PML/RARA* FG. The samples panel was composed of 2 negative samples (A2, A4) and 4 positive samples (A1, A3, A5, and A6). There were A1 for admission diagnosis, A2 for consolidation, A3 and A4 for maintenance, and A5 and A6 for follow-up. After being identified and validated, the samples panel for *PML/RARA* was randomly distributed to 50 participating laboratories (for details, see Supplementary material 2). Each participant was asked to submit real and formal clinical reports for MRD monitoring.

MRD-specific elements in clinical reports for molecular MRD monitoring

The qualified clinical reporting elements of *PML/RARA* by RT-qPCR detection consisted of two major parts: the essential elements and the MRD-specific elements (Table 1). The specific reporting elements for molecular MRD monitoring were assessed, including nine elements based on established standards and guidelines for clinical reports [5, 12, 13, 21]. In particular, it focused on the presentation of *PML/RARA* testing results in clinical reports.

Assessment of clinically significant reporting elements

Compared with the essential elements of clinical reporting, MRD-specific elements are more significant for clinicians to make APL clinical decisions. The summary analysis was made on the molecular MRD-specific elements in clinical reports. The representative clinical reports with the false-positive or false-negative MRD results were selected to examine the impact of incorrect results on clinical decision-making. According to the formula recommended by the Europe Against Cancer Program (EAC), we calculated the MRD value and the day-to-day sensitivity [14]:

$$\text{MRD value}\,(\%) = \frac{\left(\frac{\text{FG CN}}{\text{CG CN}}\right)\text{FUP}}{\left(\frac{\text{FG CN}}{\text{CG CN}}\right)\text{DX}} \times 100;\quad \text{Sensitivity}(\%)$$

$$= \frac{\left(\frac{1}{\text{CG CN}}\right)\text{FUP}}{\left(\frac{\text{FG CN}}{\text{CG CN}}\right)\text{DX}} \times 100;$$

where DX was admission diagnostic, FUP was follow-up, FG CN was fusion gene copy number, and CG CN was control gene copy number. The longitudinal MRD monitoring graph was made to observe changes in the shape of treatment trend curve, and then analyze the impact of incorrect *PML/RARA* test results on clinical treatment.

Inductive analysis of incorrect MRD results and inappropriate clinical actions

We analyzed test results of participating laboratories at different MRD monitoring time points, in order to find out which time point has a higher probability of incorrect results. Further,

Table 1 Qualified clinician-friendly reports of molecular MRD monitoring in APL

No.	Recommended reporting elements	Reporting content
1	Essential elements	
1.1	• Patient identifier	Name, age, sex, date of birth
1.2	• Sample identifier	Unique sample ID number; date of sample collected and sample arrival; ordering clinician name and department
1.3	• Laboratory identifier	Name and address of reporting laboratory; date of report; signature of lab director
2	Specific elements	
2.1	• MRD testing method and instrument employed	Real-time quantitative reverse transcription PCR (RT-qPCR), sequencing approaches
2.2	• Analyzed tissue type	Bone marrow (BM) and/or peripheral blood (PB)
2.3	• Time point of tissue sampling relative to treatment	APL treatment phase
2.4	• Sample quality	Suitable or not suitable for MRD monitoring (based on *ABL1* copy number $\geq 10^4$)
2.5	• Testing results	
2.5.1	MRD target	Fusion genes and/or mutations
2.5.2	Quantification of MRD target	Copy number and CT value
2.5.3	Control gene	*ABL1*, *B2M*, *GUSB*, or *BCR*
2.5.4	Quantification of control gene	Copy number and CT value
2.5.5	Day-to-day sensitivity	Assay sensitivity of an individual real-time qPCR measurement
2.5.6	Qualitative MRD result	Positive or negative MRD
2.5.7	Quantitative MRD result	FG_{CN}/CG_{CN}, MRD value
2.5.8	Longitudinal MRD monitoring	During treatment: at diagnosis, post-induction/consolidation, maintenance every 3 months for 3 years; After treatment: every 3 months for 2 years during follow-up
2.5.9	Diagnosis of MRD monitoring	Confirmation of APL, complete molecular remission, molecular relapse
2.6	• Clinical interpretation	The general description of clinical significance on therapy decision-making
2.7	• Properties of MRD testing method	Analytical sensitivity, specificity, linearity, and limit of detection, etc.
2.8	• Further testing recommendations	Other time points and/or other detection methods
2.9	• References for report facts	Guidelines, recommendations, expert consensus, and/or appropriate references

