Consensus on *BCR-ABL1* reporting in chronic myeloid leukaemia in the UK

Authors: Nicholas C.P. Cross,[1,2] Helen E. White,[2] Paul A.S. Evans,[3] Jeremy Hancock,[4] Mhairi Copland,[5] Dragana Milojkovic,[6] Joanne Mason,[7] Sandra Craine,[8] Adam J. Mead[9]

Affiliations: [1]University of Southampton, Southampton, United Kingdom, [2]Salisbury NHS Foundation Trust, Salisbury, United Kingdom, [3]HMDS, St James's Hospital, Leeds, United Kingdom, [4]Bristol Genetics Laboratory, Southmead Hospital, North Bristol NHS Trust, United Kingdom, [5]University of Glasgow, Paul O'Gorman Leukaemia Research Centre, Institute of Cancer Sciences, College of Medical Veterinary and Life Sciences, Glasgow, United Kingdom, [6]Hammersmith Hospital - Imperial College Healthcare NHS Trust, London, United Kingdom, [7]West Midlands Regional Genetics Laboratory, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom, [8]CML Patient Support Group, London, United Kingdom, [9]Oxford NIHR Biomedical Research Centre, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom

Correspondence:
Prof. Nicholas C.P. Cross
Wessex Regional Genetics Laboratory
Salisbury District Hospital
Salisbury SP2 8BJ
United Kingdom
Telephone: +44(0)1722429080
Fax: +44(0)1722331531
Email: ncpc@soton.ac.uk

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Summary

For patients with chronic myeloid leukaemia (CML), treatment guidelines recommend monitoring response to treatment with tyrosine kinase inhibitors (TKIs) by testing the *BCR-ABL1* fusion gene transcript level using reverse transcriptase quantitative polymerase chain reaction (RT-qPCR). Despite recent efforts to standardise protocols for *BCR-ABL1* testing, some variability remains among laboratories in the UK regarding the techniques used and the approach to reporting results. This increases the risk of misinterpretation of results by both clinicians and patients. An expert panel met to discuss current issues surrounding *BCR-ABL1* testing in the UK and to develop guidance for laboratories, with emphasis on the optimal approach to reporting laboratory results. Topics included the minimum required information to include in the laboratory report, units of measurement, test sensitivity, and *BCR-ABL1* transcript variants. To aid communication between laboratories and clinics, standard forms were generated that could be used by 1) clinics when submitting samples to laboratories, and 2) laboratories when reporting results to clinics. Standardising the way in which *BCR-ABL1* test results are reported from laboratories to clinics should help to improve communication, interpretation of results, and patient care.

Keywords: chronic myeloid leukaemia, *BCR-ABL1*, laboratory assay, laboratory report, United Kingdom

Introduction

Molecular testing for the fusion gene *BCR-ABL1* is the most sensitive routine test for monitoring response to therapy in patients with chronic myeloid leukaemia (CML) (Foroni *et al*, 2011). The technique requires reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) to estimate the amount of *BCR-ABL1* mRNA relative to an internal reference gene (typically *ABL1*, *GUSB*, or *BCR*) (Cross *et al*, 2015). Results are expressed on the International Scale (IS) as a percentage relative to the standardised baseline used in the pivotal IRIS trial, which evaluated the tyrosine kinase inhibitor (TKI) imatinib in patients with CML (Cross *et al,* 2015; Hughes *et al,* 2003; Hughes *et al,* 2006). *BCR-ABL1* testing is used to define molecular response (MR) to TKIs, and a major molecular response (MMR) is defined as a 3-log reduction from the standardised baseline (MR^3 or 0.1% *BCR-ABL*^{IS}) (Baccarani *et al,* 2013). Beyond MMR, deep molecular responses (DMRs) of MR^4, $MR^{4.5}$, and MR^5 are defined as ≤0.01%, ≤0.0032%, and ≤0.001% *BCR-ABL*^{IS}, respectively (Table I) (Cross *et al,* 2015).

As described in the current European LeukemiaNet (ELN) CML recommendations, regular ongoing *BCR-ABL1* testing provides essential information required to make timely important treatment decisions, such as whether to continue current TKI, or switch to a different TKI or alternative therapy (Baccarani *et al*, 2013). More recently, the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines have been updated to include recommendations on stopping TKI treatment in patients who have achieved a sustained DMR on TKI treatment, initiating a period of treatment-free remission (TFR) (Hochhaus *et al*, 2017; NCCN, 2017). The feasibility of TFR following achievement of DMR has been demonstrated in numerous clinical studies (reviewed in Saussele *et al,* 2016; Rea *et al,* 2017). However, across these studies, approximately 50% of patients had molecular recurrence (loss of MMR) during discontinuation and required TKI re-initiation. Patients who re-initiated treatment remained sensitive to TKI treatment, and re-achieved DMR in the majority of cases. Molecular recurrence generally occurred within 6 months following discontinuation, although more recent studies show later molecular recurrence continues to occur (Campiotti *et al,* 2017). Thus, while all CML patients on TKI treatment require ongoing regular *BCR-ABL1* monitoring, patients entering TFR require increased frequency of monitoring of *BCR-ABL1* levels (Hochhaus *et al,* 2017; NCCN, 2017). This will likely increase laboratory workload and highlights the need for fast and reliable *BCR-ABL1* test results that are effectively communicated between the laboratory and clinician.

To ensure accurate *BCR-ABL1* testing, laboratories should participate in standardisation and external quality assessment programmes, establish conversion factors or use calibrated kits for reporting on the IS, determine the variability of their assay at high and low levels of disease (Branford and Hughes, 2006; Branford *et al,* 2008), and validate that their assay is capable of detecting $MR^{4.5}$ in most patient samples. To assist accurate interpretation of *BCR-ABL1* results in the clinic, reports should be easily interpretable and use standardised definitions of MR (Cross *et al,* 2015). Despite efforts to standardise procedures (Foroni *et al,* 2011; Cross *et al,* 2015), some variability remains among laboratories in the UK regarding technique and reporting results of *BCR-ABL1* testing (Foroni *et al,* 2011), which underscores the need for further standardisation of protocols.

In June 2017, an expert panel met in London to discuss potential alignment on *BCR-ABL1* reporting in the UK. The purpose of the meeting was to develop guidance to support the accurate communication of *BCR-ABL1* molecular monitoring results from laboratories to clinics to enable optimal management of patients with CML. Topics for discussion included laboratory requirements for accurate *BCR-ABL1* reporting (such as use of standardised definitions to present results of *BCR-ABL*1^{IS}, $MR^{4.5}$, transcript type, etc.), frequency of testing, the minimum clinical information that a laboratory needs in order to provide results and accurate response interpretation, the minimum information that should be included in the laboratory report, and additional laboratory considerations for molecular monitoring requirements during TFR.

