Molecular Pathology Training in Europe
A French Perspective

Benoit Terris
Cochin Hospital, Paris Descartes, France
Introduction

• The past 10 years have brought a revolution in the understanding of molecular pathology of cancer
• Genomic analysis is now a part of patient care and its role will continue to increase:
  – To identify additional molecular alterations that will lead to better therapies
  – Due to implementation of NGS
    • single gene to multiple gene alterations
• Without significant pathologist oversight of genomic testing, there is the real risk for inaccurate results and poor patient care.
• As such, education in genomic pathology must become part of residency training.
Plan

• Pathology residency training program
• Organization of molecular genetic centers
• Molecular pathology training during the residency
Pathology Residency Training in France

• The number of new trained pathologists in France is 70/year
• Each region in France is in charge of their pathology trainees
• The length of residency is 5 years
  – Practical training: 10 training courses of 6 months each
  – Theoretical program:
    • 2 weekly teaching conferences (3H/each)
    • 20 modules:
      – General pathology
      – Pathology and cytopathology subspecialties
      – One module of molecular pathology (20H)
• Pathology examination:
  – Practical part (macroscopic - microscopic)
  – Presentation of a research or a clinical study
Molecular Genetic Centers in France

- Ensure equal access to personalized cancer treatment
- French Ministry of Health and INCA have created a specific molecular testing organization:
  - National network of 28 molecular genetics centers.
  - Located throughout the country, with an average of one center per administrative region.
- Each molecular genetics center performs innovative molecular tests for all patients in its region.
18,000 EGFR tests in lung cancers
23,000 KRAS tests in CRC

Figure 2 | Predictive molecular testing activity in France 2007–2011. Number of patients in

Nowak, 2013
Centralized system in France

**Advantages**
- Reduced cost due to large volume of tests
- Easier quality control
- Free of charge testing for patients

**Inconvenients**
- Tests frequently performed outside the primary hospital
- Tissues sent to an external platform (delay of results)
2) Pré-analytique
Date de demande : 10/04/2014.
Extraction de l’ADN tumoral :
Technique : Extraction d’ADN sur Maxwell 16 (Promega) avec le kit Maxwell 16 FFPE Plus LEV DNA Purification.
Extraction de 10 coupes paraffine à 6 µm issues du bloc n°14H06922-3, sans dissection.
Pourcentage de cellules tumorales dans le fragment extrait : environ 70%.
Concentration d’ADN obtenue : 200 ng/µL (Nanodrop®).

Les résultats de l’analyse par génétique moléculaire feront l’objet d’un complément de compte-rendu.

Le 16/04/2014
Docteur Pierre Alexandre JUST
3- Analytique

Date de réception dans le service de génétique et biologie moléculaires : 14/04/2014.

Technique : Amplification des régions exoniques et introniques flanquant des gènes BRAF, KRAS et NRAS (NM_004333.4, NM_004985.3 et NM_002524.4) par PCR multiplex et séquençage des amplicons par séquençage nouvelle génération (NGS – PGM / Ampliseq LifeTechnologies _ Référence hg19/IAD45542_031 avec kit Ion AmpliSeq 2.0 Library, Ion PGM Template OT2 200 et Ion PGM 200 Sequencing-v2, Barre-codes IonXpress). Analyse et visualisation des données par Torrent Suite 4.0.1 (LifeTechnologies), Integrative Genomic Viewer v2.3.3 (Broad Institute) et NeoGENe v2.3.3 (LifeTechnologies). Le seuil de positivité est fixé à 5% (sensibilité analytique des méthodes conventionnelles utilisées pour la validation des tests compagnons). Un résultat négatif est rendu pour une profondeur de séquençage minimum de 300X.

<table>
<thead>
<tr>
<th>Gènes étudiés</th>
<th>Exons étudiés</th>
<th>Codons étudiés</th>
<th>Mutations détectées</th>
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<tbody>
<tr>
<td>BRAF</td>
<td>Exon 15</td>
<td>V600</td>
<td>Absence de mutation</td>
</tr>
<tr>
<td>NRAS</td>
<td>Exon 2</td>
<td>G12</td>
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<tr>
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<td>Exon 4</td>
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Conclusions et commentaires :
Dans la limite des techniques utilisées, absence des mutations recherchées des gènes KRAS, BRAF et NRAS. Il n’est pas détecté de mutations de résistance aux traitements par des anticorps anti-EGFR.

Le 30/04/2014

Compte-rendu validé électroniquement par :

Professeur Eric CLAUSER
Docteur Eric PASMANT
With the advent of molecular diagnostics, pathologists will clearly need to be trained in genomics-related diagnostic tools.

What will pathologists at the end of their residency need to know in molecular diagnostics?

The level of knowledge required will differ between:
- the nonspecialist who will help in sample acquisition, integration of findings into reports, and communication with clinical colleagues
- the genomic pathology specialist who will control the testing

CoPath has decided:
- that all residency trainees will follow molecular training in genomics and personalized medicine:
  - Theoretical part
  - Practical part
Molecular and genomic training in pathology

Practical part

**BRAF**: V600E

**HER2**

**ALK**

7 in Pathology department

2 in Clinical department / one in molecular genetic center
Molecular and genomic training in pathology

Practical part

• Molecular genetic center
• Non specialist trainees will develop an understanding in genomics and personalized medicine (NGS)
  – How to perform the test
  – How to interpret diagnostic test results
  – How to report them
  – Quality and controls associated
Molecular and genomic training in pathology

• Residency trainees may follow:
  – Optional module of molecular pathology
    • 200H of lectures:
      – DNA extraction and measuring methods
      – NGS technology and application to molecular pathology
      – Quality and controls
      – Ethical issues related to personal genomic

• Practical stage of 2 months
  - Perform a fellowship subspecialized in molecular pathology
    - genomic pathology specialist
CONCLUSION

• College of pathologists in France:
  – to develop programs of training and education in genomic medicine, especially in NGS
  – Without forgotten molecular diagnostics based on IHC and ISH

• Maintain and develop the role of pathologist in genomics and personalized medicine in the future