the inappropriate clinical actions triggered by the incorrect results were analyzed based on the simulated case.

Results

The performance of MRD-specific elements in clinical reports

Of the 50 participating laboratories, 47 submitted their own clinical reports of RT-qPCR test for *PML/RARA* FG. The presentation of different MRD-specific elements in clinical reports differed significantly between various medical laboratories (Fig. 1). The elements "Time point of tissue sampling relative to treatment," "References for molecular MRD monitoring," "Sample quality," "Properties of MRD testing method," and "Further testing recommendations" were incomplete or even missing. The element "Clinical interpretation" was not fully rendered by all medical laboratories.

We conducted detailed analysis of the element "testing results" (Table 2). There were great inconsistencies in written form of testing items and data between medical laboratories. Except very few elements being stated, the elements "Day-to-day sensitivity," "Longitudinal MRD monitoring," and "Diagnosis of MRD monitoring" were almost completely not shown in clinical reports.

Assessment of clinically significant reporting elements

For clinical reports of *PML/RARA* detection, clinicians not only require clear and correct results, but also hope to obtain a larger amount of MRD testing information, including continuous recording of MRD results, properties of testing method, professional interpretation, and further recommendations. Because these missing elements in clinical reports are closely related to clinical practice, we further analyzed and summarized the clinical significance of these reporting elements (Table 3).

Based on the limited MRD monitoring time points of our designed APL-simulated cases, the time-span number represents diagnosis (0), post-induction (1), post-consolidation (2), maintenance (3 and 4), and follow-up (5 and 6). The longitudinal MRD monitoring curves with all-correct RT-qPCR

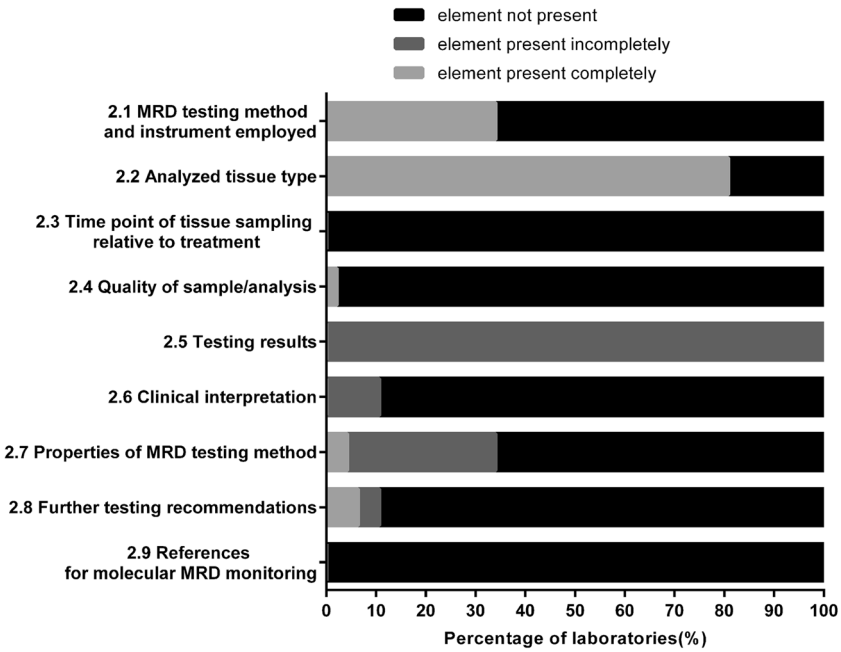

Fig. 1 The presence and fulfillment of MRD-specific elements in clinician-friendly reports of molecular MRD monitoring

