Analytical and economic evaluation of the fully automated Xpert BCR-ABL assay from Cepheid

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Talk outline

- Chronic myeloid leukemia
  - Genetic bases, Treatment and Monitoring
- Xpert BCR-ABL Monitor™ assay by Cepheid
  - Fully automated cartridge-based microfluidic system
- Performance and suitability evaluation
  - Inter-lab reproducibility
  - Alignment onto the International Scale (IS)
- Economic evaluation
  - Costs evaluation
  - Impact of annual volume activity on costs
- Xpert BCR-ABL Evolutions since 2008

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Chronic Myeloid Leukemia (CML)

Adapted from Jamieson CHM, Cancer Cell Dec. 2004:531

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Morphological and genetic features

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Molecular consequence of the t(9;22)

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA. Adapted from Faderl et al. Blood, 91:3995, 1998
Oncogenicity of BCR-ABL in haematopoietic cells

Genetic instability

Programmed cell death inhibition

Alteration of adhesion properties

Mitogenic stimulation

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Inhibition of BCR-ABL1 Tyrosine Kinase activity

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
IRIS Imatinib arm:
overall survival at 96 months

93% (death associated with CML only)

85%


Hehlmann et al. Blood 1993; 82: 398

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Molecular monitoring of CML therapy

- **Recommended for patients in CCyR**, every 3 mths until MMR has been achieved, then at least every 6 mths (ELN recommendations)
- **Expected increase in patients in CCyR with 2\(^{nd}\) generation TKI**: 96% (nilotinib) versus 45% (imatinib) at 6 months
- Unavoidable for considering **treatment interruptions**
- Recent data suggesting a high prognostic value for **early measurement** of BCR-ABL1 at 3 or 6 months
  - We will definitely face an increased demand for molecular monitoring
  - Should we move to an automated monitoring solution?

References:
- Baccarani M et al., J Clin Oncol 2009, 27:6041-6051
- Cortes J et al., JCO 2010, 28:392-397
Xpert BCR-ABL Monitor ™

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Fully automated, on demand, evolving system

Packaging Concepts

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
**Storyboard – Version 1**

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
GeneXpert

**Nested PCR Amplification**

**Reverse Transcription**

**RNA extraction**

**Patient sample**

**Résults**

- All steps enclosed in the cartridge, no risk of contamination, no need for a specialised laboratory

ABL is the endogenous control, and also serves as a sample prep/sample adequacy control

*Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.*
Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Probe Check Control (PCC)

Probe hybridized to target sequence

Heat conformation

Temp < Tm → Temp > Tm

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Software Analysis: positive result
2008 version

Test $\Delta Ct = 15 - 23 = -8$

Ratio BCR-ABL/ABL = 1.95 \((-8)\) = 0.0048

% Ratio BCR-ABL/ABL = 0.0048 x 100 = 0.48%

Result: “Positive for BCR-ABL. %BCR-ABL/ABL = 0.48%”
Best quality sample
ABL Ct = 12
Test ΔCt = 12–32 = 20
Ratio BCR-ABL/ABL = 1.95 \(^{\text{-20}}\) = 0.0000016
% Ratio BCR-ABL/ABL = \times 100 = 0.00016%

Result: “BCR-ABL not detectable at a detection limit of 0.00016%"

Worst quality sample
ABL Ct = 18
Test ΔCt = 18–32 = 14
Ratio BCR-ABL/ABL = 1.95 \(^{\text{-14}}\) = 0.000086
% Ratio BCR-ABL/ABL = \times 100 = 0.0086%

Result: “BCR-ABL not detectable at a detection limit of 0.0086%”
Results Reporting

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Xpert BCR-ABL Monitor™ summary

- Fully automated solution
- Adaptable to all test volume
- Random access
- 2 min hands on time, 2.5 hours TAT
- Internal control and extraction control included
- LOD in between 0.01% and 0.0001%
- Automated analysis and report, LIS connectivity

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Cartridge-based automated BCR-ABL1 mRNA quantification: solving the issues of standardization, at what cost?