Laboratory requirements for providing an optimal report

According to the ELN CML recommendations, molecular testing to determine *BCR-ABL1* transcript level is recommended for patients with CML treated with TKIs to establish the level of response and to monitor changes over time (Baccarani *et al,* 2013). In addition, it may be useful to quantify *BCR-ABL1* levels prior to starting therapy to determine the velocity of response at 3 months, which can help identify patients at risk of treatment failure (Branford *et al,* 2014; Hanfstein *et al,* 2014).

Depending on local circumstances, patients can be monitored using molecular tests such as RT-qPCR or cytogenetic tests such as G-band analysis or fluorescence *in situ* hybridization (FISH), or both (Baccarani *et al,* 2013). When using molecular tests, it is recommended to use standardised sensitive assays capable of detecting $MR^{4.5}$ on the IS, since these allow for

accurate response monitoring during TKI treatment and during TFR. Furthermore, IS results are necessary for comparing patient results with the ELN recommendations and data from clinical trials.

Before initiating therapy, the *BCR-ABL1* transcript variant type should be determined in all patients so that molecular testing can target the correct subtype and false-negative results can be excluded (Foroni *et al,* 2011). Identification of the individual transcript type is also important as this may correlate with clinical outcome (Claudiani *et al,* 2017). Standard *BCR-ABL1* testing and reporting in IS units can only be applied reliably in patients with typical transcript variants (e13a2 and/or e14a2), which account for 97–98% of CML patients (Foroni *et al,* 2011). For patients with atypical variants, bespoke assays that target the correct variant can be used to monitor general trends in disease levels on treatment. This may be used to inform clinical management, but the results cannot be expressed on the IS. Since these patients with atypical variants are so rare, we consider that these bespoke monitoring assays should be carried out by specialised laboratories or ideally a single central laboratory. However it is essential that all laboratories should be able to detect atypical variants in patients before treatment, in order to provide faster and comprehensive in-house testing results.

For patients achieving TFR, molecular monitoring is a critical part of care to identify a potential loss of MR^3, necessitating restarting of TKI treatment. From the laboratory perspective, TFR presents many challenges: more frequent monitoring is required and the need for rapid results with a 2-week turnaround will likely increase laboratory workload. Patients entering TFR have very low or undetectable *BCR-ABL1* levels, and laboratories monitoring these patients must ensure that they are capable of detecting $MR^{4.5}$, using regular external or internal validation, and reporting on the IS to ensure DMR can be accurately monitored prior to and during TKI discontinuation. Due to the requirement for standardised results reported on the IS prior to and during TFR, treatment discontinuation is currently only recommended in patients with typical transcripts and where IS results are available (NCCN, 2017). In addition, regular monitoring of patients in long-term TFR will require careful coordination between the laboratory and haematologist/oncologist to ensure that reintroduction of treatment in the case of molecular recurrence can be started promptly.

BCR-ABL1 kinase domain point mutations reflect disease evolution and may be used to inform subsequent therapy (Soverini *et al,* 2011). Therefore, mutational analysis is recommended in case of disease progression, treatment failure, and for patients in the ELN ‘Warning’ response

category (Baccarani *et al,* 2013). According to the ELN recommendations, mutational analysis should be performed using Sanger sequencing until the clinical relevance of mutations detected with more sensitive techniques has become clear.

Frequency of monitoring

International treatment guidelines are generally consistent with regard to the frequency of *BCR-ABL1* testing when monitoring response to TKIs. The ELN recommends testing every 3 months until *BCR-ABL1* ≤0.1%^{IS} (MMR) is achieved and then every 3–6 months thereafter (Baccarani *et al,* 2013). In the American NCCN guidelines, testing is recommended at diagnosis, every 3 months after starting treatment until *BCR-ABL1* 0.1–1%^{IS} is achieved, then every 3 months for 2 years, and every 3–6 months thereafter (NCCN 2017).

The ELN CML recommendations include response categories (Optimal, Warning, and Failure) and monitoring frequency requirements for patients receiving TKIs as first-line (Table II) or second-line treatment in the case of failure to first line imatinib (Baccarani *et al,* 2013). If a patient falls in the 'Failure' category, they should initiate a different treatment (e.g. an alternative TKI or allogeneic stem cell transplant) in order to decrease the risk of disease progression and mortality. In addition, cytogenetic analysis of marrow cell metaphases, RT-qPCR, and, when appropriate, mutational analysis should be performed. In some cases, repeat testing on the same sample, if possible, may be required. If a test result is significantly different from the previous result, the test should be repeated within the laboratory before being reported. If the result remains significantly different, the clinician should be notified and arrangements should be made for the patient to return for repeat sampling. It should be noted that repeat sampling can cause anxiety in patients; efforts to minimise distress regarding repeat testing should be considered.

How to report: clinician to laboratory

Good communication among members of the multidisciplinary team is essential for supporting good communication between the clinician and patient, thus ensuring more effective disease management (Fig 1). This includes submitting sufficient clinical information with blood samples, and providing a comprehensive yet practical laboratory report. Currently, samples are often

submitted for *BCR-ABL1* testing without sufficient clinical information about the patient, leading to difficulty in providing an interpretative laboratory report (Claustres *et al,* 2014). Although providing brief clinical details with a *BCR-ABL1* test request can be challenging within the context of a busy clinic, this information is important to ensure good laboratory–clinician communication. To reduce workload, some laboratories have developed CML-specific online forms that clinicians can fill out when submitting samples, and this approach is encouraged. Ideally, the following clinical information should be submitted to the laboratory: TKI therapy and any recent known treatment interruptions (e.g. pregnancy, TFR, intolerance) and possible issues with treatment adherence. For patients who are being transferred between hospitals, *BCR-ABL1* transcript type and, in cases where resistance has been encountered, TK domain mutation status should be reported as well. Sample forms are shown in Fig 2 and Fig 3. Various aspects of the clinician's report are discussed in more detail below.

Clinical details

Accurate clinical details are essential in order to offer appropriate clinical guidance for patients receiving TKI therapy. Bespoke online request forms offer an attractive means to achieve this. Linked to a departmental laboratory information management system, patient demographics can be populated using the National Health Service (NHS) number following a patient's initial registration on the system, usually at diagnosis. Additional disease and treatment information can then be added using a simple drop-down menu each time the patient attends the clinic for molecular monitoring. Phase of disease, line of therapy, and current TKI usage can all be captured on the form, making informed clinical interpretation possible. Dose escalation, modification, and cessation of TKI can also be documented in a similar manner on the request form. If clinical details are not available, laboratory reports should clearly state that interpretation of the results according to ELN recommendations is not possible.

Therapy

Samples submitted for *BCR-ABL1* testing should include the line of therapy of TKI treatment, which is essential to provide ELN response category as part of the report, and should be included in the laboratory report whenever possible. Changes in treatment can influence the interpretation of results, and the laboratory should be informed of any significant changes to treatment, including switching to a different TKI, treatment interruptions, or discontinuation.