results showed a "W" shape, which, at the post-consolidation (2) and maintenance (4), coincided with the day-to-day sensitivity curves (Fig. 2a). When false-positive MRD result was reported at maintenance (4) due to cross-contamination, even if ultra-low copies of *PML/RARA* increased in the PCR system, the MRD value curve will be significantly upward away from day-to-day sensitivity (Fig. 2b). For two positive MRD monitoring (5 and 6) during the follow-up period, only one error type occurred: the first test result was false-negative, the second result was correctly positive. Because the low-quality RNA samples can lead to false-negative results, the day-to-day sensitivity curve will be higher than the sample quality curve (Fig. 2c).

Incorrect MRD results and inappropriate clinical actions

There were different numbers of incorrect results at each MRD time point, especially when *PML/RARA* was low-copy level, such as false-positive MRD results after consolidation therapy and false-negative MRD results during maintenance therapy (Table 4). False-positive or false-negative results at different time points triggered different clinical actions, which have different degrees of impact on clinicians and patients (Table 4).

Discussion

The Chinese health authorities have adopted the approval system for PCR amplification laboratories and conducted technical reviews on a series of projects including test reports. Although basic elements of test reports are specified, detailed and professional report templates for fusion gene in leukemia are unable to be given. In order to standardize test reports for MRD monitoring in leukemia, the European LeukemiaNet presented the report template in order to better serve the clinic [12]. The clinician-friendly clinical report was essential to APL management, which can help the clinician to grasp detailed and reliable MRD results and to determine molecular relapse status. The results of the reporting performance showed that the great majority of laboratories missed some MRD-specific elements required in clinical reports according to the consensus document from the European LeukemiaNet (ELN) MRD Working Party [13].

As can be seen from Table 4, most laboratories can correctly monitor MRD in APL management. At critical clinical decision-making points, such as post-consolidation, and the fixed time during maintenance and follow-up, MRD monitoring results can trigger a range of adverse clinical actions (Table 4). Samples of low-copy *PML/RARA* transcript or Taq enzyme inhibitors can cause false-negative MRD results, while aerosol or cross-contamination can lead to false-positive results, which may be the main reasons for out-of-control in clinical laboratories. The correctness of MRD monitoring results is the first part of clinicians' attention in qualified clinical reports, followed by the standardization and intuitiveness of reporting form.

Various differences in the content of MRD monitoring results were obviously found in clinical reports (Table 2). A small number of medical laboratories clearly presented qualitative MRD results (positive or negative). Fusion gene, control gene, and FG_{CN}/CG_{CN} were all presented in written reports of most laboratories, while few laboratories only reported MRD

Table 2 The specific performance of the element "testing results"

