Implementation of nation-wide molecular testing in oncology in the French Health care system: quality assurance issues & challenges

Frédérique Nowak - 21 October 2015

"Putting Science into Standards event: Evidence-based quality assurance – an example for breast cancer"
Molecular profiling of tumors is now necessary to guide treatment

- Molecular abnormalities subdivide most frequent cancers in several rare entities

Example of Lung cancer

- gefitinib
- erlotinib
- crizotinib

The same genetic abnormality can be found in different types of cancers

- A same targeted therapy can be used to treat several different tumours:
  - Imatinib for CML (BCR-ABL) and GIST (KIT)
  - Trastuzumab in breast and gastric cancers expressing HER2
### Predictive tests for targeted therapies

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Cancer type</th>
<th>Targeted therapies</th>
<th>Patients nb in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCR-ABL translocation</strong></td>
<td>Chronic Myeloid Leukemia/Acute Lymphoblastic Leukemia</td>
<td>Imatinib, nilotinib, dasatinib, ponatinib, bosutinib</td>
<td>7453</td>
</tr>
<tr>
<td><strong>KIT and PDGFRA mutations</strong></td>
<td>GIST</td>
<td>Imatinib, nilotinib, dasatinib</td>
<td>1189</td>
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<tr>
<td><strong>HER2 amplification</strong></td>
<td>Breast and gastric cancers</td>
<td>Trastuzumab, lapatinib (breast)</td>
<td>9680</td>
</tr>
<tr>
<td><strong>KRAS mutations</strong></td>
<td>Colorectal cancer</td>
<td>Panitumumab, cetuximab</td>
<td>22011</td>
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<tr>
<td><strong>EGFR mutations</strong></td>
<td>Lung cancer</td>
<td>Gefitinib, erlotinib</td>
<td>24558</td>
</tr>
<tr>
<td><strong>ALK translocations</strong></td>
<td>Lung cancer</td>
<td>Crizotinib</td>
<td>21183</td>
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<td><strong>ROS1 translocations</strong></td>
<td>Lung cancer</td>
<td>Crizotinib</td>
<td>5414</td>
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<tr>
<td><strong>BRAFV600 mutation</strong></td>
<td>Melanoma</td>
<td>Vemurafenib, dabrafenib</td>
<td>5534</td>
</tr>
<tr>
<td><strong>g/t BRCA mutation</strong></td>
<td>Ovarian cancer</td>
<td>Olaparib</td>
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</tbody>
</table>
France organisation of molecular centres for personalized medicine

Provides nationwide molecular diagnostic tests

**Objectives**
- Perform molecular testing for all patients;
- Whatever the healthcare institution status (public hospitals, private hospitals...);
- Perform high quality tests;
- Leukemia, solid tumours

**28 regional centres**
- Partnerships between several laboratories located in University hospitals and cancer centers
- Regional organization
- Cooperation between pathologists and biologists

The program is operated by the INCa/French Ministry of Health since 2006
Rapid access to innovation

Offer each patient in France an equal access to molecular tests as soon as a therapy is available

Colorectal cancer:
- **Mid 2008**: EMA approvals for panitumumab and cetuximab for patients with **wild type KRAS tumours**
  - INCa started to allocate €2.5M to the 28 centres at the end of 2008

Lung cancer:
- **June 2009**: gefitinib approvals by EMA for patients with **activating mutations of EGFR in their tumors**
  - INCa started to allocate €1.7M to the 28 centres at the end of 2009
Scientific, technical and organisational issues

- **Multiple testing of predictive biomarkers**
  - Wide range of techniques required to assess diverse types of biomarkers: IHC, DNA & RNA-based

- **Multiple methods to assess the same biomarker**
  - Lack of agreement as to the best techniques
  - Positive thresholds?

- **Medical interpretation of results:**
  - Clinical significance of rare mutations?
  - Clinical significance of minor mutant clones?

- **Specific challenges for tests performed on solid tumours:**
  - Low quality DNA/RNA from fixed tumours samples
  - Large number of local pathology laboratories
  - Low percentage of tumour cells in samples
  - Small biopsies

- **Permanent evolution of daily practices: new biomarkers, new techniques...**
All the professionals involved in molecular testing should be part of a multi-level national network

- Joint expertise of pathologists and molecular biologists within each centre
- Collaboration between pathologists from the centres and local pathologists
- Collaborative network between the 28 centres
- Commitment of clinicians

=> Sharing of expertise and facilitating troubleshooting
Set up of working groups for the drafting of guidelines for:
- the detection of mutations in solid tumors;
- the organization of molecular testing;
- reports of molecular tests

Implementation of a national External Quality Assessment for the 28 centers:
- 2011: BCR-ABL quantification, KRAS and EGFR mutation screening;
- 2012: BRAF mutation screening
- Evolution towards multiparametric molecular testing

Guide the molecular genetics centers to becoming accredited to ISO 15189 standard as soon as possible
An increasing number of actionable molecular alterations

Implementation of targeted NGS for diagnostics in the 28 molecular genetics centers

- Targeted sequencing of a panel of genes (definition of a consensus minimal list)

- Call for proposals in 2013 to grant pilot projects and bioinformatics reference teams

- Drafting of guidelines for NGS method validation and molecular reports

- In 2015: progressive shift towards targeted NGS for all patients
From targeted NGS to tumour genomes analysis in clinical practice

In the meantime, the development of very high-throughput sequencing technologies along with costs decrease allows to consider tumour genomes sequencing in clinical practice.

- Progressive shift from the « gene by gene » approach towards targeted NGS
- Progressive shift from targeted NGS towards tumour genome sequencing (Whole Exome Sequencing + RNAseq)

=> Clinical WES and RNAseq will be implemented within the framework of dedicated clinical trials
Implementation of WES and RNAseq in routine practice: challenges

- Technologies **mature as research tools**

- **Specific challenges for their clinical use**: 

  - Fixed samples;
  
  - **Quality criteria** for sequencing techniques compatible with clinical use;
  
  - Operational NGS sequencing platforms;
  
  - Optimized pipelines for NGS data analysis and qualified dedicated staff;
  
  - Development of **medical decision support tools** and specific organization to guide treatment prescription;

=> How to ensure the best quality for this process?
The French molecular screening initiative:

- has been operating for 6 years;
- offers:
  - equal access to molecular testing for all patients in France;
  - fast implementation of molecular tests for new tumor biomarkers;
- shows that molecular stratification can be successfully integrated into the healthcare system;

Ensuring the best quality for molecular tests is key and new challenges are emerging with the development of high throughput technologies.
more information on

e-cancer.fr