Timing of sample in relation to start of TKI therapy

If available, including the sample time point (e.g. 3 months after starting TKI) is essential for the interpretation of results. If this information is not provided with the sample, it may be found in electronic regional prescribing systems, if available.

Expert panel opinion:

- *Ideally, when submitting samples for* BCR-ABL1 *testing, clinicians should provide the following information: line of therapy, start date for current TKI, and any recent treatment interruptions (e.g. pregnancy, TFR)*
- *Laboratories should be informed of whether the patient is in TFR and date of treatment cessation as this can affect the frequency of monitoring*

How to report: laboratory to clinician

The following minimum required information should be included in the molecular genetics laboratory report: patient and physician information, test performed, test result and broad interpretation to help guide the final interpretation by the referring clinician, and any relevant supplemental information (Scheuner *et al,* 2012; Claustres *et al,* 2014). A sample laboratory report is shown in Fig 4, and examples of laboratory reports illustrating various clinical scenarios can be found in the Supplementary Appendix. Various aspects of the laboratory report are discussed in more detail below.

BCR-ABL1 *transcript variants*

As discussed above, the *BCR-ABL1* transcript variant type should be established at the time of diagnosis to determine the most appropriate method for monitoring changes in *BCR-ABL1* transcript level (Foroni *et al,* 2011). Variant type has important implications not only for testing protocols but also for treatment decisions. For example, stopping nilotinib in patients who have achieved sustained DMR is currently only recommended for patients with confirmed typical variants (i.e. e13a2 and e14a2) (Tasigna (Nilotinib) Summary of Product Characteristics 2017; Hochhaus *et al*, 2017; NCCN 2018). Therefore, the variant type should be included in the laboratory report, and atypical variants should be highlighted.

Cumulative timeline of BCR-ABL1 *transcript level*

A list or graph describing previous test results is strongly recommended to present results over time to allow the clinician to easily interpret the current result in the context of previous results. Ideally a graph should include some indication of the limit of detection of the assay and ELN response category. This interpretation would mandate the date of TKI initiation and line of therapy to be stated. Examples of such graphs are given in the Supplementary Appendix.

TK domain mutations

Ideally, a timeline graph should be generated indicating the time points at which mutation analysis was carried out, the type of mutation(s) present (using Human Genome Variation Society [HGVS] nomenclature; see http://varnomen.hgvs.org) and the time point at which each mutation was first detected, as well as the sensitivity of mutation detection, the level of the mutation, and a brief summary of whether it is likely to be sensitive or resistant to other TKIs.

Units

All laboratories should report results using the IS (Hughes *et al,* 2006). Unconverted results should only be included during a transition phase to IS, as routine reporting of unconverted results can lead to misinterpretation of ELN response by clinicians. At this time, not all laboratories in the UK report *BCR-ABL1* results using the IS, and some laboratories are currently transitioning to the IS system. If units other than IS are used, the laboratory report should state clearly that the results are not reported in IS. Transitioning requires good communication with clinicians and patients. It is essential that patients are adequately counselled about the change to IS, so that they are not unduly alarmed by a marked change in their test results.

Reference gene

The laboratory report should mention which reference gene (*ABL1*, *GUSB*, or *BCR*) was used.

Test sensitivity

For patients with undetectable *BCR-ABL1* levels, it is important to state the level at which *BCR-ABL1* is undetectable (e.g. MR^4 vs $MR^{4.5}$). In the laboratory report, placing the result in context by including standard levels of response (MMR, MR^4, $MR^{4.5}$) may aid clinicians. Efforts to establish confidence intervals are under way at individual laboratories, but there is no consensus on how to report this information at this time. Nevertheless, testing laboratories need to understand their measurement uncertainty at high and low *BCR-ABL1* levels (Branford and Hughes, 2006; Branford *et al,* 2008).

Technique used

Technical details, such as the level of sensitivity and methodology used, should also be included in the laboratory report.

Response status (MMR, MR^4, $MR^{4.5}$)

Laboratory reports should include both the actual *BCR-ABL1* result (e.g. 0.08%) and the corresponding response status (e.g. MMR) to aid in interpretation.

Response status according to ELN CML recommendations

The current ELN recommendations include 3 response categories (Optimal, Warning, and Failure) (Baccarani *et al,* 2013). In some cases, laboratories may not have access to sufficient clinical information to determine response status according to the ELN recommendations. If the information is available, interpretation of results according to the current ELN recommendations could be a useful addition to the laboratory report. As a minimum, a reference to the ELN recommendations for clinical interpretation should be provided on the report.

Suggestions for frequency of testing

Frequency of monitoring should be as per current ELN recommendations (see Table II). The laboratory should promptly notify the clinician and/or other members of the multidisciplinary team when there is a significant increase in *BCR-ABL1* level and/or when a change in monitoring frequency is required. What constitutes a significant change needs to be defined locally on the basis of the level of disease and the uncertainty of measurement of the assay used, but in general a 1-log increase or loss of MMR in a patient with previous stable MMR would be considered as a significant change. Any change reported as potentially significant should be confirmed before making any alterations to management, and the laboratory report should contain appropriate caveats plus a request for an urgent repeat sample. A laboratory may suggest a change in testing frequency, but it should be noted that the suggestion may be incorrect if the laboratory is provided with incomplete or inaccurate clinical information (see below).

Date of next test

Providing or suggesting a date for the next test may be useful but is considered optional, because the laboratory may not have sufficient clinical information to determine the date of the next test. If a patient misses a visit, it may be useful for laboratories to have standard procedures in place to alert the multidisciplinary team so that the patient can be contacted. While this is not normally the laboratory's responsibility, this could help ensure that patients are followed appropriately.

Expert panel opinion

The laboratory report should ideally include the following:

- *Transcript variant type*
- *Line of therapy*
- *Results reported in IS only*
  - *If units other than IS are currently used, it should be clearly stated in the laboratory report that results are not reported in IS*
  - *Unconverted results should only be included during a transition phase to IS*
- *Reference gene used* (ABL1, GUSB, *or* BCR)
- *Technical details, such as the level of sensitivity*
- *Both the actual* BCR-ABL1 *result (e.g. 0.08%) and the corresponding response status (e.g. MMR)*
  - *Laboratory results should be interpreted in the context of prior results, response status, and clinical circumstances*
  - *Results should be interpreted according to the current ELN recommendations*
- *The laboratory should promptly notify the clinician and/or multidisciplinary team when there is a marked change in* BCR-ABL1 *level and/or when a change in monitoring frequency is required. What constitutes a 'marked' change needs to be defined locally on the basis of the level of disease and the measured variation of the essay used, but in general a 1-log increase or loss of MMR would be considered as a marked change*
  - *Changes to monitoring frequency should be finalised after the laboratory has consulted with the treating haematologist/oncologist; this is usually determined by the clinician rather than the laboratory*

If available, the laboratory report could also include the following:

- *Mutation status and the time at which the mutation was first detected (including details of TKI sensitivity)*
- *Timing of the test in relation to the start of TKI (e.g. 3 months after start of TKI)*
- *A list or graph describing previous* BCR-ABL1 *test results is strongly recommended*
- *Suggesting a date for the next test is considered optional*

How to report: patient-directed communication

Increasingly, patients have access to laboratory results, and complex or poorly worded reports can lead to unnecessary alarm and confusion. The UK government has made a commitment that patient clinical records will be digitalised and accessible to patients and healthcare providers in real time by 2020.