No.	Testing results	Presentation of reporting content	Specific performance (%, specific lab/total labs)
2.5.1	MRD target	Inconsistent nomenclature of fusion gene	PML-RARA (23.4%, 11/47) *PML/RARα* (10.6%, 5/47) PML-RARα (63.8%, 30/47) None-stated (2.2%, 1/47)
2.5.2	Quantification of MRD target	Inconsistent format of "copy number"	Scientific notation (48.9%, 23/47) Original number (44.7%, 21/47) None-stated (6.4%, 3/47)
		Inconsistent unit of quantitative value	Copy number per test (0) Copy number per volume (14.9%, 7/47) None-stated quantitative range (85.1%, 40/47)
2.5.3	Control gene	Inconsistent nomenclature of control gene	ABL1 (10.6%, 5/47) ABL (74.5%, 35/47) None-stated (14.9%, 7/47)
2.5.4	Quantification of control gene	Inconsistent format of "copy number"	Scientific notation (48.9%, 23/47) Original number (44.7%, 21/47) None-stated (6.4%, 3/47)
		Inconsistent unit of quantitative value	Copy number per test (0) Copy number per volume (14.9%, 7/47) None-stated quantitative range (85.1%, 40/47)
2.5.5	Day-to-day sensitivity	The individual assay sensitivity	Clearly stated (0) None-stated (100%, 47/47)
2.5.6	Qualitative MRD result	Positive or negative MRD	Clearly stated (40.4%, 19/47) None-stated (53.2%, 25/47)
2.5.7	Quantitative MRD result	FG_{CN}/CG_{CN}, MRD value	FG_{CN}/CG_{CN} (100%, 47/47) MRD value (0)
2.5.8	Longitudinal MRD monitoring	A graph for presentation of longitudinal MRD data	Clearly stated (2.13%, 1/47) None-stated (97.87%, 46/47)
2.5.9	Diagnosis of MRD monitoring	Diagnosis confirmation, complete molecular remission, molecular relapse	Clearly stated (0) None-stated (100%, 47/47)

value. Furthermore, there was marked inconsistency in the nomenclature of FG and CG, the number format of "copy number," and the unit of quantitative value (Table 2). From the perspective of facilitating clinical practice, these inconsistent situations can cause uncertain recognition of MRD results by different clinicians or patients, making it impossible to compare test results among different patients or between different laboratories. Therefore, medical laboratories should offer the unified format and content of test results according to the corresponding guidelines. The gene symbol should adopt the HGVS nomenclature, e.g., *PML/RARA* and *ABL1* [17, 25]. In addition to clearly indicating the qualitative results of MRD monitoring, the absolute copy numbers of *PML/RARA* for RT-qPCR results should be in clinical reports, to enable the clinician to make his/her own judgments [13]. Thirdly, it was necessary to report the exact number format and unit of copy number detected by RT-qPCR.

The clinically significant reporting elements were the main focus in clinician-friendly reports, especially the intuitiveness of the change of MRD results. The element "Time point of tissue sampling relative to treatment" should be clearly marked to facilitate clinicians to judge the status of MRD and adjust clinical treatment plans. The NCCN recommend that APL patients should undergo RT-qPCR detection for *PML/RARα* in the same laboratory to ensure the consistent accuracy in MRD monitoring [4]. Simultaneously, the Europe Against Cancer Program (EAC) further recommend laboratories use FG_{CN}/CG_{CN} to calculate MRD value and day-to-day sensitivity to plot the longitudinal MRD monitoring curve on the logarithmic scale as a presentation form for MRD results [11, 12, 14]. As shown in Fig. 2d, the ideal MRD monitoring curve for a durable molecular remission should be "L" shaped, MRD value decreasing from 100% at diagnosis to low level after induction treatment, then turning negative at post-consolidation, continuous negative result at subsequent regular MRD monitoring. The comparison of time series MRD values provided by medical laboratories can facilitate clinician's comprehensive understanding of the treatment of

Table 3 The clinically significant reporting elements for all-correct MRD results

