Standardisation needs for the measurements of genetic biomarkers

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Meeting Place: JRC Ispra, Italy

21 October 2015
Breast cancer is not a single disease

Different subtypes with different treatment response and prognosis

→ No single optimal therapy for all patients

Biomarkers

- Predictive: identify the target population for certain therapies
  adjuvant endocrine therapy or specific chemotherapy

- Prognostic: probability of disease free survival with surgery alone

- Crucial tools for personalized medicine and health economics
Assays to detect and quantify biomarkers

**Immunohistochemistry (ICH) or in-situ hybridisation (ISH)**
Estrogen and progesterone receptor (ER and PR), Human epidermal growth factor receptor 2 (HER2), Marker of proliferation Ki-67 (MKI67)

**Multigene tests based on reverse transcriptase real time PCR (RT-qPCR) or DNA micro array**
- Oncotype DX™: 16 + 5 genes
- Breast cancer index™: 7 genes
- EndoPredict assay™: 8 + 3 genes
- MammaPrint™: 70 genes
- Prosigna kit™: 50 + 5 genes

20% of the ICH test results may be inaccurate*
Several efforts to improve between-laboratory reproducibility over the past years.

Comparative studies**:
- Each test has prognostic value
- Individual risk assignments often discordant (up to 30%)

*Source: ASCO-CAP Guideline Recommendations, 2010 J Clin Oncol. 28(16): 2784-95

1Single centralized laboratory
General problem of biomarkers in oncology

Several billions invested in research
Hundreds of publications every year

30-50% of biomarkers coupled to drug development*

3-5% of biomarkers for clinical use*

*Source: Presentation of A. Huriez, "Personalized medicine, introduction, business impact on the healthcare sector and regulatory aspects"
Important issue: Reproducibility

Reports from Bayer and Amgen*:

Only 11% to 25% of the findings of ground breaking basic sciences studies in oncology and related area can be reproduced.

*Sources: Prinz et al. 2011, Nat Rev Drug Disc. 10: 712
Begley and Ellis 2012, Nature 483: 531–3
Analytical challenges

Analytical characteristics of an assay:

- Sensitivity
- Specificity
- Precision
- Trueness
- Robustness: to allow translation from well-designed small scale studies to wide-spread clinical use
Reference measurement systems

Characteristics of reference materials

- Fit for purpose
  Calibration ↔ quality control
- Homogeneity
- Stability
- Certified reference material:
  Certified value with uncertainty
  (e.g. reliable calibration)
Example of chronic myeloid leukaemia

- BCR-ABL protein: constitutively active tyrosine kinase causing uncontrolled cell division
- Lifelong treatment with specific tyrosine kinase inhibitors
- Treatment monitoring by quantification of the BCR-ABL transcript
## Two types of reference materials needed

<table>
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<th>Criterium</th>
<th>Cell mixtures (provided by WHO)</th>
<th>Plasmid calibrant (provided by JRC-IRMM)</th>
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<tbody>
<tr>
<td>Mimic real patient samples</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Control entire measurement procedure</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Quantify measurement sensitivity</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Large availability, allowing daily use</td>
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## ERM-AD623

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</table>
Use of ERM-AD623 in field trials

- 52 routine laboratories
- 3 common samples mimicking different disease stages
- Improved level of agreement between results from different laboratories

Publication: White et al. 2015, Leukemia 29: 369-76
Conclusions

- Genetic biomarkers are crucial tools for personalized medicine and treatment optimisation.
- Current use of genetic biomarkers in the broad clinical field is limited.
- International standardisation efforts are required.
- Reference materials are essential in the measurement standardisation process.
Thank you for your attention