If reports are being sent to the patient, these should contain the most important information only, such as the *BCR-ABL1* level and whether the level has increased, decreased, or remained stable since the last test, as shown in Fig 5. Their current test result should be contextualised by including their two previous *BCR-ABL1* testing results. It would also be important to indicate to patients if the sample had been a technical failure or not, if a result cannot be given. A comment could be added to the report that the patient should contact their clinician if they have a concern about their test results.

Expert panel opinion:

- *If reports are being sent to the patient, these should include only the most relevant information, such as the* BCR-ABL1 *level and whether the level has significantly increased or decreased, contextualised by including at least 2 previous test results*

Concluding remarks

The remarkable improvements in outcomes observed in patients with CML in recent years have occurred in tandem with advances in molecular monitoring of the disease. However, considerable variability persists among laboratories in the UK regarding testing methods and reporting results for *BCR-ABL1* transcript levels. This consensus report provides a framework for developing a more standardised approach to presenting *BCR-ABL1* results. This will hopefully encourage greater uniformity across laboratories in the UK and support the accurate translation of results from laboratory to clinic, which is essential for the delivery of optimal CML patient care and disease management.

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Table I. Molecular response in patients with CML: *BCR-ABL1* transcript levels according to the International Scale (Cross *et al,* 2015; Baccarani *et al,* 2014)

***BCR-ABL*^{IS}, %**	**Log reduction from standardised baseline**	**MR category**	**Minimum number of *ABL1* transcripts**
100	0	-	-
≤0.1	3	MR^3 (MMR)	>10,000
≤0.01	4	MR^4	10,000−31,999
≤0.0032	4.5	$MR^{4.5}$	32,000−99,999
≤0.001	5	MR^5	≥100,000

CML, chronic myeloid leukaemia; MMR, major molecular response; MR, molecular response

Table II . ELN response criteria and recommended monitoring frequency in first-line treatment of CML* (Baccarani *et al,* 2013)

<table>
<tr><th rowspan="3">Time since start of TKI treatment</th><th colspan="6">ELN Response Category</th></tr>
<tr><th colspan="2">Optimal</th><th colspan="2">Warning</th><th colspan="2">Failure</th></tr>
<tr><th>Response criteria</th><th>Monitoring</th><th>Response criteria</th><th>Monitoring</th><th>Response criteria</th><th>Monitoring</th></tr>
<tr><td>Baseline</td><td>NA</td><td>CBA, Qualitative PCR</td><td>High risk or CCA/Ph$^+$, major route</td><td>CBA, Qualitative PCR</td><td>NA</td><td>CBA, Qualitative PCR</td></tr>
<tr><td>3 months</td><td>BCR-ABL1 ≤10% and/or Ph$^+$ ≤35%</td><td rowspan="4">RT-qPCR every 3 months until MMR, then every 3–6 months and/or CBA at 3, 6, and 12 months until CCyR, then FISH</td><td>BCR-ABL1 >10% and/or Ph$^+$ 36–95%</td><td rowspan="4">Molecular/Cytogenetic tests to be performed more frequently (up to monthly)**</td><td>No-CHR and/or Ph$^+$ >95%</td><td rowspan="4">RT-qPCR, mutational analysis, and CBA should be performed. Immunophenotyping in blastic phase.</td></tr>
<tr><td>6 months</td><td>BCR-ABL1 <1% and/or Ph$^+$ 0</td><td>BCR-ABL1 1–10% and/or Ph$^+$ 1–35%</td><td>BCR-ABL1 >10% and/or Ph$^+$ >35%</td></tr>
<tr><td>12 months</td><td>BCR-ABL1 ≤0.1%</td><td>BCR-ABL1 >0.1–1%</td><td>BCR-ABL1 >1% and/or Ph$^+$ >0</td></tr>
<tr><td>≥12 months</td><td>BCR-ABL1 ≤0.1%</td><td>CCA/Ph$^-$ (–7, or 7q$^-$)</td><td>Loss of CHR, Loss of CCyR, confirmed loss of MMR***</td></tr>
</table>

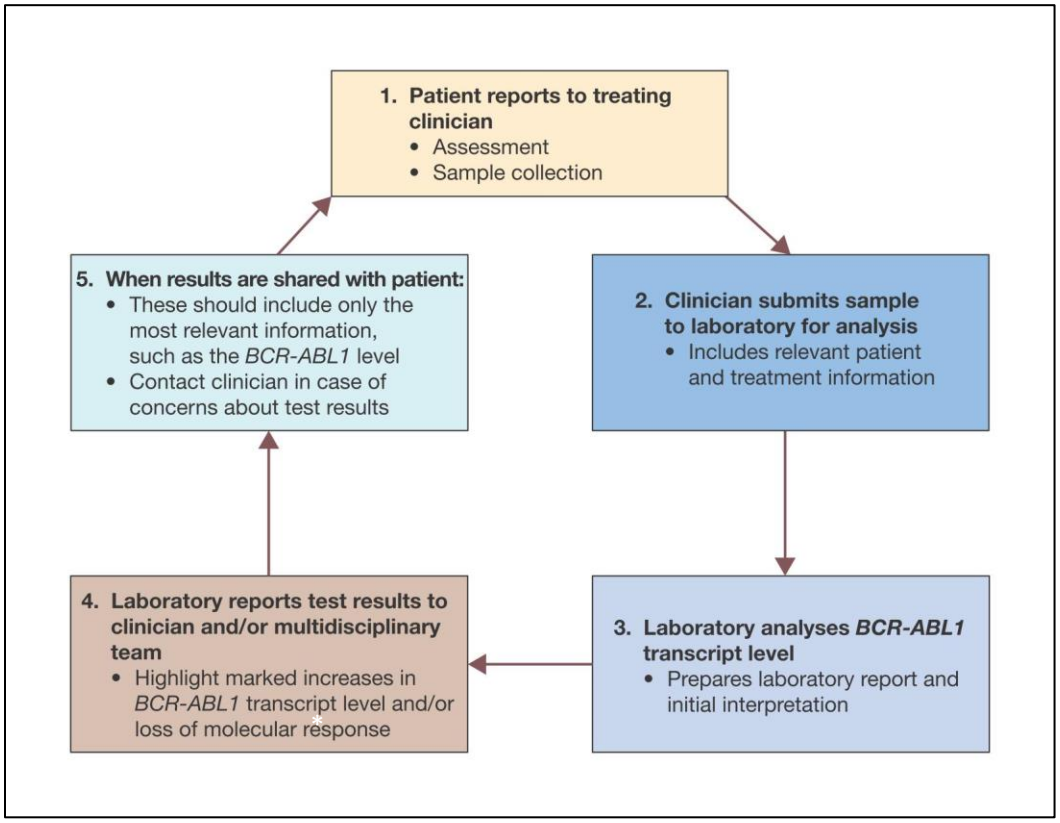
CBA, chromosome banding analysis of marrow cell metaphases; CCA/Ph$^+$, clonal chromosome abnormalities in Philadelphia chromosome-positive cells; CCA/Ph$^-$, clonal chromosome abnormalities in Philadelphia chromosome-negative cells; CCyR, complete cytogenetic response; CHR, complete haematological response; CML, chronic myeloid leukaemia; ELN, European LeukemiaNet; FISH, fluorescence *in situ* hybridisation; MMR, major molecular response; NA, not applicable; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; RT-qPCR, reverse transcriptase quantitative polymerase chain reaction