Reporting elements	Clinical significance	Example for all correct MRD results
Time point of tissue sampling relative to treatment	The corresponding phase of APL management at the sampling time, such as diagnosis, post-induction, post-consolidation, maintenance, and follow-up [13].	After 2 cycles of standard consolidation chemotherapy.
Sample quality	Determine the definitive criteria (*ABL1* CN/test $\geq 10^4$), the quality of the submitted BM or PB samples can be applied to MRD monitoring [13, 23].	The BM was suitable for MRD monitoring.
Day-to-day sensitivity	Comparing MRD value with "day-to-day sensitivity," it can be judged whether the MRD monitoring result is acceptable, especially for negative results [11, 14].	See Fig. 2a "Day-to-day sensitivity"
Longitudinal MRD monitoring	Drawing longitudinal MRD monitoring curve to visualize the change of MRD values [11, 14].	See Fig. 2a "line 23"
Diagnosis of MRD monitoring	• Complete molecular remission (CR_{MRD}-) [13]. • MRD result is positive [13]. • MRD result is not reliable and the false-negative result cannot be excluded [13, 23]. • Molecular relapse [13].	APL patients are in complete molecular remission.
Clinical interpretation	• Diagnosis should be confirmed by molecular detection for *PML/RARA* [4, 5]. • Detectable levels of *PML/RARA* by RT-qPCR during active treatment of APL should not change the treatment plan for an individual patient [4, 13]. • The goal of consolidation therapy for APL is a durable CR_{MRD}- [4, 13]. • At the current level of test sensitivity/specificity, a change in status of *PML/RARA* by RT-qPCR from negative to positive status, and confirmed by a repeat sample within 2 to 4 weeks, should be regarded as molecular relapse in APL [4, 13]. • Because of the poor sample quality, the MRD result may lack precision and should be treated with caution [13, 23].	APL maintenance therapy can be continued.
Further testing recommendations	• Molecular remission in the bone marrow should be assessed at completion of consolidation by RT-qPCR assay affording a sensitivity of at least 1 in 10^4 [4, 13]. • After completion of consolidation therapy, every 3-month-MRD monitoring of bone marrow should be offered to all patients for up to 3 years [4, 13]. • During follow-up of patients with *PML/RARA*, molecular MRD monitoring every 3 months for 2 years after the end of treatment in BM and in PB [4, 13]. • A repeat sample should be sent for testing [4, 13, 23].	*PML/RARA* fusion gene should be detected in BM samples 3 months later.
Properties of MRD testing method	Analytical sensitivity, specificity, linearity, and limit of detection, etc.	Linearity, 10^6~10^2, limit of detection, 10
References for report facts	Providing a reference for MRD monitoring diagnosis and further recommendation	Minimal/measurable residual disease in AML: consensus document from ELN MRD Working Party. *Blood*, 2018.