Jean-Michel Cayuela,1,2,3 Elizabeth Macintyre,4 Meryl Darlington,4 Raouf Ben Abdelali,4 Xavier Fund,4 Patrick Villarese,4 Michel Tulliez,5 Emmanuel Raffoux,6 François Sigaux,5,6 Delphine Rea,5,7 and Valerie Seror8

Study design

- 181 samples from TKI treated CML patients
  - 63 included in a pre-test phase, oct. 2006 – sept. 2007
  - 118 included in the test phase, oct. 2007 – jan. 2008
  - 14 mL of EDTA blood, stored and shipped at RT

- 3 Laboratories, A, B and C
  - Non automated assay highly standardized in lab. A and B but « home brew » in lab C
  - Xpert BCR-ABL Monitor ™ + Genexpert Dx System (Cepheid) in all labs

- Conversion to international scale (IS)
  - 0.48 conversion factor validated within the EUTOS program by lab A
# Feasability

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patient Samples</td>
<td>181</td>
</tr>
<tr>
<td>Xpert BCR-ABL Monitor™ measurements</td>
<td>378</td>
</tr>
<tr>
<td>Assay invalidations</td>
<td>2</td>
</tr>
<tr>
<td>Assay interruptions</td>
<td>2</td>
</tr>
<tr>
<td>Total failures</td>
<td>4/378 (1.1%)</td>
</tr>
</tbody>
</table>
### Within laboratory reproducibility (Lab. A)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Xpert BCR-ABL Monitor™</th>
<th>Non automated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Samples</strong></td>
<td>E65</td>
<td>E26</td>
</tr>
<tr>
<td><strong>Nb of repeats</strong></td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td><strong>Mean Ratio</strong></td>
<td>2.46</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>CV</strong></td>
<td>29%</td>
<td>48%</td>
</tr>
</tbody>
</table>
Inter-laboratory reproducibility A vs B

Xpert BCR-ABL

CC: 0.92

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Inter-laboratory reproducibility
A vs C

Xpert BCR-ABL

Manual

Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.
Impact of pre-analytical delay on inter-laboratory reproducibility

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Reporting Genexpert Dx System results on the Internationale Scale

\[ \text{Xpert BCR-ABL Monitor is CE-IVD marked and not available for sale in the USA.} \]
Concordance for MMR IS and CMR between automated and non-automated methods.

Data obtained with the 1st series of samples are cited (n = 65)

<table>
<thead>
<tr>
<th></th>
<th>Either methods</th>
<th>Xpert BCR-ABL™</th>
<th>Non automated</th>
<th>Both methods (% of concordance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of samples with ratio ≤ 0.1% (MMR IS) in laboratory A*</td>
<td>39</td>
<td>39</td>
<td>35</td>
<td>35 (90)</td>
</tr>
<tr>
<td>Number of samples found negative (CMR) in laboratory A</td>
<td>13</td>
<td>10</td>
<td>11</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Number of samples found negative (CMR) in laboratory B</td>
<td>17</td>
<td>14</td>
<td>15</td>
<td>12 (71)</td>
</tr>
</tbody>
</table>

* CFs of 2.3 and 0.48 were applied to ratios generated by automated and non-automated methods, respectively.

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RuBIH Cost Evaluation in 2009

With non-automated methods
- Labor (technician time) +++
- Equipment ++
- Reagents +

With GeneXpert
- Reagents ++++
- Technician time +

➢ With the time and the tests volume we can expect the labour cost to increase and the reagent cost to decrease.

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Impact study of BCR-ABL1 quantification volume on costs (Xpert 2008 prices)

- Xpert BCR-ABL Monitor assay
- Non automated method (shared equipment)
- Non automated method (dedicated equipment)

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New Xpert BCR-ABL volume discount structure

(Data extracted from the RuBIH 2010 study and updated by Cepheid)

Xpert BCR-ABL Monitor assay
Non automated method (shared equipment)
Non automated method (dedicated equipment)
Automated Xpert BCR-ABL (2012 prices)

Euros
Annual activity levels
Conclusions

- Efficient measurement of BCR-ABL mRNA in virtually all TKI treated CML pts
- Similar inter-laboratory reproducibility to standardized non-automated assays
- Reproducible bias with IS over the whole measurement range, allowing alignment of the results by a CF
- High level of concordance with non-automated method for MMR IS
- Economic evaluation (2008 catalog prices)
  - high impact of reagent costs
  - advantageous costs for an annual activity below 300
Xpert BCR-ABL Evolutions since 2008

- Kit storage at room temperature
- International Scale (IS) reporting inclusion (2011)
  1. Xpert BCR-ABL quantitative results are converted to the IS in order to be directly compared to results reported in IRIS (International Randomized Study of Interferon vs STI571)
  2. Using the IS, a result $\leq 0.1\%$ is equivalent to a major molecular response (MMR)
- IS reporting improvement with WHO standards calibration on every lot (2012)
  1. Cepheid is now aligning all their Xpert BCR-ABL production lots with the WHO standards to prevent potential drifting
  2. Every laboratories can reliably report their results on the IS
- New pricing structure with volume discount (2012)
Suitable automated solution for the BCR-ABL monitoring
Adaptable to all test volume
Random access
International Scale reporting
Suitable for all laboratories (WHO standards alignment for every lot)
Cost effective
Thanks

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