* The definitions are the same for patients in CP, AP, and BP and apply also to second-line treatment, when first-line treatment was changed for intolerance.

** CBA recommended in case of myelodysplasia or CCA/Ph- with chromosome 7 involvement.

***In two consecutive tests of which one is with a *BCR-ABL1* transcript level of ≥1%.

Fig 1. Patterns of communication among the CML healthcare team regarding *BCR-ABL1* testing.



CML, chronic myeloid leukaemia

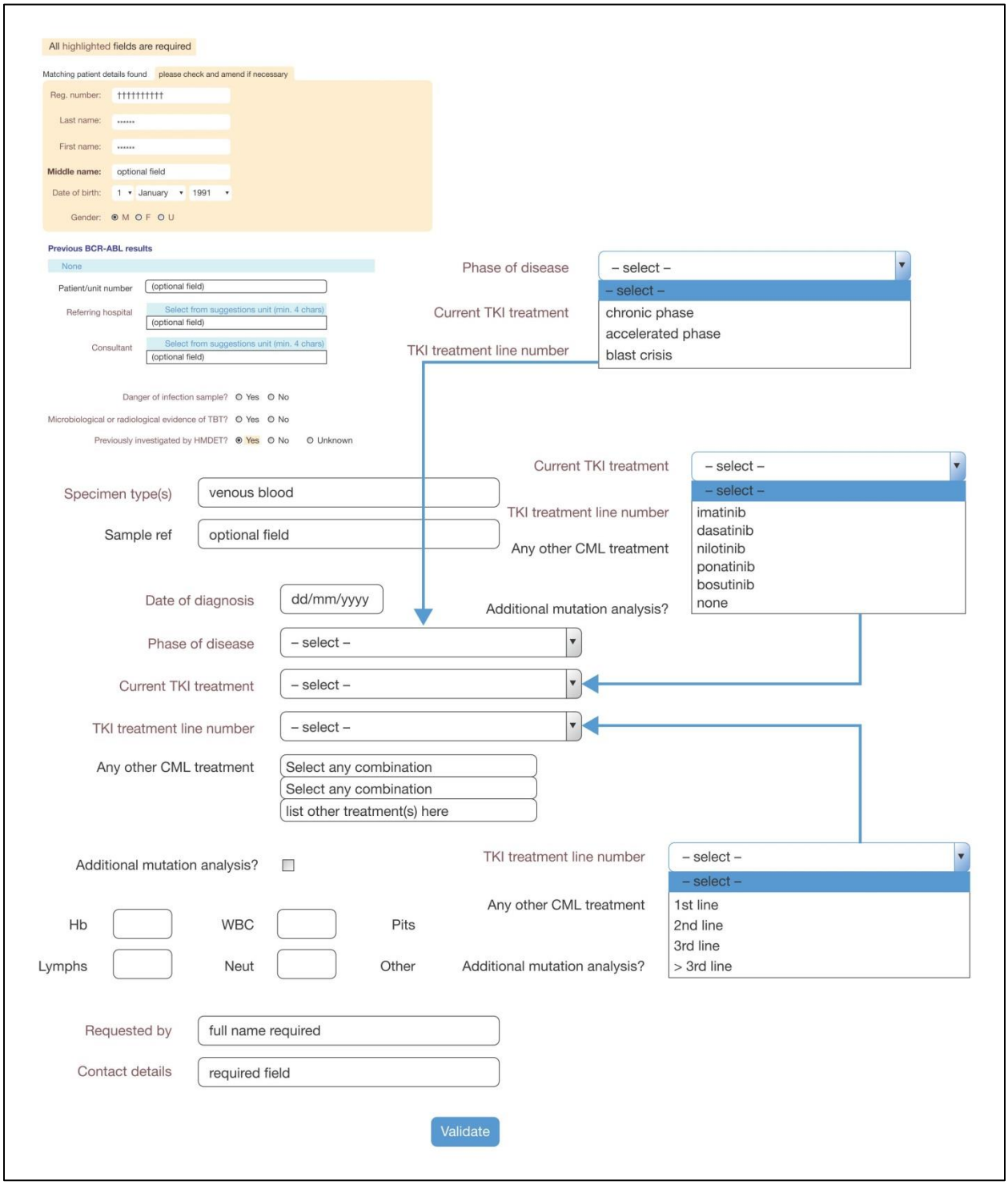
*Multidisciplinary team: including pharmacy.

Fig 2. Information to accompany samples submitted for *BCR-ABL1* testing.

Physician name_____ Hospital/Clinic_____ Contact information (telephone, email)_____
Sample collection date_____ Sample type_____
If available, attach patient-specific label Patient name_____ Gender_____ Date of birth_____ NHS number_____ Hospital number_____ PLEASE NOTE THAT THREE IDENTIFIERS ARE NEEDED ON THE FORM AND LABEL OR THE SAMPLE WILL BE DISCARDED
Current TKI therapy and dose_____ Start date of current TKI_____ Current line of TKI therapy_____
Is the patient in treatment-free remission? □Yes □No Start date of treatment-free remission_____
Mutation status (if known)_____
Other relevant information_____

NHS, National Health Service; TKI, tyrosine kinase inhibitor

Fig 3. Online request form for *BCR-ABL1* testing.



CML, chronic myeloid leukaemia; Hb, haemoglobin; Lymphs, lymphocytes; Neut, neutrophils; Plts, platelets; TKI, tyrosine kinase inhibitor; WBC, white blood cell

Fig 4. Standard laboratory report for *BCR-ABL1* testing [Adapted from Claustres *et al*, 2014].