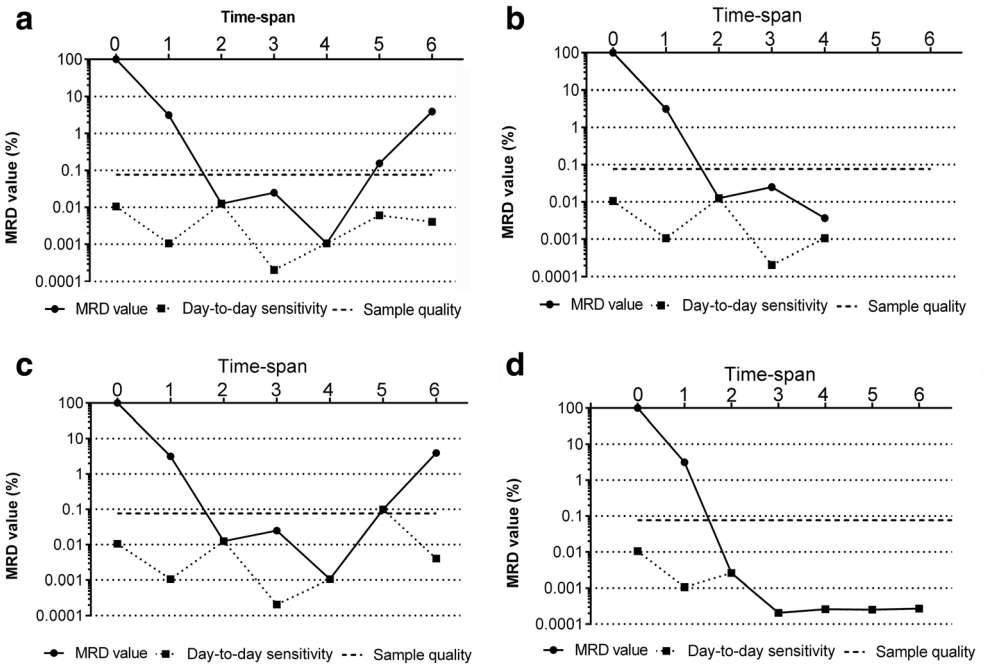

Fig. 2 Ideal and incorrect longitudinal MRD monitoring curves. The number 0~6 on the *x*-axis represents MRD monitoring time points, including diagnosis, post-induction, post-consolidation, maintenance 1, maintenance 2, follow-up 1, and follow-up 2. **a** All-correct MRD results based on simulated APL case. **b** False-positive MRD result at maintenance 2 due to cross-contamination. **c** False-negative MRD result at follow-up 2 due to the low quality of RNA samples. **d** Ideal MRD monitoring curve for a durable molecular remission

APL patients. During the induction and consolidation phases in APL management, the decreasing slope of longitudinal MRD curve can be used to judge the patient's sensitivity to ATRA treatment regimens, especially MRD values after 2 courses of consolidating treatment. The complete molecular remission (CR_{MRD-}) was defined as two successive MRD negative samples obtained within an interval of ≥ 4 weeks based on complete morphologic remission (CR) at a sensitivity level of at least 1 in 1000 [13]. We used 1×10^4 copies of *ABL1* as the lowest value for calculating CG CN_{FUP} in day-to-day sensitivity and plotted "sample quality" line on longitudinal MRD monitoring curve [13, 14, 23]. The significance of drawing "sample quality" line was: for MRD monitoring after consolidation treatment, if day-to-day sensitivity was above

Table 4 Incorrect MRD results and inappropriate clinical actions

Time point of MRD monitoring	Sample ID	Established MRD value	False-negative (FN) OR false-positive (FP) MRD results	Clinical actions and corresponding adverse events	Ref.
Admission	A1	Positive	FN, 0/50	Failure to molecularly confirm the clinical presumptive diagnosis requires a new sample for inspection and delays the specific targeted therapy for APL.	[5–8]
Induction	Given	Positive	/	Incorrect test results for judging clinical treatment effectiveness reduce the clinicians' and patients' confidence for better prognosis, and even adjust treatment regimen.	[9]
Consolidation	A2	Negative	FP, 8/50	The pre-emptive ATO therapy will be taken and confirmed molecular relapse by a repeat sample within 2 to 4 weeks.	[9, 24]
Maintenance	A3	Positive	FN, 8/50	Clinicians are misled to continue the original treatment plan and miss the timely preemptive treatment, which result in potential patients more prone to hematologic relapse.	[4, 5, 9]
	A4	Negative	FP, 7/50	The pre-emptive ATO therapy will be taken and confirmed molecular relapse by a repeat sample within 2 to 4 weeks. Detection of RARA or ATO resistance mutation points.	[4, 9, 10, 24]
Follow-up	A5	Positive	FN, 6/50	Clinicians are misled to continue the original treatment plan and miss the timely preemptive treatment, which result in potential patients more prone to hematologic relapse.	[4, 5, 9]
	A6	Positive	FN, 1/50	Clinicians are misled to continue the original treatment plan and miss the timely preemptive treatment; the hematological relapse may have occurred.	[4, 5, 9]

the line, this result was not reliable and a repeat sample should be sent for test, especially for a negative result. Molecular relapse was defined as an increase of MRD level ≥ 1 log 10 between 2 positive samples in the patient who previously tested negative in technically adequate samples [13]. These clinically significant reporting elements are summarized in Table 3.

