

- Title** Assessment of BCR-ABL fusion gene testing or quantification using RT-PCR in the diagnosis and therapeutic follow-up of chronic myeloid leukaemias and acute lymphoblastic leukaemias
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### Aim

The BCR-ABL fusion gene, also called the Philadelphia gene or chromosome Ph1, is the result of a reciprocal translocation between chromosomes 9 and 22. The BCR-ABL fusion gene codes for a fusion protein with a deregulated tyrosine kinase activity, which activates various mechanisms involved in cell multiplication.

The BCR-ABL fusion gene is present in all chronic myeloid leukaemias (CML), 3 to 5% of acute lymphoblastic leukaemias (ALL) in children and between 15 to 30% of ALL in adults. Therefore, routine testing is done when CML or ALL is suspected.

The BCR-ABL fusion gene is evidenced by cytogenetics (karyotype), molecular cytogenetics (FISH), or by RT-PCR. BCR-ABL fusion transcript can also be quantified by quantitative PCR (RT-qPCR).

Currently, only BCR-ABL fusion gene testing is included in the list of the laboratory medicine procedures reimbursement by the health insurance system in France (NABM). BCR-ABL transcript testing by molecular biology is included in the additional list of laboratory medicine and anatomo-cytopathology procedures outside of the nomenclature.

HAS has taken the initiative to assess the relevance of BCR-ABL gene transcript testing or quantification using RT-PCR, to define the methods and the conditions under which it should be performed, with a view to its inclusion in the NABM.

The aim of this work was:

- to assess the clinical utility of RT-PCR: (i) for testing for BCR-ABL fusion transcripts as part of the initial diagnosis of CML and ALL, (ii) for quantification of BCR-ABL fusion transcript as part of the therapeutic follow-up and to define the conditions for it;
- to establish the place of BCR-ABL fusion transcript testing and quantification using RT-PCR in the health care management strategy;
- to assess the conditions for performing the RT-PCR used for BCR-ABL fusion transcript testing or quantification.

### Conclusions and results

The data thus collected and analysed allow the following conclusions:

- BCR-ABL fusion transcript testing using RT-PCR is indicated for the initial diagnosis of CML and ALL;
- BCR-ABL fusion transcript quantification using RT-qPCR is indicated for the follow-up of patients treated with tyrosine kinase inhibitors (TKIs). The first quantification of BCR-ABL fusion transcript using RT-qPCR should be done once the diagnosis is confirmed and serve as a starting point for therapeutic follow-up.  
Performing an RT-qPCR every three months is indicated as part of follow-up. Note that these intervals may be extended to six months if a sustained major molecular response is obtained. Conversely, these intervals may be shortened to four to six weeks in case of discontinuation of treatment.
- no preference between RT-PCR and cytogenetics is possible; each technique provides clinical utility in the health care management strategy.

Finally, considering the significant decrease achieved with RT-PCR, the conditions for performance are well established in France, in particular through laboratory accreditation requirements and standard ISO 15189. Note that a Group of Molecular Biologists for Haematological Malignancies (GBMHM) has been formed. This network was selected as part of a call for tenders organised by the National Cancer Institute (INCa) in collaboration with the French National Agency for Medicines and Health Products Safety (ANSM) in 2011; it regularly organises external quality assessment campaigns in France.

### Methods

The method first involved a critical analysis of the synthetic literature identified through a systematic literature search covering the period 2012-2017. Eight good practice guidelines, two expert consensus reports and one chronic condition guide were selected for analysis. No technology assessment reports, meta-analyses or systematic reviews were identified at the end of this literature search. HAS carried out a supplemental analysis of TKI development

studies to assess the role of RT-qPCR in therapeutic follow-up; this supplemental search identified five references. Finally, the justified positions of the National Professional Council of Haematology and the INCa were collected via a questionnaire.

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