[Laboratory logo]	[Laboratory header]	[Accreditation logo]
Report to: Physician name Clinic Contact information		Laboratory name Contact information Contact person Clinical lead
Patient name Date of birth ID number		Sample type Sample date Report date
Referral reason: [patient background, disease history, TKI treatment, line of therapy, duration of current TKI therapy, mutation status]		
***BCR-ABL1* ANALYSIS**		
Test [specific test/method]		**Result** **[*BCR-ABL*^{IS}, %]**
Interpretation: • Response status (MR level) and level of sensitivity • ELN 2013 guideline status (Optimal, Warning, Failure) • Trends over time (graph) with interpretation whether current result is significantly different to the previous • Suggestions for monitoring frequency/date of next test		
Additional information: • Explanation of International Scale • Explanation of MR levels • Explanation of ELN 2013 guideline response levels		

CML, chronic myeloid leukaemia; ELN, European LeukemiaNet; MR, molecular response; TKI, tyrosine kinase inhibitor

Fig 5. Standard patient-directed report of *BCR-ABL1* testing results.

Physician name _____

Hospital/Clinic _____

Contact information (telephone, email) _____

Patient name _____

Gender _____

Date of birth _____

Current test result:

Date: _____

Your *BCR-ABL1* level, as measured on the International Scale, is _____%.

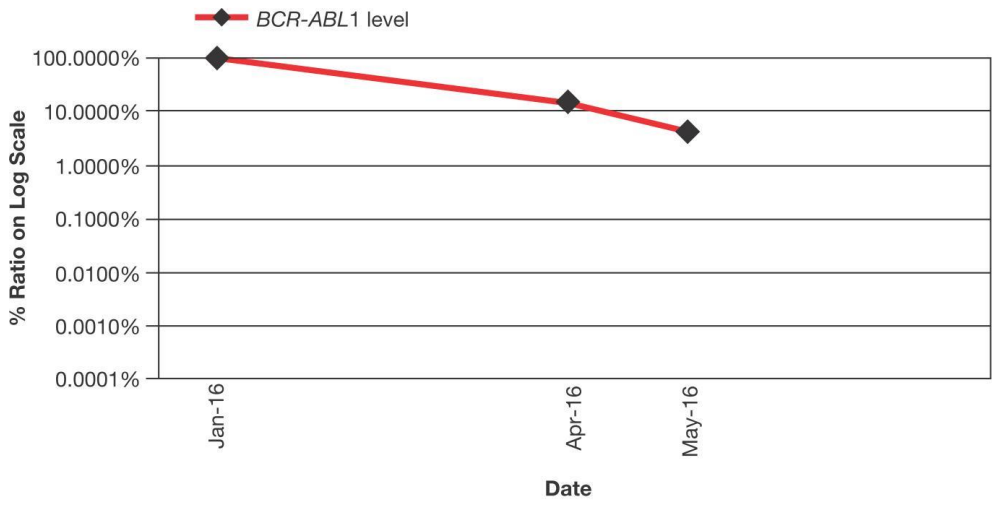
Your *BCR-ABL1* level has _____ [increased / decreased / remained stable] since your last test on _____ [date].

Please contact your doctor if you have any questions or concerns about this test result.

Previous test results:

On _____ [date], your *BCR-ABL1* level was _____%.

On _____ [date], your *BCR-ABL1* level was _____%.



Supplementary Appendix

Summary table

The result for the sample under investigation should be summarised in a table including the following:

- Treatment response based on response categories defined by the ELN recommendations (i.e. Optimal, Warning, and Failure) (Baccarani *et al,* 2013). If clinical details are not available, this interpretation is not possible and this should be clearly stated on the report
- *BCR-ABL1*:*ABL1* ratio on IS
- MR level
- Date of next sample due – suggesting a date when the next sample is due may be useful but is considered optional since this is dependent upon the laboratory receiving sufficient clinical information to enable it to do so. The suggested date could be replaced with the phrase '*As clinically required'*

The summary table included can be easily adapted to accommodate testing for TFR, treatment dose adjustments or modifications, and monitoring after BMT (bone marrow transplant) monitoring by removing the treatment response based on the ELN recommendations and replacing it with TFR, treatment dose adjustments or modifications, or post-BMT monitoring.

Reporting statements

The following reporting statements can also be included:

- This patient shows a warning response to first-line TKI therapy following 3 months of treatment according to the ELN recommendations (Baccarani *et al,* 2013)
- In view of the continued ELN warning response to TKI therapy, *ABL1* kinase domain mutational analysis will be performed on this sample or should be considered for this patient. Discussion at the multidisciplinary team (MDT) is recommended
- This patient may be being monitored too frequently (7 samples within the past 12 months). ELN 2013 recommendations include RT-qPCR monitoring every 3–6 months for patients on standard-dose therapy

- Please note we were unable to confirm the presence of a p210 e13a2 or e14a2 breakpoint in this patient at presentation. Rarer breakpoints are not detectable using our RT-qPCR assay and this will lead to a false-negative result on follow-up. Please contact the laboratory if you would like us to forward the sample to another centre that is able to detect atypical *BCR-ABL1* fusions
- Although achieving a complete cytogenetic response following XX months of TKI therapy, this patient has not yet achieved an MMR. Please continue to monitor by RT-qPCR at 3-monthly intervals
- This patient shows a warning response to imatinib therapy following XX months of treatment according to the ELN recommendations (Baccarani *et al,* 2013). Discussion at the MDT is recommended
- This patient shows a warning response to second-generation TKI therapy following XX months of treatment according to the ELN recommendations (Baccarani *et al.* 2013). However, a single RT-qPCR result showing change should always be treated with caution and confirmed by analysis of another sample
- The significance of this result should be treated with caution until any genuine trend is confirmed by RT-qPCR of a subsequent sample
- At low levels of minimal residual disease, variation inherent in the technique can lead to apparent differences in the reported ratios even when the underlying level of disease is stable
- Minor fluctuations in the *BCR-ABL1:ABL1* ratios when disease levels are low may reflect variation inherent in the RT-qPCR technique, rather than changes in disease status

Notes and references

Laboratories should consider including the following notes and references as supplementary data in the report to detail the methodology used and the best-practice guidelines used for interpretation and reporting:

Notes

- This laboratory is a CPA/ISO15189 accredited laboratory (reference number) and participates in the UKNEQAS LI EQA programme for *BCR-ABL1* quantitation and the pilot scheme for AKD mutation testing
- *BCR-ABL1* RT-qPCR monitoring is reported on the IS
- Superimposed *BCR-ABL1:ABL1* and sensitivity plots do not reflect level of disease but indicate a negative result at that level of sensitivity
- The target sensitivity of the assay is $MR^{4.5}$ in most samples
- Quantitative testing for the common *BCR-ABL1* fusion transcripts associated with CML was carried out using RT-qPCR on the Applied Biosystems 7500 real-time PCR system using the Europe Against Cancer probes and primers described in Gabert *et al*, 2003

References

1. Baccarani *et al*, European LeukemiaNet Recommendations for the management of chronic myeloid leukemia (CML). Update 2013. Blood (2013) 122, 872-884.
2. Cross *et al*, Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. Leukemia (2015) 29, 999-1003.
3. Foroni *et al*, Guidelines for the measurement of *BCR-ABL1* transcripts in chronic myeloid leukaemia. British Journal of Haematology (2011) 153, 179-190.
4. Gabert *et al.,* Standardization and quality control studies of 'real-time' quantitative reverse transcriptase polymerase chain reaction of fusion gene transcripts for residual disease detection in leukemia – A Europe Against Cancer Program. Leukaemia (2003) 17, 2318-2357.