"Sample quality" and "Day-to-day sensitivity" were missing in clinical reports submitted by almost all medical laboratories. For molecular MRD monitoring in APL management, false-negative MRD results were more detrimental than false-positive results, because false-negative results made potential patients more prone to hematologic relapse for missing the timely pre-emptive therapy. Therefore, sample quality must be evaluated before confirming the molecular MRD monitoring results, which can reduce the risk of false-negative results MRD and provide accurate reports. The EAC/UK Clinical Molecular Genetics Society recommend the "Sample quality" must be evaluated for amplification of *ABL1* (at least 10^4 *ABL1* molecules per reaction volume) to verify RNA quality [11, 12, 14, 23]. Furthermore, the EAC/the European LeukemiaNet MRD Working Party recommend that the "day-to-day sensitivity" should be calculated to meet the detection limit of at least 10^{-3} for the particular assay to determine the reliability of the result obtained [11–14]. As shown in Fig. 2c, in the longitudinal MRD monitoring curve at follow-up (5), "MRD value" and "day-to-day sensitivity" curve overlapped, which can be visually observed above the "sample quality" curve. This suggested that the MRD result may be false-negative due to the suboptimal quality of extracted RNA (*ABL1* CN/test, $< 10^4$). At the same time, medical laboratories should further clarify "Diagnosis of MRD monitoring" (MRD result is not reliable and the false-negative result cannot be excluded), "Clinical interpretation" (because of the poor sample quality, the MRD result may lack precision and should be treated with caution), and "Further testing recommendations" (a repeat sample should be sent for testing). Based on the clinician-friendly reports for false-negative MRD result, clinicians had to quickly inform APL patients in follow-up to re-collect BM samples for *PML/RARA* detection, and confirm the actual MRD status, and take appropriate treatment measures as soon as possible.

When APL patients in CR_{MRD-} emerged the first time change in status of *PML/RARA* by RT-qPCR from negative to positive, clinicians will take pre-emptive ATO therapy and confirm molecular relapse by a repeat sample within 2 to 4 weeks [9, 24]. Cross-contamination or artificial sampling mistake between specimens can cause false-positive MRD results. Thus, the second positive MRD results should be considered carefully, especially in low copy number range, which results in patients receiving standard therapy for relapse. In order to judge conversing accuracy of MRD from negative to positive, the European LeukemiaNet MRD Working Party recommend that CT value of the patient sample should be within the valid range of *PML/RARA* standard curve to ensure the linearity measured at the measured MRD level, and molecular relapse should be diagnosed as MRD increases in the second samples ≥ 1 $\log_{10}$ [13]. The "linearity" and "limit of detection (LOD)" should be clarified in clinical reports. As shown in Fig. 2b, in longitudinal MRD monitoring curve at maintenance (4), the day-to-day sensitivity was lower than "sample quality" curve; MRD value was higher than the day-to-day sensitivity, but relatively increased < 1 than the first sample. When the linear range of RT-qPCR assay is 10^6~10^2, and the LOD is 10/test, the copy number of *PML/RARA* (3 copies/test) was lower than LOD, and which highly suspected due to aerosol or cross-contamination. Medical laboratories should further report "Diagnosis of MRD monitoring" (MRD result is not reliable and the false-positive result cannot be excluded), "Clinical interpretation" (the molecular relapse cannot be confirmed and should be treated with caution), and "Further testing recommendations" (a repeat sample should be sent for testing). Thus, clinicians should actively request medical laboratories to conduct sample review to eliminate the possibility of contamination and ensure the reliability of positive MRD results.

Clinician-friendly MRD monitoring reports should get more attention and improvement because the intuitive results and clinically important MRD-specific elements can provide a good description of the reliability and clinical significance of MRD results. Medical laboratories should improve and standardize clinical reports from the perspective of clinical practice, making the MRD report more conducive to the clinical decision-making. It not only identified time point of tissue sampling relative to treatment and ensured the reliability of the negative MRD results, but also gave a clear MRD diagnosis, clinical interpretation, and further recommendation.

Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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