Supplemental Fig 1. Example laboratory report for treatment response: optimal.

Genetics Report

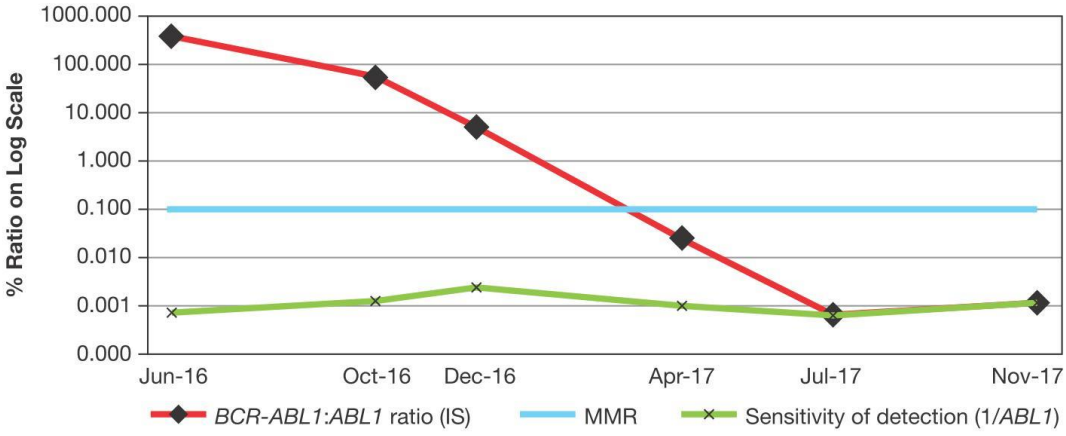
Patient details:	**Sample details:**

Clinical Summary: CML on imatinib for 18 months. For *BCR-ABL1* monitoring by RT-qPCR.

***BCR-ABL1* quantitative PCR (RT-qPCR) monitoring report (transcript type = e13a2/e14a2)**

Treatment response	*BCR-ABL1*:*ABL1* % ratio on IS	MR level	Date next sample due
Optimal	Undetectable	$MR^{4,5}$	May 2018

Level of *BCR-ABL1* normalised to *ABL1* on the International Scale (IS)



Reported by: Authorised by:

Laboratory Number (Sample Type)	Date received	Copies of *BCR-ABL1*	Copies of *ABL1*	*BCR-ABL1*: *ABL1* ratio (IS)	*BCR-ABL1*: *ABL1* ratio on IS (%)	Sensitivity of detection (*1/ABL1*)	Molecular Response (MR)
	23/06/2016	360,000	137,000	3.664	366.35	0.000007	
	04/10/2016	31,000	79,000	0.543	54.32	0.000013	#NA
	06/12/2016	1,500	41,000	0.052	5.22	0.000025	MR^{1}
	19/04/2017	15	96,000	0.0002	0.023	0.000010	MR^{3}
	26/07/2017	0	146,000			0.000007	MR^{5}
	15/11/2017	0	82,000			0.000012	$MR^{4,5}$

Supplemental Fig 2. Example laboratory report for treatment response: warning.

Genetics Report

Patient details:	**Sample details:**

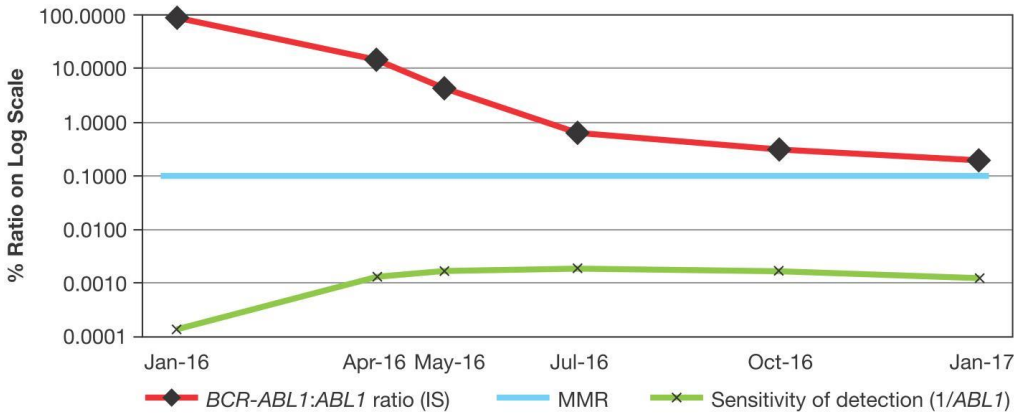
Clinical Summary: CML on imatinib for 18 months. For *BCR-ABL1* monitoring by RT-qPCR.

***BCR-ABL1* quantitative PCR (RT-qPCR) monitoring report (transcript type = e13a2/e14a2)**

Treatment response	*BCR-ABL1*:*ABL1* % ratio on IS	MR level	Date next sample due
Warning	0.1910	MR[2]	April 2017

Please note that this result could signify a resistance to treatment that may be due to an acquired mutation in the *ABL1* kinase domain (AKD) of the *BCR-ABL1* fusion gene and therefore AKD mutation testing is recommended.
Please notify the laboratory if AKD testing is required on the current sample.

Level of *BCR-ABL1* normalised to *ABL1* on the International Scale (IS)



Reported by: Authorised by:

Laboratory Number (Sample Type)	Date received	Copies of *BCR-ABL1*	Copies of *ABL1*	*BCR-ABL1*: *ABL1* ratio (IS)	*BCR-ABL1*: *ABL1* ratio on IS (%)	Sensitivity of detection (*1/ABL1*)	Molecular Response (MR)
	27/01/2016	478,000	726,000	0.922	92.20	0.000001	#NA
	18/04/2016	7,900	78,000	0.142	14.17	0.000013	#NA
	09/05/2016	1,900	61,000	0.044	4.38	0.000017	MR[1]
	21/07/2016	240	53,000	0.006	0.64	0.000019	MR[2]
	21/10/2016	140	62,000	0.003	0.32	0.000016	MR[2]
	19/01/2017	110	84,000	0.002	0.19	0.000012	MR[2]

Supplemental Fig 3. Example laboratory report for treatment response: failure.

Genetics Report

Patient details:	**Sample details:**

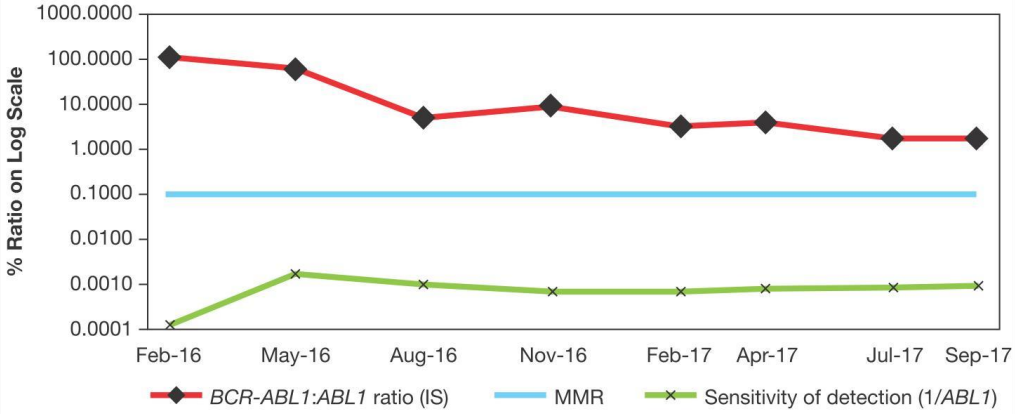
Clinical Summary: CML on imatinib for 18 months. For *BCR-ABL1* monitoring by RT-qPCR.

***BCR-ABL1* quantitative PCR (RT-qPCR) monitoring report (transcript type = e13a2/e14a2)**

Treatment response	*BCR-ABL1*:*ABL1* % ratio on IS	MR level	Date next sample due
Failure	1.6905	MR[1]	As clinically required

Please note that this result could signify a resistance to treatment that may be due to an acquired mutation in the *ABL1* kinase domain (AKD) of the *BCR-ABL1* fusion gene and therefore AKD mutation testing should be considered.
Please notify the laboratory if AKD testing is required on the current sample.

Level of *BCR:ABL1* normalised to *ABL1* on the International Scale (IS)



Reported by: Authorised by:

Laboratory Number (Sample Type)	Date received	Copies of *BCR-ABL1*	Copies of *ABL1*	*BCR-ABL1*: *ABL1* ratio (IS)	*BCR-ABL1*: *ABL1* ratio on IS (%)	Sensitivity of detection (*1/ABL1*)	Molecular Response (MR)
	17/02/2016	660,000	784,000	1.178	117.84	0.000001	
	16/05/2016	25,000	55,000	0.634	64.43	0.000018	#NA
	04/08/2016	3,500	94,000	0.052	5.24	0.000011	MR[1]
	28/11/2016	8,300	137,000	0.085	8.51	0.000007	MR[1]
	12/02/2017	3,200	140,000	0.032	3.17	0.000007	MR[1]
	13/04/2017	4,000	120,000	0.047	4.67	0.000008	MR[1]
	25/07/2017	1,200	106,000	0.016	1.59	0.000009	MR[1]
	06/09/2017	1,200	99,000	0.017	1.69	0.000010	MR[1]

Supplemental Fig 4. Example laboratory report for treatment switch and ABL kinase domain mutation.

Genetics Report

Patient details:

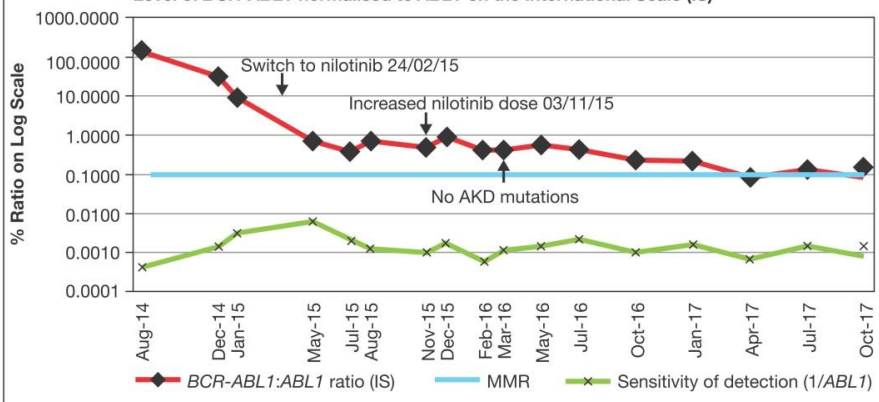
Sample details:

Clinical Summary: CML on second-line nilotinib for 2 years and 8 months. For *BCR-ABL1* monitoring by RT-qPCR.

***BCR-ABL1* quantitative PCR (RT-qPCR) monitoring report (transcript type = e13a2/e14a2)**

Treatment response	*BCR-ABL1:ABL1* % ratio on IS	MR level	Date next sample due
Optimal	0.080	MR[3]	January 2018

Level of *BCR-ABL1* normalised to *ABL1* on the International Scale (IS)



Reported by: Authorised by:

Laboratory Number (Sample Type)	Date received	Copies of *BCR-ABL1*	Copies of *ABL1*	*BCR-ABL1*: *ABL1* ratio (IS)	*BCR-ABL1*: *ABL1* ratio on IS (%)	Sensitivity of detection (*1/ABL1*)	Molecular Response (MR)
	28/08/2014	242,000	233,000	1.458	145.81	0.000004	--
	02/12/2014	15,000	69,000	0.296	29.61	0.000014	--
	20/01/2015	2,200	32,000	0.094	9.44	0.000031	MR[1]
	20/05/2015	180	36,000	0.007	0.70	0.000063	MR[2]
	21/07/2015	134	50,000	0.004	0.38	0.000020	MR[2]
	18/08/2015	377	79,000	0.007	0.66	0.000013	MR[2]
	03/11/2015	373	97,000	0.005	0.54	0.000010	MR[2]
	15/12/2015	326	59,000	0.008	0.77	0.000017	MR[2]
	16/02/2016	499	174,000	0.004	0.40	0.000006	MR[2]
	15/03/2016	257	87,000	0.004	0.41	0.000011	MR[2]
	17/05/2016	227	59,000	0.005	0.53	0.000015	MR[2]
	19/07/2016	136	46,000	0.004	0.42	0.000022	MR[2]
	04/10/2016	168	100,000	0.002	0.24	0.000010	MR[2]
	17/01/2017	91	63,000	0.002	0.20	0.000016	MR[2]
	04/04/2017	91	149,000	0.001	0.09	0.000007	MR[3]
	18/07/2017	67	70,000	0.001	0.13	0.000014	MR[2]
	17/10/2017	72	126,000	0.001	0.08	0.000008	MR[3]